Evidence for Neurosurgery

Effective Procedures and Treatment

Ronald H. M. A. Bartels
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Preface

Evidence-based medicine, evidence-based surgery, or evidence-based neurosurgery is about solving clinical problems. In particular, evidence-based neurosurgery provides tools for using the medical literature to determine the benefits and risks of patient management strategies and to weigh these benefits and risks in the context of an individual patient's experiences, values, and preferences. The term evidence-based medicine first appeared in the literature in 1991; it rapidly became a buzzword or, better, a ticket of entry to high-quality medicine. In fact, EBM involve informed and effective use of all types of evidence. Not everything in neurosurgery can be studied with randomized trials, as many diseases have a low incidence, such that well-done cohort studies are going to be the highest level of evidence available on which to base our treatment decisions.

Since the beginning of neurosurgery as a medical specialty, it has been characterized as a very innovative and practical specialism. Conquering the surgical challenges due to the extreme susceptibility of the nervous system was and still is a priority. Neurosurgeons are focussed on avoiding additional neurologic deficit that might sincerely interfere with the quality of life for the patient. New techniques, approaches, and implants are entering our healthcare systems at an unprecedented pace. Such innovative techniques are often regarded as a positive development, but others have shown that only 50% of all new techniques prove to be better than the established treatments. Excellence in surgical research therefore deserves more recognition. Surgical research is, however, associated with several methodological and practical challenges. Surgical innovation is especially demanding because many of these challenges coincide. This situation leads many surgeons to view randomized controlled trials (RCTs)—although theoretically advantageous—to be too difficult and impractical to undertake and, at worst, irrelevant to their practice because of concerns of generalizability.

The implementation of new techniques or implants in neurosurgery has therefore often been based on intuition or eminence-based medicine. Propagation of new techniques was through observations in small series of patients. Gradually, comparative studies have been introduced. Since neurologic deficit or pain due to compression of neural tissue is the main cause to consult a neurosurgeon, removing the compressive lesion was thought to result in a better outcome than doing nothing. In some neurosurgical pathologies, this is clear, like an epidural hematoma causing reduced alertness and eventually death. For others, like a lumbar herniated disc, it is not so evident.

In our role as reviewers and readers of different medical journals, we are confronted with many studies with different study designs and outcome measurements reporting statistical tests of significance. To our opinion, disclosing statistical significance is not equal to evidence-based medicine. A description of the clinical relevance of the produced results is frequently missing, but essential to interpret the results correctly.

Since our goal is to emphasize the role of evidence-based knowledge development within neurosurgery and its implication in daily practice, we will not cover all aspects of neurosurgery. Instead, we focussed on questions that will be relevant in the daily practice of every neurosurgeon. Several neurosurgical practices have been proven effective in historical practice and will not be evaluated in trials, like the removal of an epidural hematoma in an unconscious patient. This resembles the situation of using a parachute when jumping from a high altitude. This is evident and will not be evaluated [1]. The topics were chosen from a personal view (RB), which was subsequently discussed with other neurosurgeons. They were based on questions that arise in daily practice. For example, is age a restricting factor when treating patients with an oncologic or vascular problem? Some topics are still a focus in the neurosurgical literature; others are not. Together, the topics provide an overview of the broadness of work done by the neurosurgeons. In all of the chapters, the main question to be answered is as follows: To what extent is the neurosurgical approach of a certain health problem based on solid evidence? In order to emphasize the relevance of evidence, we suggested a fixed format with preferably a systematic review and, if possible, a meta-analysis followed by important remarks regarding the clinical implications. However, after we had collected all the submissions, it became evident that not all subjects were fit for the proposed format. That is, the authors were frequently forced to conclude that a higher level of evidence than is currently available would be necessary in order establish the validity of the currently accepted management. We believe this is a fact of which both students and neurosurgeons need to be aware, so that they may be prepared to update and alter their clinical decision-making on the basis of higher levels of evidence when these become available. We also hope that increasing awareness of the low level of evidence upon which much neurosurgical practice is based will prompt neurosurgeons from many countries to plan or at least participate in clinical studies to achieve a higher quality of evidence upon which to base a more rational clinical practice.

We would like to congratulate and thank all of our highly distinguished authors for their generous efforts and thoughtful contributions to this compilation.

While this book represents the best evidence in neurosurgery, evidence is not static, so we will provide online updates, and we welcome all contributions or referrals to this new evidence.

Nijmegen, The Netherlands — Ronald H. M. A. Bartels
Nijmegen, The Netherlands — Maroeska M. Rovers
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Contents

Evidence in Neurosurgery

1

Ronald H. M. A. Bartels, Gert P. Westert, and Maroeska M. Rovers

Evidence-based medicine is currently state of the art also within neurosurgery. However, most of the known techniques and approaches have been developed before the nineties of the former century. Series of cases were published reporting the success of a method. These were supported by personal views of charismatic leading neurosurgeons. For example, for a long time it was well known that evacuation of an epidural hematoma can be lifesaving, that decompression of a nerve root by removing a compressing lumbar disc can relieve the pain, or the CSF drainage in case of a hydrocephalus can relief signs and symptoms or be, ultimately, lifesaving. Trials have never been performed.

In the second half of the former century the recognition of variability in clinical practice, inappropriate care and rising costs triggered the need for evidence within medical practice [1]. Until then medical practice was guided by intuition, trial and error and expert opinion. The challenge is to separate warranted from unwarranted variability of care. Structured and reproducible methods to establish a potential benefit of a treatment for the patient are sorely needed. Only the results of the best available research should be applied to clinical practice. It is of utmost importance to incorporate patient values and expertise.

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Different designs of clinical research are known, from observational to randomized controlled trials. The randomized controlled trial (RCT) is considered as the highest standard for clinical research when properly designed and performed. Although RCT is adequate to investigate the effect of a treatment, an often-heard objection of RCTs is the difficulty or even impossibility to extrapolate the results to patients encountered in daily practice. The set-up and inclusion criteria do not resemble the patients encountered in clinical practice, day by day. Because of this and other disadvantages of randomized trials an adaptive design is promoted for nearly three decennia [2, 3].

Although these research methods contribute to obtaining more valid and reliable information, and therefore evidence-based medicine, the highest level of information will be obtained by meta-analyses. The results of this method meets the definition of evidence-based medicine: "a conscientious, explicit, and judicious use of current best evidence in making decisions about the care in individual patients" [1].

Meta-analyses systematically integrate the results of individual studies in order to overcome limits as size or scope of the studies. It can be very effective for combining the findings of small trials or observational studies. The quality of a meta-analysis mainly depends on planning. A thorough design including clear definition of objective, criteria for inclusion and exclusion, target population and outcome measurements is essential. The level of evidence and the risk on bias of each included study should be monitored. For grading the level of evidence, the GRADE working group has defined guidelines [4]. It is a comprehensive framework to grade the quality of evidence and to formulate recommendations for guidelines. Although RTCs are considered the highest standard, since the introduction of the GRADE guidelines the quality of an RCT can be discussed. An inadequate designed RCT results in a lower quality of evidence compared to a very well-designed observational study.

Despite all recommendations and guidelines to adequately design a study in order to provide the best quality of evidence, many studies including meta-analyses only focus on reporting p-values. Recently, the American Statistical Association published a policy statement on statistical significance and p-values [5]. This is remarkable since this association seldom provides this kind of statements. The ASA Board was concerned about the widespread use of p-value < 0.05. According to the ASA Board misuse of the p-value contributed to a decrease of trust in the validity of science leading to extreme decisions like discouraging the use of p-values by specific journals.

In reaction to the ascertained misuse and misinterpretation of the p-value the ASA statement was formulated. In six principles, the statement emphasized how the p-value should be interpreted, and specifically how not. For proper interpretation of p-values, all contextual factors should be taken into account. This implies transparency and completeness of reporting. Multiple analyses to find a statistically significant difference (data drenching, p-hacking) is not a good practice. The statement explicitly stated that a p-value itself does not measure the size of an effect or the importance of a result. Finally, the statement stressed that the p-value itself does not

provide any evidence in favour or against a hypothesis without information about the contextual factors.

Lowering the p-value to 0.005, has been suggested as a solution to its misuse and misinterpretation. Apart from the benefit, the potential harms of lowering the threshold have been addressed by several authors [6]. Several alternatives are present. They all rely on assumptions, but they might directly address the relevance of an effect, like Bayesian methods [5, 6].

It is evident that discussion of the clinical relevance of the results is of utmost importance. The clinical relevance or significance is directly related to the design of the study. The null hypothesis, the outcome measurements and the power of the study directly influence the clinical relevance. At the start of a study it should clearly be stated which difference in outcome is considered clinically significant. Several possibilities exist among which for example minimal clinically important difference (MCID), substantially clinical benefit (SCB), or number needed to treat (NNT). For every comparative study including meta-analysis one of these can be used.

Neurosurgical literature is not characterized by high level of evidence. It has been shown that the level of evidence did not increase the likelihood of citation [7]. Although the level of evidence was increasing, it still remains low [8, 9]. In a recent survey according to neurosurgeons themselves clinical decisions are made on papers of a lower level of evidence than other medical specialities [10]. The lower level of evidence in neurosurgical literature can be explained by the characteristics of neurosurgical pathology: it is often rare and clinical observations might be valuable. Furthermore, any of the current innovations in neurosurgery are variations of well-known and clinically proven techniques. This does not facilitate defining a clear outcome for proper trials regarding clinical significance.

Many technical innovations will be launched in near future. Several barriers will exist for performing RCTs among which costs and the current very strict regulations are very important. Furthermore, the timing of RCTs is very essential. A learning curve for each new technique should be taken into consideration. Either the trial is done too early resulting in a type 2 error since the surgeons are not familiar with the technique or its possibilities, or it is too late, and it has already been adopted by surgeons and patients as standard care [11]. A recent example is the introduction of arthroplasty, either lumbar or cervical.

Emphasizing the difficulty to perform timely and reliable RCT's within neurosurgery alternatives have been suggested [9, 11]. An RCT should be conducted by surgeons from multiple, large centres to improve reliability and generalizability. All participating surgeons should be trained thoroughly to reduce a type 2 error. Other designs might also be helpful: registry randomized trials, platform trials and adaptive designs. Large observational studies still have a role for post-marketing surveillance in order to be informed about clinical effectiveness and complication rate.

Neurosurgery cannot be compared with other surgical specialities, because of the characteristics of nervous tissue, its location within the body and the frequency of diseases that are amenable for neurosurgical treatment. All these characteristics have contributed to the innovative attitude within neurosurgery. The surgical microscope was introduced within neurosurgery as was for example navigation

techniques. Due to these aspects and the high costs related to new developments, meeting standards for evidence-based medicine before their introduction is extremely challenging, but crucial. The use of new methodological designs can facilitate this process.

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The Value of Decompressive Craniectomy in Traumatic Brain Injury

2

Angelos G. Kolias, Athanasios Paschalis, Kostas N. Fountas, and Peter J. Hutchinson

Introduction

Evidence-based medicine has been defined, by Sackett et al. as "the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients" [1]. In turn, the same authors described the best available clinical evidence as "clinically relevant research, often from the basic sciences of medicine, but especially from patient centred clinical research into the accuracy and precision of diagnostic tests (including the clinical examination), the power of prognostic markers, and the efficacy and safety of therapeutic, rehabilitative and preventive regimens" [1]. Establishing an evidence-based practice in neurosurgery has always been a challenge and traumatic brain injury (TBI) has not been an exception. It is well known that trauma remains a major public health problem worldwide. Of all types of traumatic injuries, TBI is the type most likely to result in death or permanent disability. It is estimated that 69 million (95% CI 64–74 million) individuals worldwide suffer a TBI each year [2]. However, the true TBI burden is likely underestimated due to the incomplete capture of data especially in low- and middle-income countries (LMICs).

Intracranial hypertension and brain swelling are well recognised secondary insults following TBI, which are associated with increased mortality and worse

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outcomes [3]. Decompressive craniectomy (DC) refers to the practice of removing a large bone flap and opening the underlying dura. By "opening the box", the intracranial pressure (ICP) is lowered and the risk of herniation can be avoided, although not completely eliminated. In 1908, Harvey Cushing reported a drastic reduction in TBI mortality from 50% to 15% after subtemporal DC [4]. During the twentieth century, various DC techniques were described (hemi-craniectomy, circumferential, bifrontal), but a lack of consensus about indications and substantial variation in reported outcomes paved the way for randomised trials, which were initiated in the beginning of the twenty-first century [5].

Nowadays, three main options exist in terms of the site of DC. In a bifrontal DC, the bone flap extends from the floor of the anterior cranial fossa anteriorly to the coronal suture posteriorly and to the middle cranial fossa floor bilaterally. A hemi-craniectomy, which is also known as unilateral DC, essentially refers to a large fronto-temporo-parietal bone flap; decompression down to the middle cranial fossa floor is also essential. The third option is a bilateral hemi-craniectomy. In general, a bifrontal DC or bilateral hemi-craniectomy are used for patients with diffuse brain swelling, whereas a hemi-craniectomy tends to be used for patients with swelling that predominantly affects one hemisphere, which usually manifests as midline shift on imaging.

When we consider timing, it is useful to use the terms primary and secondary DC [6]. A primary DC refers to leaving a large bone flap out after evacuating an intracranial haematoma in the early phase after a TBI. The most frequent indication for a primary DC is an acute subdural haematoma (ASDH) [7]. Typically, a large fronto-temporo-parietal bone flap is left out after evacuating the haematoma either because the brain is bulging beyond the inner table of the skull or because there is a concern of increasing brain swelling (e.g. in a patient with contusions) in the post-operative period. A secondary DC refers to a DC undertaken in TBI patients who are managed in an intensive care unit (ICU) with ICP monitoring. In this setting, a DC is performed as part of tiered protocols which aim to control raised ICP and maintain the cerebral perfusion pressure (CPP) at adequate levels.

This chapter aims to critically appraise the existing evidence base in order to define the role of DC following TBI.

Methods

In view of the existence of randomised trials addressing the role of DC in TBI, we decided to include only such articles. We searched PubMed with the use of advanced search and the following query (craniectomy [Title/Abstract]) AND "randomized controlled trial" [Publication Type].

Results

Figure 2.1 includes the PRISMA chart [8]. In summary, 40 records were identified, of which 35 were excluded as they were not addressing the role of DC in TBI. Therefore, we are left with five randomised trials, which are presented below in order of publication date. For a summary of the trials, the reader can refer to Table 2.1.

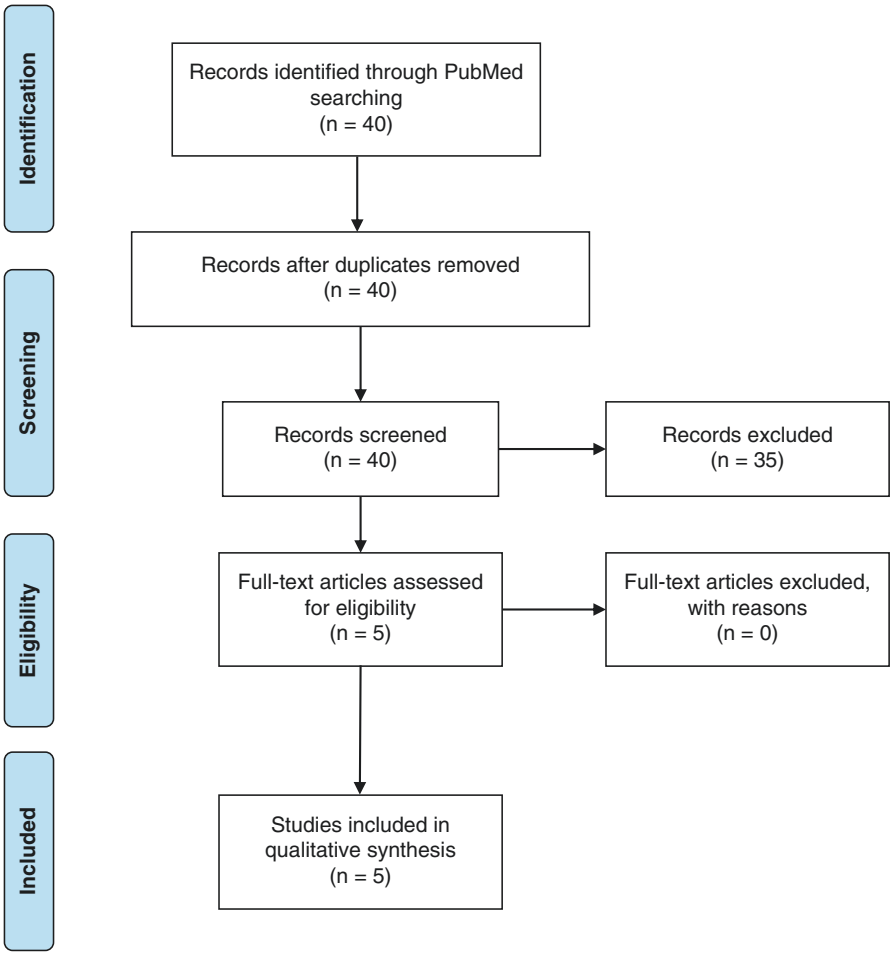

Fig. 2.1 PRISMA 2009 flow diagram

Table 2.1 Summary of trials of decompressive craniectomy included in this chapter

Authors (Ref)	Study design	Population	Intervention	Comparator	Functional outcome
Taylor et al. [9]	Randomised trial (pilot, single-centre)	27 children with a TBI and intracranial hypertension (median age 10.1 years)	Bitemporal DC (without opening dura) plus conventional medical management	Conventional medical management	DC had a risk ratio of 0.54 (95% CI 0.29–1.01) for unfavourable outcome at 6 months
Jiang et al. [10]	Randomised trial (multi-centre)	486 patients with severe TBI and large hemispheric contusions (mean age 44.5 years)	Standard-sized trauma DC (12 × 15 cm flap) vs. a	Limited DC (6 × 8 cm flap)	Standard trauma DC had a risk ratio of 0.84 (95% CI 0.74–0.96) for unfavourable outcome at 6 months
Qiu et al. [11]	Randomised trial (single-centre)	74 patients with severe TBI and a swollen hemisphere with midline shift >5 mm, contusions <25 ml and compressed basal cisterns on CT scan (mean age 40.1 years)	Standard unilateral DC (around 15 cm maximum diameter)	Limited unilateral temporo-parietal craniectomy (around 8 cm maximum diameter)	Standard unilateral DC had a risk ratio of 0.64 (95% CI 0.42–0.99) for unfavourable outcome at 12 months
Cooper et al. [12]	Randomised trial (multi-centre)	155 patients with severe TBI and mild/moderate intracranial hypertension not controlled by first-tier therapies within the first 72 h (median age 24.2 years)	Early (neuroprotective) bifrontal DC	Ongoing medical care	DC had an adjusted odds ratio of 1.90 (95% CI 0.95–3.79) for unfavourable outcome at 6 months
Hutchinson et al. [13]	Randomised trial (multi-centre)	408 patients with TBI and severe intracranial hypertension refractory to first-tier and second-tier therapies (mean age 33.5)	Last-tier DC (bifrontal or hemicraniectomy)	Standardised medical therapy (with the option of barbiturates after randomisation)	DC had an odds ratio of 0.4 (95% CI 0.27–0.62) for mortality and an odds ratio of 1.73 (95% CI 1.14–2.64) for favourable outcome at 12 months

For further details, refer to text

A Randomised Trial of Very Early Decompressive Craniectomy in Children with Traumatic Brain Injury and Sustained Intracranial Hypertension

In 2000, Taylor et al. published the first ever randomised trial of DC [9]. This was a pilot, single-centre trial (Melbourne, Australia) that enrolled 27 children with a TBI and intracranial hypertension, who had a median age of 120.9 months (range 13.6–176.4 months). Children with intracranial hypertension during the first day after admission (ICP 20–24 mmHg for 30 min, 25–29 mmHg for 10 min, 30 mmHg or more for 1 min) or who had evidence of herniation (dilatation of one pupil or the presence of bradycardia) were eligible for randomisation. Children were randomised to conventional medical management (control group) or bitemporal DC plus conventional medical management (decompression group).

Randomisation took place at a median of 16 h (range 3–29) after injury. The bitemporal DC was performed at a median of 19.2 h (range 7.3–29.3 h) after injury. Interestingly, as this was a paediatric population, the authors decided to only remove a disc of temporal bone measuring about 3–4 cm, with extension of the craniectomy to the floor of the middle cranial fossa but without opening the dura mater. The authors justified this decision by stating that they "chose the bitemporal craniectomy to promote decompression of the temporal lobes and achieve ICP control while reducing the degree of transtentorial herniation and upper brainstem compression" and that "the dura was not opened, to avoid gross cerebral herniation and further injury to the brain" [9].

Although this pilot trial was small, its findings showed that DC was associated with a risk ratio of 0.54 (95% CI 0.29–1.01) for unfavourable outcome at 6 months—defined by the authors as, death, moderate or severe disability. Moreover, in comparison to pre-randomisation ICP, the mean ICP was 3.69 mmHg lower in the 48 h after randomisation in the control group, while it was 8.98 mmHg lower in the 48 h after DC in the decompression group ($P = 0.057$).

One has to recognise the significance of this trial, as it was the first ever randomised trial of DC following TBI and additionally it focused on a paediatric population, which made it even more challenging. Nevertheless, it has a few important limitations and sources of bias. A sample size calculation was not provided. The study is reported as "pilot" by the investigators but despite this, the primary endpoint is functional outcome, which would be more suitable for a definitive multicentre study. Blinding of patients, families and treating clinicians was not possible due to the nature of the intervention but it is also unclear if any attempt was made to maintain the blinding of the outcome assessors. It is also unclear whether allocation concealment was achieved. Allocation concealment is different to blinding and it simply means that the person randomising the patient does not know and cannot predict what the next treatment allocation will be; it is an important concept as it prevents selection bias. The authors also used the Zelen method of randomisation, which is considered controversial [14]. In this approach, randomisation takes place before consent, which is only sought from those allocated to the experimental arm of a trial. Therefore, the control group is unaware that randomisation has taken place. Moreover, the investigators performed a statistical analysis on the outcome

data twice during the last 6 months of the trial prior to the final analysis, which is another source of bias. Finally, the surgical technique employed was unusual in that the DC only involved the temporal squama and the dura was not opened. For these reasons, this study cannot be considered definitive.

Efficacy of Standard Trauma Craniectomy for Refractory Intracranial Hypertension with Severe Traumatic Brain Injury: A Multicenter, Prospective, Randomized Controlled Study

In 2005, Jiang et al. published the results of a multi-centre randomised trial that took place in five centres in China aiming to compare outcomes after a standard-sized trauma DC (12 × 15 cm flap) vs. a limited DC (6 × 8 cm flap) in severe TBI patients with refractory intracranial hypertension [10]. They enrolled patients with "refractory intracranial hypertension, caused by unilateral massive fronto-temporo-parietal contusion, intracerebral/subdural hematoma, and brain edema". The authors recruited 486 patients in total and found that the mortality rate was lower (26% vs. 35%) and favourable outcome rate higher (39.8% vs. 28.6%) after standard trauma DC compared to limited DC ($p < 0.05$). The larger DC had a risk ratio of 0.84 (95% CI 0.74–0.96) for unfavourable outcome, which was defined as death, vegetative state and severe disability on the Glasgow Outcome Scale at 6 months. Additionally, they found that the larger DC was associated with fewer complications, such as delayed intracranial hematoma, repeated surgical intervention, and CSF fistula, compared to the small DC.

This trial also has a few limitations. A sample size calculation was not provided and it is also unclear whether allocation concealment was achieved. Additionally, although this was supposedly a trial of patients with refractory intracranial hypertension, pre-operative ICP data were only available for 17% of the patients enrolled and an ICP threshold was not included in the inclusion criteria. It is likely that the authors mistakenly used the term "refractory intracranial hypertension" instead of severe unilateral post-traumatic brain swelling. One positive aspect was that the outcome assessors were not aware of the patients' treatment assignments.

To some extent, the results of this study are not surprising as the observation that if the flap is too small, the expanding brain can herniate through the cranial defect with the development of new haemorrhagic and ischaemic lesions had been made by others [15]. Nevertheless, this is a useful trial as it provides evidence regarding the optimal size of unilateral DC and definitive evidence that small-sized bone flaps should be abandoned in the context of DC.

Study of the Effectiveness of Craniotomy on Patients with Acute Post-Traumatic Brain Swelling After Severe Traumatic Brain Injury (ISRCTN14110527)

In 2009, Qiu et al. published the results of a single-centre randomised trial from China, which again compared a standard unilateral DC (around 15 cm maximum

diameter) vs. a limited unilateral temporo-parietal craniectomy (around 8 cm maximum diameter) [11]. The investigators included TBI patients with a Glasgow Coma Scale (GCS) of 8 or less at admission, and swollen hemisphere with midline shift >5 mm, contusions <25 ml and compressed basal cisterns on CT scan. Mean time to surgery from admission was 5.8 h, and 74 patients were enrolled in total, equally distributed in the two groups. In this trial, the larger DC had a risk ratio of 0.64 (95% CI 0.42–0.99) for unfavourable outcome, which was defined as death, vegetative state and severe disability on the Glasgow Outcome Scale at 12 months. In this trial, the investigators also found a much larger mortality difference between the two groups (27% in the unilateral DC group vs. 57% in the control group; $p = 0.010$) compared to the previous multi-centre trial from China. On the other hand, they found that the larger DC was associated with more complications, namely delayed intracranial haematoma (21.6% vs. 5.4%; $p = 0.041$) and subdural effusion (10.8% vs. 0, $p = 0.040$).

This trial also has a few limitations. A sample size calculation was not provided and it is also unclear how allocation concealment was achieved. In comparison to the earlier multi-centre trial from China, it had a much smaller sample size and was only conducted at a single centre. This likely explains the much larger treatment effect in terms of mortality and unfavourable outcome, as it is well known that small and single-centre trials tend to overestimate treatment effects [16, 17].

Multi-Centre Prospective Randomised Trial of Early Decompressive Craniectomy in Patients with Severe Traumatic Brain Injury: DECRA (DEcompressive CRAniectomy) Trial (ACTRN012605000009617)

The DECRA trial aimed to address the role of early, neuroprotective bifrontal DC for patients with severe TBI and mild/moderate intracranial hypertension not controlled by first-tier therapies [12, 18]. The study enrolled 155 patients in three different countries (Australia, New Zealand, and Saudi Arabia). Patients were eligible for randomisation within the first 72 h after TBI, if the ICP was higher than 20 mmHg for >15 min (continuously or intermittently) within a 1-h period and refractory to first-tier ICP-lowering interventions. External ventricular drainage pre-randomisation was used in 70% of the patients enrolled in the study. Patients were randomised to bifrontal DC or ongoing medical care. The primary outcome measure was the extended Glasgow Outcome Scale (GOSE) score at 6 months. The mortality was similar in both groups (19% vs. 18%), but more surgical patients had an unfavourable GOSE (70% vs. 51%; $p = 0.02$). Following post hoc adjustment for pupil reactivity at baseline, which is an important prognostic factor that was not balanced between the two groups, the rate of unfavourable outcome was no longer significantly different between the two arms (adjusted OR 1.90; 95% CI 0.95–3.79). The authors also found that after randomisation, the mean ICP was lower in the craniectomy group than in the medical group (14.4 mmHg vs. 19.1 mmHg, $p < 0.001$).

This was a well conducted and high-quality trial that tried to address a very specific hypothesis, namely that “early decompressive craniectomy will improve long

term neurological outcome in patients with severe traumatic brain injury" [12]. There are no major methodological concerns but the sample size was limited with the caveats previously mentioned about small trials. The limited sample size is probably responsible for the imbalance in pupil reactivity at baseline, as the risk of imbalance in baseline characteristics is greater for trials with small samples [19]. Additionally, the length of follow-up was 6 months, which is rather limited given that the GOSE trajectory for TBI patients peaks near year 10 with changes occurring most rapidly in the initial years after TBI [20]. Finally, almost one quarter of the medical group underwent a DC (15 patients (18%) underwent a craniectomy after 72 h as a lifesaving intervention, while four patients (5%) underwent a craniectomy less than 72 h). The intention-to-treat (ITT) principle, which was how the analysis was conducted in the DECRA trial, includes every patient who is randomised according to the initial randomised treatment assignment. From the statistical perspective, the ITT principle is a robust method that maintains the balance between the treatment and control groups, in terms of observable and non-observable characteristics, generated from the original random treatment assignment. However, due to the cross-over from the medical to the surgical arm, it is possible that the DECRA trial has overestimated the harmful effects of early bifrontal DC.

Although DECRA has been widely criticised for various reasons but mostly about its hypothesis and enrolment criteria [21, 22], we view it as a valuable trial that addressed a very specific question. On the basis of its findings, we can conclude that bifrontal DC should not be used as a neuroprotective measure for moderate intracranial hypertension after TBI in well-resourced intensive care units (ICUs) that have the means to manage elevated ICP with medical measures and external ventricular drainage.

Randomised Evaluation of Surgery with Craniectomy for Uncontrollable Elevation of Intracranial Pressure: RESCUEicp Multi-Centre Trial (ISRCTN66202560)

The RESCUEicp trial aimed to address the role of DC as a last-tier measure for severe and refractory intracranial hypertension after TBI [13]. The study enrolled 408 patients in 20 countries. Patients were eligible for randomisation at any time point after TBI if the ICP was higher than 25 mmHg for at least 1 h and was refractory to first-tier and second-tier ICP-lowering interventions. External ventricular drainage pre-randomisation was used in 19% of the patients enrolled in the study. Patients were randomised to decompressive craniectomy or standardised medical therapy. Barbiturates became an option for the medical group after randomisation. The surgical treatment was either a large unilateral fronto-temporo-parietal craniectomy (hemi-craniectomy), which was recommended for patients with unilateral hemispheric swelling, or a bifrontal craniectomy, which was recommended for patients with diffuse brain swelling that affected both hemispheres. However, as this was a pragmatic 'real-world' trial, the exact site of craniectomy was left at the discretion of the neurosurgeons.

The primary outcome measure was the GOSE score at 6 months. The pre-specified ordinal regression showed a difference in the GOSE distribution between the two groups ($\chi^2 = 7.72$, 1 df, $p = 0.005$). Craniectomy resulted in substantially lower mortality (26.9% vs. 48.9%) but higher rates of vegetative state (8.5% vs. 2.1%), lower severe disability (21.9% vs. 14.4%), and upper severe disability (independent at home; 15.4% vs. 8%) than medical care. The rates of moderate disability and good recovery were similar in the two groups. However, surgical patients continued improving beyond the 6 months, and at 12 months, 45.4% of surgical patients had a favourable outcome (upper severe disability or better) compared to 32.4% in the medical group ($p = 0.01$). Additionally, craniectomy patients had fewer hours than medical patients with ICP above 25 mmHg after randomisation (median, 5.0 vs. 17.0 h; $p < 0.001$) but also had a higher rate of complication (16.3% vs. 9.2%, $p = 0.03$).

This was also a well conducted trial with no major methodological concerns. Additionally, it had a larger sample size and longer follow-up in comparison to DECRA. One of the main limitations of the trial is the fact that a DC was performed in 37.2% of the patients in the medical group due to failure to control ICP. This was allowed by the protocol, as well as the administration of barbiturates in surgical patients in case of further deterioration, on the basis that potentially life-saving treatments should not be withheld from patients simply because they were enrolled in a trial. Nevertheless, this occurrence has likely diluted the observed treatment effect. Finally, data on cranioplasty, a procedure that aims to reconstruct the skull defect a few months after craniectomy, were not systematically obtained.

In summary, the RESCUEicp findings suggest that secondary DC can be helpful as a last-tier intervention to reduce mortality in the subset of TBI patients with severe and refractory posttraumatic intracranial hypertension. Of the extra survivors generated by DC, approximately 60% are independent (at least at home) and 40% dependent on others at 12 months.

Level of Evidence

When considering the five randomised trials presented above, it is evident that they addressed four different questions concerning the role of decompressive craniectomy in TBI:

1. The role of early bitemporal DC vs. conventional medical management in children with intracranial hypertension after TBI
2. The role of a large fronto-temporo-parietal DC (around 15 cm) vs. a small unilateral DC (around 8 cm) for patients with unilateral hemispheric swelling (with large or small-size contusions)
3. The role of early, neuroprotective bifrontal DC vs. medical management for patients with severe diffuse TBI and moderate intracranial hypertension
4. The role of last-tier DC vs. medical management for patients with severe and refractory intracranial hypertension after TBI.

The first question has been addressed by one small pilot RCT [9], which provides low quality evidence according to the GRADE criteria [23].

The second question has been addressed by one large multi-centre randomised trial and one small single-centre randomised trial, which provides moderate quality evidence [10, 11].

The third question has been addressed by a multi-centre RCT of small/moderate sample size, which provides moderate quality evidence [12].

The fourth question has been addressed by a large multi-centre RCT, which provides high quality evidence [13].

Patient Preferences

After a TBI, patients who survive can have varying levels of disability ranging from vegetative state to moderate disability on the GOSE. Vegetative state and lower severe disability (dependent on others for care) are considered unfavourable outcomes by most individuals, at least in western societies. However, patients in upper severe disability are independent at home but require assistance outside (e.g. for shopping or travelling), and patients in moderate disability are usually employed in a paid or a voluntary capacity but have not returned to their pre-TBI employment.

It is useful to bear in mind these descriptions, as it is evident that lower severe disability is very different from upper severe disability, for example. In fact, when discussing with families in the acute setting, given that patients are incapacitated due to the TBI, we advocate against using loaded terms such as "favourable" or "unfavourable" which inevitably reflect our own value judgments [24]. It is preferable to simply state that the best available evidence suggests that:

- DC, when used before other treatment options have been exhausted, does not improve mortality or functional outcome
- DC, as a rescue intervention when most other interventions have failed, reduces mortality by about 20% in severe and refractory intracranial hypertension
- At 12 months, about 60% of these additional survivors would be at least independent at home. The rest would be dependent at home or not recover consciousness.

Our experience is that, when presented with this information, some families favour proceeding to DC, and some do not. This is because the degree of acceptable disability varies from person to person and is dependent on many factors, such as culture, social environment, and religion [25]. Moreover, one should also bear in mind that patients can adapt to a level of significant disability that they may have previously regarded as unacceptable [26].

For these reasons, we do not think that clinicians should be unilaterally deciding whether a given degree of disability is "acceptable" or "unacceptable"—the person who needs to accept an outcome is the patient [24]. Therefore, we believe that the

indirect input of patients through their families, is critical when determining the degree of acceptable disability, and consequently whether a secondary DC should be undertaken.

Discussion

The limitations of each trial have already been presented in the respective sections. Therefore, in this section, we will address some general limitations of the current evidence base and present some further considerations.

Although primary DC is undertaken more frequently than secondary DC [7], no trials on primary DC have been published. The RESCUE-ASDH trial (www.rescueasdh.org) is an ongoing multi-centre randomised trial that aims to define the best surgical strategy for patients with ASDH [25]. The trial was launched in 2014 with the aim of comparing primary DC (bone flap left out) with craniotomy (bone flap replaced and fixed) for patients with a serious TBI undergoing evacuation of an ASDH. Similar to "real-world" practice, patients are randomised intraoperatively after evacuation of their ASDH. Patients who have significant brain swelling preventing safe replacement of the bone flap are not suitable for randomisation and are being followed-up as part of a parallel observational cohort. The study is ongoing, and nearly 450 patients have been randomised from 37 sites worldwide. As recruitment will end in April 2019 and the primary outcome is GOSE at 12 months, the study results are expected during early 2021.

Even though intracranial hypertension is associated with an increased risk of death [27, 28], it is not the only driver of poor outcome. For example, the presence of large bilateral dorsolateral brainstem lesions or severe diffuse axonal injury are likely to be drivers of poor outcome which DC, or for that matter any ICP-lowering intervention, cannot modify. Unfortunately, early MRI studies that allow the exclusion of these pathologies, with a high level of confidence, are not currently feasible in most patients.

Moreover, there is ongoing debate as to whether DC itself contributes to some of the disability. This may be generic, e.g. through deformation of brain tissue [29], or might only apply to a specific surgical technique, such as a bifrontal craniectomy with a strip of bone over the superior sagittal sinus or a bifrontal craniectomy where the falx cerebri is not divided. In theory, these techniques could be leading to pressure on genu of the corpus callosum, thereby contributing to secondary injury and poorer outcomes [30]. Additional research is currently in progress to elucidate these issues. Nevertheless, it is very likely that the poorer outcomes of DC in comparison to medical treatment observed in the DECRA trial can be explained by the fact that as DC was applied early, any potential benefit that could be derived from it was outweighed by the surgical morbidity, including that of the subsequent cranioplasty. The latter is also an issue that deserves more attention, as neurological dysfunction in relation to large skull defects has been proposed as an important factor that can affect the outcome of DC patients [31]. Small, uncontrolled studies suggest that earlier cranioplasty (within 3 months of DC) may independently improve long-term

outcome [32]. This is an area that would benefit from the conduct of high-quality randomised trials.

It is important to emphasise that the DECRA and RESCUEicp trials had different hypotheses, inclusion criteria and addressed different research questions. The DECRA trial, when compared to the RESCUEicp trial, enrolled patients with a lower ICP threshold (20 mmHg vs. 25 mmHg) for shorter intervals (15 min vs. 1–12 h), after lower intensity therapies (stage 1 interventions vs. stage 1 and 2 interventions), and within a shorter interval after injury (all patients enrolled within 72 h after injury vs. 44% of patients enrolled >72 h after injury) [33]. Moreover, patients with mass lesions were enrolled in the RESCUEicp trial, but not in the DECRA trial. At enrolment, the populations also differed with respect to expected outcome, as the requirement for stage 2 interventions increases the relative risk of death by 60% [34]. This explains the fact that, at 6 months, the pooled mortality was 37.5% in the RESCUEicp trial versus 18.7% in the DECRA trial.

Finally, although 90% of worldwide trauma-related deaths occur in LMICs, less than 10% of the RESCUEicp patient population was enrolled in LMICs, whereas all patients in the DECRA study were from high-income countries (HICs) [25]. This fact raises some important issues. Firstly, one cannot necessarily extrapolate the results from studies in HICs, where prehospital, acute neurosurgical, and post-acute care are generally delivered in a more systematic way, to the results that can be expected in LMICs. Secondly, it is probably not possible for neurosurgeons working in LMICs to follow recommendations derived from the DECRA and RESCUEicp studies, given that ICP monitoring is often not available in their daily practice. Nevertheless, the burden of TBI is much higher in LMICs, and patients receive care for TBI despite the absence of high-quality evidence directly applicable to these countries. These are issues that are being examined as part of efforts to improve the care of TBI patients globally, in the context of the NIHR Global Health Research Group on Neurotrauma [35].

Conclusions

The evidence from the 5 published randomised trials of DC can be summarised as follows:

1. Unilateral or bifrontal DC used as a last-tier therapy for patients with severe, sustained, and refractory posttraumatic intracranial hypertension leads to a substantial mortality reduction but increases disability [both lower (dependent) and upper (independent at home) severe disability] compared to medical management (high quality evidence)
2. Early neuroprotective bifrontal DC for mild to moderate intracranial hypertension is not superior to medical management for patients with diffuse TBI (moderate quality evidence)
3. A large fronto-temporo-parietal DC (around 15 cm) is superior to a small unilateral DC (around 8 cm) for patients with unilateral hemispheric swelling with large or small-size contusions (moderate quality evidence)

4. A small pilot study found a trend towards improved survival and functional outcomes with bitemporal decompression compared to medical management in children with post-traumatic intracranial hypertension (low quality evidence).

The neurosurgical community should focus on the roles of DC, cranioplasty, and other decompressive procedures (such as floating or hinge craniotomy) not just in HICs but also in LMICs due to their much greater TBI burden.

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Conflicts of Interest Angelos Kolias and Peter Hutchinson were involved as investigators with the RESCUEicp trial. All authors are involved as investigators with the RESCUE-ASDH trial.

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Cranioplasty: Does Timing Have Any Effect on the Degree of Neurological Recovery or the Complication Rate?

3

Zayan Mahmooth, James G. Malcolm, Rima S. Rindler, and Faiz U. Ahmad

Introduction

Decompressive craniectomy is commonly performed to relieve elevated intracranial pressure caused by trauma, stroke, hemorrhage, or edema [1–9]. Cranioplasty is often subsequently performed to restore cranial cosmesis, provide cerebral protection, and facilitate neurological rehabilitation [10, 11]. Cranioplasty itself has been shown to provide neurological improvement and the question of how long to wait before cranioplasty has received considerable attention [12–18]. Most surgeons wait for recovery from the initial indication for decompressive craniectomy with resolution of edema and inflammation, but often these patients can be lost to follow up for months to years [19]. Recent studies indicate that earlier cranioplasty may improve neurologic recovery and avoid certain complications [12, 15, 18, 19]. This chapter will use findings from two published meta-analyses on the association between the timing of cranioplasty on neurological improvement and complication rate to evaluate the current level of evidence and provide clinical and research recommendations [12, 18].

Method

For both studies, a systematic literature review was conducted in accordance to Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines [20]. The search strategy was designed in accordance to Peer Review

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of Electronic Search Strategies (PRESS) criteria [21]. The search string was for the keywords "cranioplasty, early" or "cranioplasty, timing" in the title, abstract, or keyword list. The search was conducted in PubMed/MEDLINE, Scopus, and the Cochrane databases for original clinical studies published between January 1990 and April 2016. The references of literature reviews, meta-analyses, and included studies were also reviewed for further articles for inclusion. The quality of included individual articles were assessed using the Oxford Center for Evidence Based Medicine (OCEBM) guidelines [22]. The quality of evidence and resulting strength of recommendations were assessed using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) guidelines [23].

Data Analysis

Complete details of the data analysis is reported in the relevant prior publications by this research group [12, 18]. Data were analyzed using Review Manager 5.3.5 (The Cochrane Collaboration, London, United Kingdom).

Neurological Outcome

For the neurological improvement outcome analysis, all but one study dichotomized patients into "early" and "late" cohorts based on time interval between craniectomy and cranioplasty most often using a threshold at or near 90 days. We followed this convention in our analysis: "early" cranioplasty was defined as less-than-or-equal-to 90 days after craniectomy, "late" was defined as beyond 90 days. For studies that did not provide raw data or used a different time-point than 90 days, the study's reported definition was accepted.

The standard mean difference (SMD) was used to normalize neurological measures to allow for comparison across different outcome scales. Change in pre- and postcranioplasty scores was compared between early and late groups to evaluate the difference in magnitude of neurological change over the follow-up period. The difference in means and standard deviation of the difference between sample means was used for this calculation.

The pre-cranioplasty neurological status of early and late cranioplasty groups was then compared to determine preoperative similarity between both groups. Finally, raw postcranioplasty neurological scores were compared to evaluate difference in final outcome. The reported mean and standard deviation from each study was used for these calculations.

Complications

For the complications analysis, complications were first grouped by specific type (e.g. overall complications, infection, seizure, etc.) and analysis was done comparing trauma and mixed populations. If overall complications were not reported in a

study, individual complications were summed. Complications were then grouped by "early" and "late" cranioplasty time-points. "Early" cranioplasty was defined as less than or equal to 90 days after craniectomy. The 90-day time-point was chosen for several reasons: (1) in the authors' experience, cranioplasty procedures often occur around 90 days after initial craniectomy; (2) several studies utilized the median time to cranioplasty in their data as a cutoff for defining early/late time-points, which was around 90 days; (3) grouping around 90 days allowed for inclusion of more studies in the pooled analysis. Studies that provided raw timing data were dichotomized at this time-point for analysis. For studies that did not provide raw data or used a different time-point than 90 days, the study's reported definition was accepted, and the results were pooled in the overall analyses.

Results

The search, screening, and selection of articles for inclusion for both neurological outcomes and complications analyses are presented in the PRISMA flow diagram (Fig. 3.1). A total of 313 and 323 non-duplicate studies were screened from a search on comparisons between early and late cranioplasty in our previous analyses on neurological outcomes and the complications, respectively. No studies were identified for inclusion that were published prior to 2000. Detailed reasons for article exclusion is reported in our previous studies.

For the neurological outcomes analysis (Fig. 3.1a), 24 articles were identified from bibliographic review and 16 articles were excluded after full-text review. Five authors were able to provide data not included in the original publication that allowed inclusion in this analysis [24–27]. Eight studies were included in the neurological outcomes analysis.

The final eight included studies for the neurological outcomes analysis represent 551 cranioplasty procedures (248 early, 303 late). Table 3.1 lists individual study characteristics. All studies were either retrospective cohort studies or case series and met criteria for OCEBM Level 4 evidence. Indications for initial craniectomy included trauma (78% of patients), ischemic stroke (9.4%), subarachnoid hemorrhage (4.9%), unspecified intracerebral hemorrhage (4.7%), and infection (1.5%) among other less common indications. Four studies included only trauma patients [26, 28, 29, 31]. One study dichotomized early and late cranioplasty at 42 days and did not report data to allow regrouping around 90 days [28]. All other studies were dichotomized within 1 week of the 90-day threshold.

For the complications analyses (Fig. 3.1b), 58 articles were identified from bibliographic review and 33 articles were excluded after full-text review. Two articles were not in English but were included because they appeared in a previous meta-analysis on cranioplasty [15, 32, 33]. Twenty-five studies were included in the complications analysis.

The final twenty-five studies that met inclusion criteria for the complications analysis represented 3126 cranioplasty procedures (1421 early, 1705 late). Table 3.2 lists individual study characteristics. All were retrospective cohort

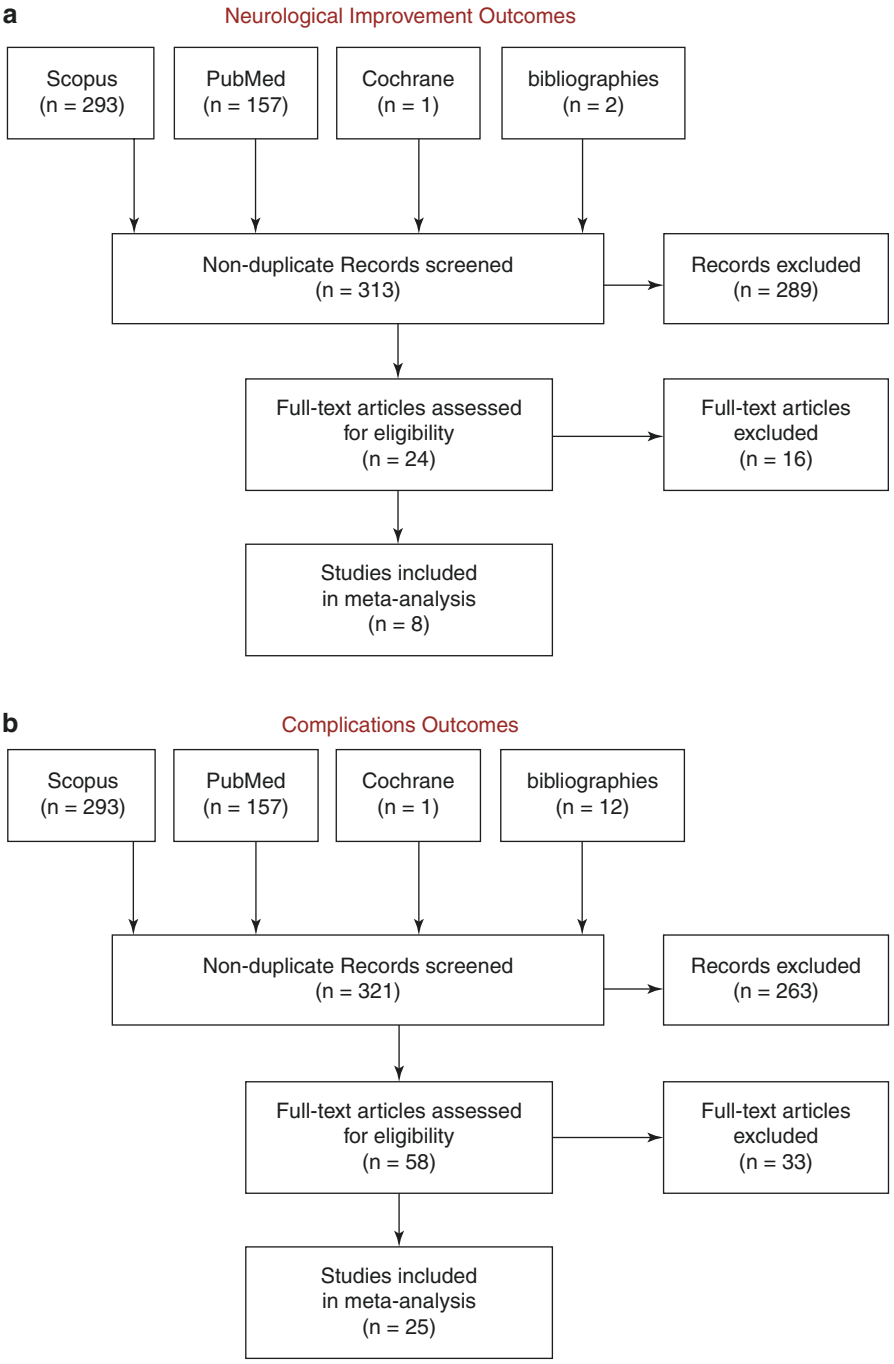

Fig. 3.1 (**a**) PRISMA flow diagram for neurological improvement outcomes analysis. (**b**) PRISMA flow diagram for complications outcomes analysis

Table 3.1 Characteristics of included studies reporting neurological outcomes related to cranioplasty timing

Reference	Type	Level of evidence	Quality	Indication for DC	Location	Early CP (days)	Number of procedures	
							Early	Late
Bender et al. [24]	Cohort	4	7	ICH, ischemic stroke, SAH, SDH, TBI	Bifrontal, unilateral	86	75	72
Cho and Park [28]	Cohort	4	5	TBI	NR	42	15	21
Cong et al. [29]	Cohort	4	5	TBI	Unilateral	90[a]	22	55
Honeybul et al. [27]	Case series	4	7	ICH, infection, ischemic stroke, SAH, TBI, tumor	Bifrontal, unilateral	90	20	28
Huang et al. [26]	Case series	4	6	TBI	Bifrontal, bilateral, unilateral	90	76	29
Kuo et al. [30]	Case series	4	7	ICH, ischemic stroke, TBI	NR	90	7	6
Paredes et al. [25]	Cohort	4	7	AVM, ICH, infection, ischemic stroke, SAH, reabsorption, TBI	Bifrontal, unilateral	85	10	45
Zhang et al. [31]	Cohort	4	7	TBI	Unilateral	90	23	47
Totals							*248*	*303*
							551	

AVM arteriovenous malformation, *CP* cranioplasty, *DC* decompressive craniectomy, *ICH* intracerebral hemorrhage, *NR* not reported, *SAH* subarachnoid hemorrhage, *SDH* subdural hematoma, *TBI* traumatic brain injury

[a]Article reports individual case data or data at various time intervals. Patients were divided at a 90-day cutoff

studies with non-matched cohorts, with an OCEBM Level 4 evidence. Indications for initial craniectomy included arteriovenous malformations, ischemic or hemorrhagic stroke, infection, ruptured aneurysm, trauma, or tumors. Six of twenty-five studies dichotomized early and late cranioplasty at a time-point other than 90 ± 10 days (range 42–120 days), and the reported data did not allow for regrouping around 90 days [13, 14, 28, 42, 43, 49]. Six studies included only trauma patients [13, 28, 31, 36, 38, 46].

Neurological Outcome Measures

Multiple neurological assessment tools were used across included studies (Table 3.1). Four studies reported more than 1 assessment to evaluate neurological outcome [24, 28, 30, 31]. For pooled analysis, the "primary" measure was designated as whichever measure the study focused on; for all 4 studies this was Barthel Index (BI). The timing of neurological assessment evaluation varied among studies. Three studies did not provide pre-cranioplasty assessments. The remaining studies

Table 3.2 Characteristics of included studies reporting complications related to cranioplasty timing

Reference	Indication for DC	Location	Early CP cutoff (days)	Number of patients		Complications
				Early	Late	
Archavlis et al. [34]	ICH, infection, ischemic stroke, rupture aneurysm, TBI	Unilateral	90[a]	147	53	Complication
Bender et al. [24]	ICH, ischemic stroke, ruptured aneurysm, TBI	Bifrontal, unilateral	86	75	72	EDH, hydrocephalus, ICH, infection, ischemic stroke, local bone graft complication, seizure
Chang et al. [35]	AVM, elective AVM/aneurysm, ICH, infection, ischemic stroke, other, ruptured aneurysm, TBI, tumor		90[a]	89	119	Complication
Chaturvedi et al. [36][b]	TBI	Bifrontal, unilateral	90	20	54	Complication
Cheng et al. [37]	Arachnoid cyst, AVM, ICH, ischemic stroke, ruptured aneurysm, tumor, venous sinus thrombosis		90	41	43	Infection
Cho and Park [28]	TBI		42	15	21	Infection, subdural fluid collection, ventriculomegaly
Chun et al. [38]	TBI	Unilateral	90	30	15	Dural tear, infection, inadequate dissection, soft tissue injury, subdural fluid
Gooch et al. [39]	Infection, intraoperative swelling, stroke, trauma	Bifrontal, bilateral, unilateral	100	31	31	Complication, reoperation

Hng et al. [40][b]	Infection, ruptured aneurysm, stroke, TBI, tumor	Bifrontal, unilateral	90	121	66	Complication, contour irregularity, extra-axial collections requiring evacuation, infection requiring removal, superficial infection, postop shunting, resorption requiring removal, seizures
Im et al. [41]	TBI, tumor, vascular	Bifrontal, unilateral	90	84	47	Infection
Kim et al. [33]	Trauma, non-trauma		90[a]	76	35	Infection
Kim et al. [42]	ICH, infection, ischemic stroke, rupture aneurysm, TBI, tumor		60	23	83	Epidural fluid collection
Mukherjee et al. [43]	AVM, ICH, intracranial infection, infected bone flap, ischemic stroke, ruptured aneurysm, TBI, tumor	Bifrontal, unilateral	120	29	145	Complication, post-op length of stay, removal
Nagayama et al. [32]	ICH, ischemic stroke, ruptured aneurysm, TBI, other		90[a]	181	25	Infection
Paredes et al. [25][b]	AVM, ICH, ischemic stroke, reabsorption, ruptured aneurysm, TBI	Bifrontal, unilateral	85	10	45	Complication
Piedra et al. [13]	Stroke		70	37	37	Complication, hematoma, hydrocephalus, infection, resorption
Piedra et al. [13]	TBI		90[a]	78	79	Complication, hematoma, hydrocephalus, infection, resorption
Piitulainen et al. [44]	Infection, stroke, TBI		90	21	79	Reoperation

(continued)

Table 3.2 (continued)

Reference	Indication for DC	Location	Early CP cutoff (days)	Number of patients		Complications
				Early	Late	
Rosseto et al. [45]	Infection, TBI, tumor		85	18	27	Infection
Schuss et al. [14]	ICH, ischemic stroke, other, ruptured aneurysm, TBI	Bifrontal, unilateral	60	54	226	Abscess, cerebrospinal fluid fistula, EDH/SDH, hygroma, wound healing disturbance
Song et al. [46]	TBI	Unilateral	90	25	18	Infection, subdural fluid
Tsang et al. [47][b]	Cerebrovascular disease, infection, TBI, tumor		90[a]	60	102	Flap depression, infection
Walcott et al. [48][b]	Stroke, TBI	Convexity, bifrontal, bilateral convexity	90	71	168	Infection, seizure, wound healing disturbance, surgical site infection, hydrocephalus, hematoma
Yang et al. [49]	ICH, ischemic stroke, SAH, TBI, tumor		60	62	68	Infection
Zhang et al. [31]	TBI	Unilateral	90	23	47	Epilepsy, infection, perioperative meninges breakdown, postoperative fluid below skin flap, wound healing
Totals				*1421*	*1705*	
				3126		

AVM arteriovenous malformation, *CP* cranioplasty; *DC* decompressive craniectomy, *EDH* epidural hematoma, *ICH* intracerebral hemorrhage, *OCEBM* Oxford center for evidence-based medicine, *SAH* subarachnoid

[a]Article reports individual case data or data at various time intervals. Patients were divided at a 90-day cutoff

[b]Data obtained via correspondence with author

performed assessments within 1 week preceding cranioplasty. Postcranioplasty assessments ranged from 72 h to over 6 months after the procedure [24, 26, 27, 31]. The following neurological measures were reported in the included studies. The Glasgow Coma Score (GCS) is an assessment of mental status typically used in acute trauma management. The Glasgow Outcome Score (GOS) categorizes cognitive disability following head injury, ranging from 1 (death) to 5 (resumption of normal life). The Karnofsky Performance Scale (KPS) was originally designed to assess the functional status of patients with cancer to determine if they could endure chemotherapy treatment. It ranges from 0 to 100, with values over 70 indicating relative functional independence in carrying out normal activities of daily living (ADLs) [50]. The BI is a more granular assessment of a patient's ability to perform each of 10 ADLs. It ranges from 0 to 100, with higher scores indicating higher functional independence [51–53]. The Function Independence Measure (FIM) evaluates disability in spinal cord injury, assessing both motor and cognitive performance. It ranges from 0 to 126, with higher scores indicating more independence [54, 55].

Change in Pre- and Postcranioplasty Neurological Status

Regardless of timing, improvement in neurological outcome was observed after cranioplasty [24, 25, 27, 29–31]. Pooling the results across studies, using only the primary measure (BI) for the two studies with multiple measures, showed cranioplasty at any time being significantly associated with improvements in neurological outcome (SMD 0.56; CI 0.11–1.01; calculation not shown in Figures).

Pre-cranioplasty, there was no significant difference in baseline neurological score between early cranioplasty and late cranioplasty groups in the 7 studies reporting pre- and post-cranioplasty scores, except for the study reporting KPS [24, 25, 27–31]. The KPS study by Cong et al., had lower baseline neurological score pre-cranioplasty in the early cranioplasty group compared to the late cranioplasty group (SMD –0.46; CI: −0.96–0.04). On all individual neurological outcome measures in those 7 studies, early cranioplasty was favored over late cranioplasty for greater neurological improvement from pre- to post-cranioplasty but was only statistically significant in the Karnofsky Performance Status measure (SMD: 7.22; CI: 5.95–8.49) (Table 3.3, Fig. 3.2). There was significant heterogeneity across outcomes

Table 3.3 Summary of findings of effect of early versus late cranioplasty after decompressive craniectomy on neurological improvement

	Number of patients				
Outcome	No. of studies	Early cranioplasty	Late cranioplasty	Relative effect (95% CI)	GRADE certainty of the evidence
Barthel index	4	115	170	SMD 2.51 (−0.76–5.78)	Very low due to inconsistency
Karnofsky performance status	1	22	55	SMD 7.22 (5.95–8.49)	Low
Functional independence measure	2	95	100	SMD 2.77 (−2.14–7.68)	Very low due to inconsistency
Glasgow coma scale	1	7	6	SMD 1.20 (−0.02–2.42)	Very low due to small sample size

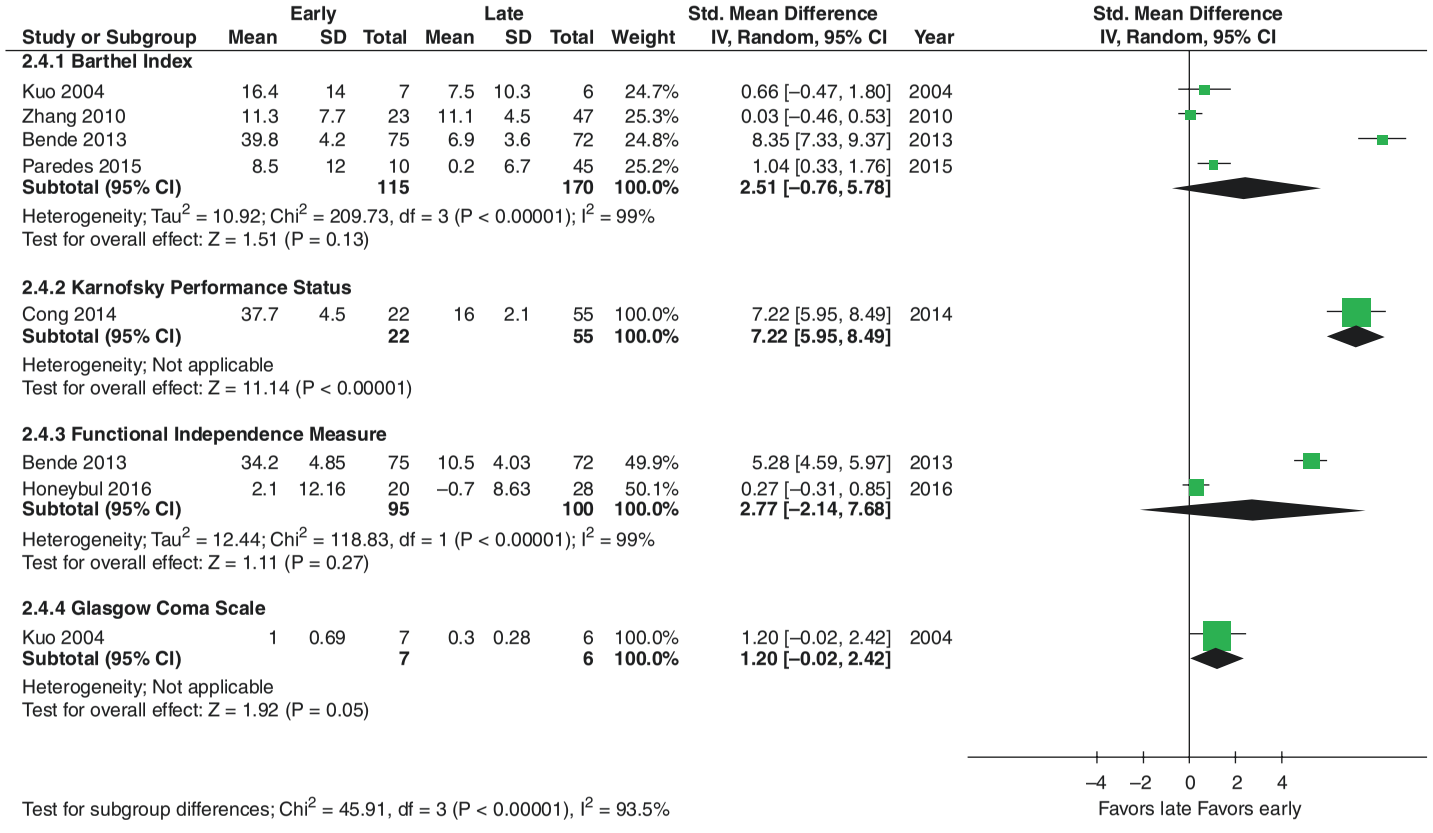

Fig. 3.2 Forest plot of studies reporting both pre- and post-procedure neurological scores for early and late cohorts. The early cohort showed greater improvement in every measure, and both KPS (SMD 7.22) and the overall pooled primary measures showed significant improvement (SMD 2.9, see text). *Reprinted with permission* [12]

($I^2 = 93.5\%$). Pooling the results across studies, using only the primary measure (BI) for the two studies with multiple measures, revealed early cranioplasty being associated with significant improvements in neurological outcome (SMD 2.90; CI 0.46–5.34; calculation not shown in Fig. 3.2).

Complications

Complications from cranioplasty after decompressive craniectomy reported in the literature included infections (18 studies), complications requiring reoperation (11 studies), intracranial hemorrhage (6 studies), extra-axial fluid collections (5 studies), hydrocephalus (6 studies), seizures (4 studies), and bone resorption (3 studies) (Tables 3.2 and 3.4).

There was no significant difference in the odds of overall complications between the early cranioplasty group and the late cranioplasty group looking at the trauma group (OR 0.74, 95% CI 0.30–1.83) or the mixed group (OR 1.24, 95% CI 0.92–1.66) (Fig. 3.3). There was also no significant difference when specifically looking at infection (Trauma: OR 0.46, CI 0.17–1.23; Mixed: OR 1.38, CI 0.96–1.99), reoperation (Trauma: OR 0.52, CI 0.18–1.47; Mixed: OR 0.82, CI 0.57–1.18), intracranial hemorrhage (Trauma: OR 3.12, CI 0.32–30.66; Mixed: OR 0.64, CI 0.33–1.23), seizures (Trauma: OR 0.67, CI 0.07–6.79; Mixed: OR 1.02, CI 0.50–2.11), or resorption (Trauma: OR 0.78, CI 0.35–1.79; Mixed: OR 1.23, CI 0.36–4.24). There was a significantly lower odds of developing a non-hemorrhagic extra-axial fluid collection with early cranioplasty in the trauma group (OR 0.24, CI 0.07–0.88) but not in the mixed group (OR 1.56, CI 0.69–3.53). The odds of developing hydrocephalus was significantly higher with early cranioplasty in both the trauma group (OR 4.99, CI 1.00–24.88) and the mixed group (OR 2.03, CI 1.01–4.07).

Level of Evidence

Neurological Outcome

All studies included in assessing neurological outcome as a function of cranioplasty timing were observational in design. To date, there are no randomized control trials related to this that are found in the literature and therefore the quality of evidence is low by GRADE standards. As these are all observational and retrospective, it is highly likely that those who were selected for an earlier versus later cranioplasty had significantly different clinical characteristics beyond the commonly controlled factors (e.g. age, gender) that may have led to the surgeons to perform the cranioplasty at a preferred time. These characteristics were likely to be more favorable, such as earlier resolution of swelling, in the early cranioplasty group. This would decrease the strength of any conclusions that can be made about the timing.

There were 4 different measures of neurological outcome across the 8 studies. We therefore had to look at these measures as different outcomes with consideration to overall trends. The level of evidence was further decreased to “very low” for the

Table 3.4 Summary of findings for effect of early versus late cranioplasty after decompressive craniectomy on complication rate by indication

Complication	Number of patients				
	No. of studies	Early Cranioplasty	Late Cranioplasty	Relative effect (95% CI)	GRADE certainty of the evidence
Complications, any					
Trauma subgroup	6	191	234	OR 0.74 (0.30–1.83)	Very low due to inconsistency
Mixed subgroup	19	1230	1471	OR 1.24 (0.92–1.66)	Low
Infection					
Trauma subgroup	2	108	94	OR 0.46 (0.17–1.23)	Low
Mixed subgroup	12	895	924	OR 1.38 (0.96–1.99)	Low
Reoperation					
Trauma subgroup	1	78	79	OR 0.52 (0.18–1.47)	Low
Mixed subgroup	9	592	696	OR 0.82 (0.57–1.18)	Low
Intracranial hemorrhage					
Trauma subgroup	1	78	79	OR 3.12 (0.32–30.66)	Low
Mixed subgroup	5	358	569	OR 0.64 (0.33–1.23)	Low
Non-hemorrhagic extra-axial fluid collection					
Trauma subgroup	3	70	54	OR 0.24 (0.07–0.88)	Low
Mixed subgroup	2	77	309	OR 1.56 (0.69–3.53)	Low
Hydrocephalus					
Trauma subgroup	2	93	100	OR 4.99 (1.00–24.88)	Low
Mixed subgroup	4	304	343	OR 2.03 (1.01–4.07)	Low
Seizures					
Trauma subgroup	1	23	47	OR 0.67 (0.07–6.79)	Low
Mixed subgroup	3	267	306	OR 1.02 (0.50–2.11)	Low
Resorption					
Trauma subgroup	1	78	79	OR 0.78 (0.35–1.79)	Low
Mixed subgroup	2	158	103	OR 1.23 (0.36–4.24)	Low

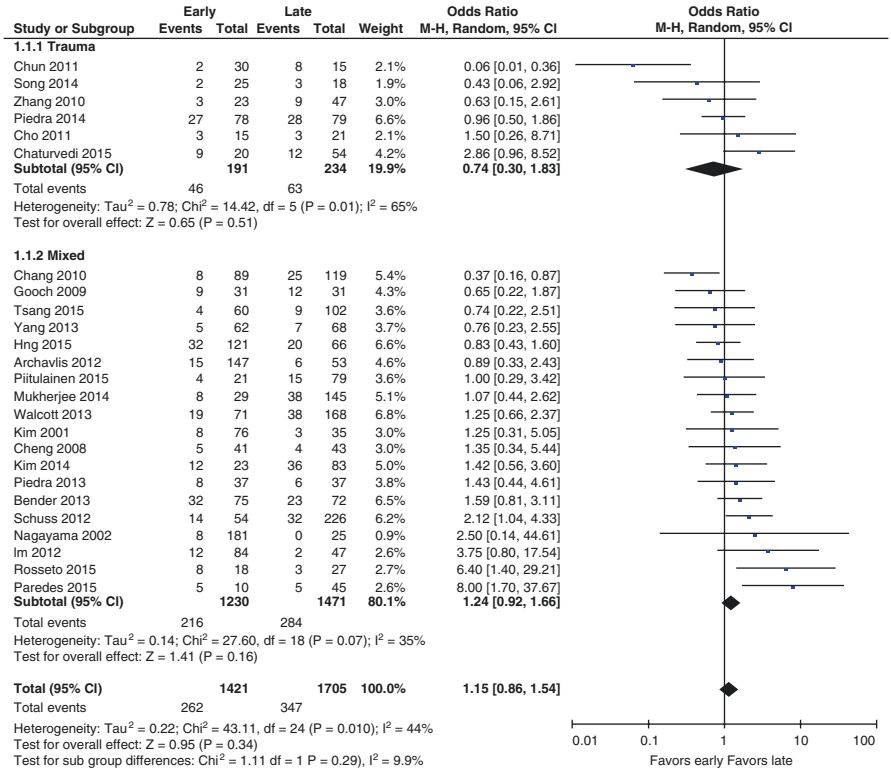

Fig. 3.3 Forest plot of studies reporting overall complications with early or late cranioplasty stratified by population type (trauma versus mixed). The blue square data markers indicate odds ratios (ORs) from primary studies, with sizes reflecting the statistical weight of the study using random-effects meta-analysis. The horizontal lines indicate 95% confidence intervals (CIs). The diamond data markers represent the subtotal and overall OR and 95% CIs. The vertical solid line indicates the line of no effect (OR 1). Results indicate no difference in odds of overall complications with early cranioplasty. *Reprinted with permission* [18]

BI and FIM outcomes due to very high heterogeneity among their included studies. The KPS and GCS outcomes only had 1 study each. The GCS outcome was based on a small sample of 13 patients and therefore also was graded "very low" due to imprecision.

Complications

The studies in the assessment of complication outcomes were similarly all retrospective and observational. Also similarly, we do not know if the patients who received early cranioplasty had significant characteristics that were different from the late cranioplasty group. To separate the effect of the initial indication for decompressive craniectomy on complication rate, the analysis and evidence was compiled separately for traumatic and mixed indications.

All outcomes had low quality of evidence by GRADE standards due to being only observational studies. The overall complication outcome in the trauma group was further rated down to very low due to inconsistency as measured by I^2 for heterogeneity between studies.

Patient Preferences

Considering the effect of earlier versus later cranioplasty timing after decompressive craniectomy on both neurological outcome and complications, there is insufficient evidence to strongly recommend one approach routinely over the other. The risks and benefits comparing early versus late cranioplasty is presented in Table 3.5.

Cranioplasty after decompressive craniectomy is associated with neurological improvement regardless of timing, with a potentially better outcome with early cranioplasty based on limited evidence.

There are risks to undergoing cranioplasty regardless of timing. These including hemorrhage (bleeding), infection, bone resorption, hydrocephalus, non-hemorrhagic extra-axial fluid collection, and seizures. There is limited evidence which suggests that the probability of certain complications differs by timing, with earlier cranioplasty being associated with increased risk of hydrocephalus and later cranioplasty being associated with increased risk of extra-axial fluid collection if there was a traumatic cause for the initial craniectomy.

Discussion

There has been no consensus on the ideal timing for cranioplasty after decompressive craniectomy. Several factors contribute to the desired interval before cranioplasty. These include the optimal timing to derive the most neurological improvement and the greatest reduction in complications.

After decompressive craniectomy has been performed to relieve the acute problem of elevated intracranial pressure, there are biological changes that can arise from altered cerebral hemo- and hydrodynamics. These changes specifically include

Table 3.5 Summary of risks and benefits comparison to guide patient preferences

	Early cranioplasty after decompressive craniectomy	Late cranioplasty after decompressive craniectomy
Benefits	Neurological improvement	
	Potentially better neurological outcome than later cranioplasty	
Risks	Bleeding, infection, bone resorption, hydrocephalus, extra-axial fluid collection, seizures	
	Possible increased risk of hydrocephalus compared to later cranioplasty	Possible increased risk of extra-axial fluid collection compared to earlier cranioplasty if craniectomy was for a traumatic indication

altered cerebrospinal fluid dynamics which can lead to hydrocephalus and pseudomeningoceles, increased perfusion in response to inflammation, and hypoperfusion in the long term [56–58]. Beyond providing better cosmesis through subsequent cranioplasty, it also likely helps by reducing the level of these changes or restoring the dynamics to a state closer to the pre-injury state [30, 59–62]. Though not the focus of this chapter, this is likely the reason why cranioplasty, regardless of timing, is associated with neurological improvement [63–65].

Neurological Outcome

Neurological improvement was measured by different measures in the reviewed studies. There is no commonly accepted measure for assessing neurological improvement after cranioplasty, though BI was the most common measure in our review. BI and FIM addresses both cognitive and motor performance. GCS also addresses cognitive function, but is likely too simple and not as sensitive to small improvements such as BI. Due to the differences in measures and the different indications for decompressive craniectomies, there was very high heterogeneity in the analysis of neurological improvement even with reporting of standard mean difference.

Early cranioplasty is likely to provide better neurological improvement outcomes based on the most recent studies. All included studies, except for 2, had similar neurological scores pre-cranioplasty between early and late cranioplasty groups [25, 31]. The improvement post cranioplasty was greatest in the study using the KPS measure with a SMD of 7.22 (CI 5.95–8.49) [29]. When pooling all neurological measures for overall improvement, there was still statistically significant improvement in the early cranioplasty group over the late cranioplasty group (SMD 2.90; CI 0.46–5.34) even though the separate subgroups measuring BI, FIM, and GCS were trending toward, but not significantly favoring, early cranioplasty. The large SMD of the KPS study likely contributed to the overall statistical significance. Additionally, there was a high degree of heterogeneity among subgroups (I^2 93.5%) which suggests that caution must be taken when interpreting these findings.

We did not separate our analyses in the assessment of neurological improvement by initial indication for decompressive craniectomy. The benefits of early or late cranioplasty may differ based on this factor and if so, the recommendations will need to be specific for this. Further studies with separate analysis based on initial pathology such as trauma, infection, or hemorrhage are therefore warranted.

Complications

Early cranioplasty after decompressive craniectomy is more likely to have associated hydrocephalus than late cranioplasty. In the trauma subpopulation, later cranioplasty is more likely to develop associated extra-axial fluid collection than early cranioplasty. With the potential benefits of more neurological improvement with early

cranioplasty, the findings taken together suggest that early cranioplasty is preferred over late cranioplasty. This would require more expectant management and observation for hydrocephalus. For trauma populations, the benefit of early cranioplasty may be greater due to the decreased risk of extra-axial fluid collection as well.

The literature describes a wide range of complication rates, partly due to the types of complications reported. From our review, the overall complication rate after cranioplasty is 19.5%. The pooled rate of infection was 8.1% with no significant difference in odds of infection between early and late cranioplasty in the trauma and mixed groups. The study by Rosseto et al. found a significant increased odds of infection with early cranioplasty but also found other factors that may play role which includes having the cranioplasty in the same hospitalization as the decompressive craniectomy, having a recent systemic infection before cranioplasty, neurological deficits as evaluated by a low GCS or motor deficits, and lower levels of hemoglobin [45].

Reoperations, not including placement of a ventriculoperitoneal shunt for hydrocephalus, were a common complication at 12.9% but there was no significant difference in odds between early and late cranioplasty in the trauma or mixed groups. Though the odds of reoperation appeared to favor early cranioplasty (OR 7.8, CI 0.55–1.10), this may have been due to bias in selecting patients who have less severe pathology for earlier cranioplasty.

We found a 4.6% rate of intracranial hemorrhage with no difference between early or late cranioplasty in the trauma and mixed groups. A previous study by Zanaty et al. found that other factors such as gender (male), race (African American), and hypertension are associated with an increased risk for intracranial hemorrhage [66].

We found a 13.9% rate of non-hemorrhagic extra axial fluid collections. This was largely due to high percentage of this complication in both early and late cranioplasty reported in Kim et al. study [42]. In the mixed group, which included the study by Kim et al. there was no significant difference between early and late cranioplasty. There was a significantly lower odds of extra-axial fluid collection with early cranioplasty in the trauma group. It may be postulated that in an early cranioplasty, the space between the cranioplasty flap and the brain is less but increased when edema further decreases at later time points.

There was an overall 6.0% rate of hydrocephalus. The odds of hydrocephalus with early cranioplasty were increased in both the trauma group (OR 4.99, CI 1.00–24.88) and the mixed group (OR 2.03, CI 1.01–4.07). The evidence suggests that patients with existing hydrocephalus should be considered at an increased risk for hydrocephalus but interestingly delaying cranioplasty in this subgroup can also increase the risk of persistent hydrocephalus [67]. The cause of the hydrocephalus is therefore not easily attributed to initial insult, decompressive craniectomy, or subsequent cranioplasty. If there is no pre-existing hydrocephalus, there might be a benefit to delaying cranioplasty due to the increased odds with early cranioplasty in trauma and mixed groups.

We found a 6.1% rate of seizures after cranioplasty with no difference between early or late cranioplasty in the trauma and mixed groups.

The overall rate of bone resorption was 10.8% with no difference in odds by timing in either the trauma or mixed groups. There are literature reporting higher rates of resorption in the pediatric population [68, 69]. We do not know if younger age in the adult population is associated with increased rate of resorption as well and if age has an interaction with timing for cranioplasty. There is evidence that the presence of a ventriculoperitoneal shunt is associated with increased resorption [17].

Limitations

The definition of early and late for cranioplasty is most frequently whether before or after 90 days. This is an artificial date but commonly used in studies and so is what is most reflected in our results. There may be more significant differences in neurological benefits or complication rates that are more noticeable at different time cut-offs. In the complication rate analysis, five studies used different time points for early and late other than before or after 90 days [14, 28, 42, 43, 49]. Therefore the time point at which the benefits and risks begin to be significantly different may be different that the conventional 90 days or may not follow a simple early/late classification. Regardless, the existing studies provide some direction to surgeons when deciding between several factors on when is the ideal time to perform the cranioplasty.

The research findings on cranioplasty timing both on neurological improvement and rate of complications are limited by the low quality of evidence. We are therefore unable to make strong recommendations, but due to the lack of contrary evidence, the findings may be useful to surgeons and patients. Perhaps the most significant limitation is the absence of any randomized controlled trials in the review. All studies identified were retrospective observational studies. Without randomization, we are unable to control for selection bias which was highly likely. Patients selected for early cranioplasty may have had less severe injury or earlier resolution of pathology that were clinically important but not accounted for in the analysis, e.g. degree of swelling on imaging, trauma versus ischemic stroke versus hemorrhage. In assessing neurological outcomes, unlike complications, it is possible to perform pre- and post-procedure assessments using the same neurological function measure. While there was no overall difference, two studies had different baseline neurological function between groups, with the late cranioplasty group having better scores at baseline in the Paredes et al. study whereas the early cranioplasty group had better baseline scores in the Zhang et al. study [25, 31]. Therefore, in addition to other clinical indicators, there might have been neurological function differences at baseline between the early and late cranioplasty groups. Only randomized studies with consistent measurement timing and long term follow-up can answer these questions.

Even though all neurological outcome studies tended towards favoring early cranioplasty, the high degree of heterogeneity among subgroups of separate neurological outcome measures and in the pooled analysis is another limitation. The studied population also had variation in type of injury as the evidence for neurological improvement is not separated by initial indication for decompressive craniectomy (e.g. trauma versus stroke versus hemorrhage). The pooled analysis is a combination of four different measures with different sensitivities and specificities for neurological improvement. The evidence base will be strengthened if the studies used more comprehensive measures as BI or FIM and separate analyses based on initial indication for decompressive craniectomy. Studies using GCS and GOS appear too coarse.

Conclusion

Within the limited evidence, we suspect that early cranioplasty (within 90 days) after decompressive craniectomy is a safe option. Though surgeons should be aware of a potentially greater risk for hydrocephalus, it is likely to provide better neurological improvements. Taking the results from the analyses together, this would make early cranioplasty the preferred option over later cranioplasty.

Box Summary

1. What is known?
   Cranioplasty after decompressive craniectomy is associated with neurological improvement regardless of timing. There are several complications associated with cranioplasty after decompressive craniectomy which include hemorrhage, infection, reoperation, hydrocephalus, extra-axial fluid collection, bone resorption, and seizures.
2. What is new?
   Early cranioplasty (within 90 days) after decompressive craniectomy may provide more neurological improvement but may increase the risk of hydrocephalus compared to later cranioplasty. In the trauma population, early cranioplasty may be associated with decreased risk of non-hemorrhagic extra-axial fluid collection.
3. What are the consequences for clinical practice?
   Further research with prospective clinical trials are recommended for better quality evidence on the timing of cranioplasty after decompressive craniectomy on neurological improvement and complication rate. Pending ongoing and future research, surgeons should consider early cranioplasty (within 90 days) as potentially preferable to later cranioplasty for better neurological improvement with anticipatory management of increased risk of hydrocephalus.

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4 Age: A Criterion to Offer Surgical Treatment as a Cytoreductive Tool for Malignant Primary Brain Tumour?

Joseph H. McAbee, Aida K. Golahmadi, and Colin Watts

Introduction

Glioblastoma (GB), the most common and malignant form of brain cancer, is a devastating disease that is difficult to treat due to its intratumoral heterogeneity and its ability to undergo clonal evolution when confronted with therapeutic selection pressures [1–4]. While glioblastoma can afflict people of all ages, it is most often diagnosed in the fifth or sixth decade of life or later, namely the elderly population [5].

Elderly Definition

There is not a standard minimum age for classifying a person as "elderly" in use among all practicing geriatricians because individual patients possess varying levels of fitness and comorbidities. Defining strict age cutoffs is not always feasible. However, for the purposes of this chapter and to collect information related to older

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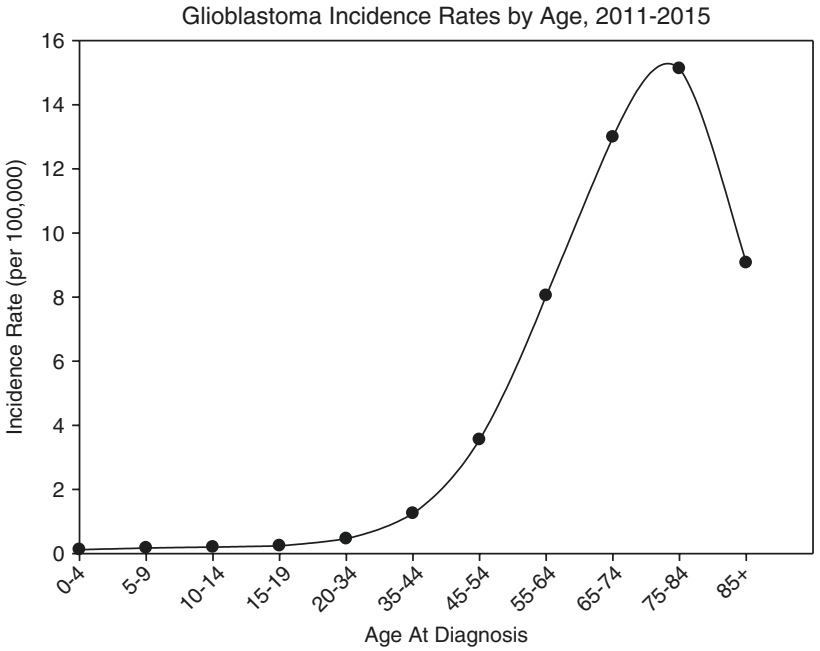

Fig. 4.1 Incidence rates for glioblastoma by age at diagnosis, CBTRUS Statistical Report: NPCR and SEER, 2011-2015. Incidence rates are per 100,000 and age-adjusted to the 2000 US standard population. The average annual age-adjusted incidence rate across all age groups was 3.21 (4.00 and 2.53 for males and females, respectively). [6]

adults with glioblastoma, we have defined "elderly" to be the population of patients 65 years of age or older. It is important to note that over half of newly diagnosed GB patients are 65 years of age or older and the incidence rate is increasing due to the aging population (Fig. 4.1) [6].

Standard of Care

In the general adult population, GB is treated with maximum safe surgical resection, radiotherapy, and concomitant and adjuvant Temozolomide. Despite this multimodal, radical treatment option, the median overall survival is still only about 15 months [7, 8]. Adding to this dismal prognosis is the inability of some patients to complete a full treatment course due to postoperative complications, radiotherapy-induced cerebral necrosis, chemotherapy side effects such as myelotoxicity, or rapid neurocognitive decline. Many medical advances have been designed to improve patient outcomes and avoid complications, such as intraoperative MRI, 5-ALA fluorescence guided surgical resection, fractionated and targeted radiotherapy protocols, and targeted chemotherapeutics. While these advances have been helpful in improving the outcomes for

certain patients at large medical institutions, the treatment and survival of glioblastoma patients, in general, has not changed significantly in the last decade.

Difficulties of Treating Elderly Glioblastoma Patients

Advanced age adds the potential for further difficulties in providing effective treatment regimens. Elderly patients are more likely to have more comorbidities and lower physiologic reserves at baseline which can lead to postoperative complications, longer recovery time, and increased risk of therapy-induced side effects [9–11]. Because of these risks, elderly patients are not always treated optimally and are often excluded from clinical trials despite the fact that they make up such a large proportion of GB cases. Due to these discrepancies, the proper treatment regimen for elderly GB patients remains unclear. One of the first and most difficult considerations for elderly patients seems to be whether or not to offer surgical resection. While some studies are beginning to point toward a survival benefit following surgical resection for elderly GB patients, a consensus has still not been reached. The purpose of this study is to examine the evidence for or against offering cytoreductive surgery for GB patients on the basis of age.

Methods

Search Strategy and Selection Criteria

We performed a systematic review to identify articles published in English from January 2000 that reported human survival and outcome data for elderly GB patients who underwent surgery. Potential articles were identified by literature searches of Ovid utilizing the following search terms: *glioblastoma*, *HGG*, *high grade glioma*, *malignant glioma*, *malignant brain tumor*, *resection*, *surgery*, *surgical*, *biopsy*, *elderly*, *advanced age*, *old*, *survival*, *management*, *outcome*, and *performance status.* Articles were chosen for full text review if the title and abstract suggested the desired topic, involved the appropriate intervention, included the correct population, and contained survival data. Elderly was defined as 65 years of age or older. The literature search was performed according to the PRESS [12] criteria and the level of evidence assessed according to the GRADE [13, 14] criteria.

Data Extraction and Analysis

The articles selected for inclusion were further reviewed to extract relevant study data and outcomes such as age, number of patients, extent of resection, overall and progression free survival, performance status, and baseline comorbidities. Summary of findings table and associated analyses were generated with the use of gdt.gradepro.org.

Results

Included Studies

Our literature search provided 568 possible studies. After screening titles and abstracts for duplicates and articles with incorrect populations, interventions, or topics, 459 articles were excluded. The remaining articles were reviewed as full text to determine their eligibility. Ultimately, 59 articles met our criteria (Fig. 4.2). For a full list of articles used, please see Supplementary Table 1 [15, 16, 18, 19, 36–90]. The studies yielded 49,074 patients and were of varying levels of evidence, with retrospective, observational studies being the most common.

Outcomes Based on Extent of Resection

The summary of findings table is displayed in Table 4.1. An elderly patient undergoing surgical resection is more likely to experience longer overall and progression free survival than elderly patients who receive either a biopsy or no surgical intervention. In addition, gross total resection has a survival benefit when compared to subtotal resection (Table 4.2). While mortality and morbidity rates were not as consistently recorded between treatment groups, it seems that morbidity and mortality rates were similar between resection and biopsy patients. This suggests that elderly patients are able to tolerate these procedures, especially when

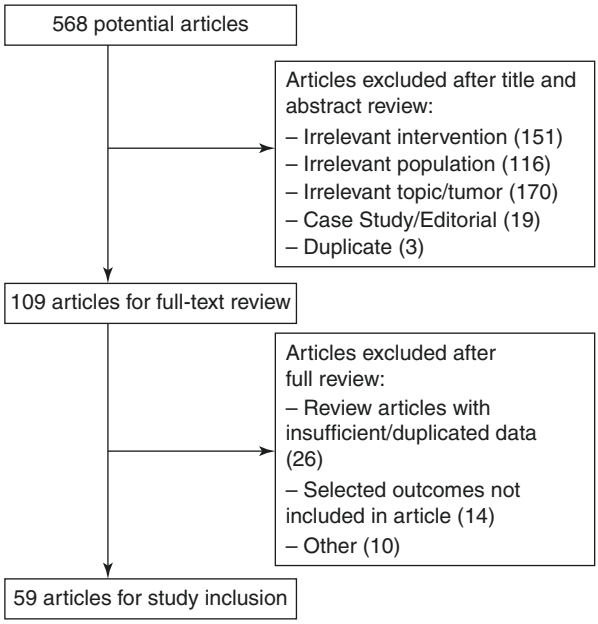

Fig. 4.2 Flow diagram of search and selection process

Table 4.1 Summary of findings: surgical resection compared to biopsy/no surgical intervention for glioblastoma in the elderly

Outcomes	Anticipated absolute effects[a] (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with biopsy/no surgical intervention	Risk with surgical resection				
Overall survival <6 months	98 per 100	17 per 100 (17–18)	RR 0.1784 (0.1735–0.1835)	36,219 (34 observational studies)	⨁⨁⨁◯ MODERATE[b]	An elderly patient undergoing surgical intervention for malignant glioma is more likely to survive longer than 6 months than a patient undergoing biopsy/no surgical intervention
Progression free survival <3 months	34 per 100	0 per 100 (0–5)	RR 0.0095 (0.0006–0.1527)	281 (3 observational studies)	⨁⨁◯◯ LOW	Similar to overall survival, elderly patients undergoing surgical resection are more likely to experience longer progression free survival compared to those receiving biopsy or no surgical intervention
Mortality risk >5% assessed with: Inpatient death	17 per 100	0 per 100 (0–3)	RR 0.0120 (0.0007–0.1940)	487 (4 observational studies)	⨁◯◯◯ VERY LOW[c]	Mortality rates were similar between resection and biopsy groups
Morbidity risk >5% assessed with: Seizure, infection, thrombotic/hemorrhagic event	59 per 100	43 per 100 (36–51)	RR 0.7185 (0.6007–0.8594)	487 (4 observational studies)	⨁◯◯◯ VERY LOW[d]	Postoperative complication rates were similar between resection and biopsy groups and compare reasonably well with rates observed in younger glioma patients

[a]*The risk in the intervention group* (and its 95% confidence interval) is based on the assumed risk in the comparison group and the *relative effect* of the intervention (and its 95% CI)

CI Confidence interval, *RR* Risk ratio

GRADE working group grades of evidence:

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect*Moderate certainty:* We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Table 4.2 Gross total resection compared to subtotal resection for glioblastoma in the elderly

Outcomes	Anticipated absolute effects' (95% CI)		Relative effect (95% CI)	No. of participants (studies)
	Risk with subtotal resection	Risk with gross total resection		
Overall survival <9 months	97 per 100	3 per 100 (3–4)	RR 0.027 (0.0249–0.0292)	34,843 (24 observation studies)

Table 4.3 Factors associated with survival in elderly HGG patients

Factors associated with *increased* survival	Factors associated with *decreased* survival
Higher preoperative KPS[a], triple modality therapy[a], radiotherapy[a], younger age[a], chemoradiotherapy, chemotherapy, reoperation, MGMT promoter methylation	Lower preoperative KPS[a], older age[a,b], comorbidities (specific and generally), increased frailty, no adjuvant therapy, higher tumor grade, tumor infiltration, MMSE < 25

[a]Mentioned in at least 5 studies
[b]At least 5 studies mentioned that older age was not associated with survival

presenting with a higher performance status and lower comorbidity profile. In addition to extent of resection, Table 4.3 displays several factors found to be associated with survival for elderly GB patients. Significant among these factors are preoperative Karnofsky Performance Status, presence of adjuvant therapy, and age; although older age was found in at least 5 studies not to be associated with survival.

Operative Risks and Benefits

When counseling elderly patients on their treatment options, the decision to undergo surgery or not should be the first discussion. Table 4.4 provides a brief overview of extent of surgical resection and the associated risks and benefits of each type. Whenever possible, elderly patients should also be counseled to consider enrolling in available clinical trials related to surgical advancements and local, implantable/injectable treatments.

Discussion

Glioblastoma is an incredibly difficult disease to treat even in the best of medical circumstances. Adding to this difficulty is the fact that over half of patients are elderly and thus have larger numbers of baseline comorbidities, greater risk of postoperative complications, and increased susceptibility to treatment-induced toxicities. Due to these concerns, it is easy to understand why it has been a challenge to develop an appropriate standard of care for elderly GB patients. However, as this

Table 4.4 Risks and benefits based on extent of resection

Extent of resection	Risks	Benefits
No resection	No diagnostic material obtained; no molecular analysis available for targeted treatments; no debulking to relieve mass effect so symptomology may remain same as upon presentation (or worsen)	No risk of postoperative complications such as infection, stroke, death, or neurocognitive decline
Biopsy	Potential to collect insufficient amount of tumor tissue for diagnosis/molecular analysis; lack of extensive reduction could mean little improvement of preoperative status; postoperative complications possible	Potential to collect tissue for diagnosis and molecular analysis; Postoperative complications less likely than for more extensive interventions
Subtotal or partial	Typical postoperative complications possible (infection, stroke, death, neurocognitive decline)	Tissue collected for diagnosis and molecular analysis - treatment can potentially be tailored; reduction in mass effect may lead to improved symptoms; cytoreduction may increase survival and improve response to adjuvant therapies
Gross total	Typical postoperative complications possible (infection, stroke, death, neurocognitive decline)	Tissue collected for diagnosis and molecular analysis - treatment can potentially be tailored; reduction in mass effect may lead to improved symptoms; cytoreduction may increase survival and improve response to adjuvant therapies

chapter demonstrates, evidence is growing that maximal safe surgical resection is not only well tolerated by some elderly patients, but is beneficial for increasing survival in this population, just as it is in younger patients. While most of this evidence is based upon retrospective observational studies, there has been one randomized clinical trial which addresses extent of surgical resection for the elderly. Vuorinen et al. demonstrated that patients randomized into the open craniotomy group had a 2.757 times higher median survival time (171 days) versus those assigned to biopsy (85 days) [15]. While the time to deterioration between the two groups only trended toward significance (105 days for debulking versus 72 days for biopsy), it did demonstrate at least a modest increase in time of independence, suggesting that debulking can lead to an improved quality of life. A recursive partitioning analysis of GB patients aged 70 years or older established extent of resection as the most important survival predictor as biopsy patients consistently had the shortest survival [16]. Age was only prognostic among patients who actually received resection as those under 75.5 years of age had a 9.3 month median survival compared to 6.4 months among those older than 75.5. However, highly functional patients who only received a biopsy had a median survival of only 4.6 months, demonstrating that surgery eligible patients of all ages would be expected to benefit from glioma resection.

A few prospective studies further support the notion of offering surgery to elderly GB patients. Pirracchi et al. demonstrated low mortality rates one year after surgical resection of intracranial masses (including meningiomas) and suggested preoperative Activities of Daily Living scores were a good predictor of functional outcome following surgery [17]. Similarly, preoperative Karnofsky Performance Score has been shown to be an important tool for prognostication and decision making [18]. While these studies demonstrate that elderly patients, particularly higher functioning patients, are able to enjoy longer periods of independence and longer delays to deterioration after debulking, it is important to note that Seicean et al. demonstrated that advanced age also does not increase the odds for poorer short term outcomes [19]. Surgical resection seems to be well tolerated in elderly patients that are deemed fit enough to undergo surgery. As with younger patients, the more complete the cytoreductive resection, the better the anticipated outcome and the more potential for increased survival with adjuvant therapies. As such, elderly patients should be afforded the same surgical options as any GB patient: maximal safe resection for mass effect reduction, symptom improvement, tissue diagnosis, and molecular analysis.

Age alone should not be a criterion for withholding surgical resection from an elderly GB patient. It is of course prudent to consider each patient from a holistic perspective. For an elderly GB patient, this would involve considering the risks of any and all baseline comorbidities, the influence of polypharmacy, the negative impact of lower physiologic reserves on recovery and susceptibility to toxicity. It is also crucial to consider preoperative performance scores, quality of life goals, and, ultimately, patient preferences when developing individualized treatment plans. A comprehensive geriatric assessment or modified geriatric assessment should be completed to provide a good indication of level of frailty and to suggest probable outcomes [9–11]. It is also recommended to consult not only with oncologists and palliative care specialists, but also geriatricians or geriatric oncologists, where available.

Regarding the surgery itself, techniques utilized for younger patients are appropriate for elderly patients as the goals of surgery are the same. Advanced preoperative MR imaging, intraoperative navigation and monitoring should be utilized and intraoperative MRI or 5-ALA fluorescence-guided imaging can be utilized to improve extent of resection [20, 21]. The neurosurgeon must be very responsive to potential complications such as intractable bleeding or changes in intraoperative monitoring, particularly when operating near eloquent brain areas, as older patients are not as well equipped to make functional recoveries following surgical complications. While maximal surgical resection is the primary goal, maintenance of quality of life is paramount in elderly GB surgery and intraoperative surgical decision-making should be based on both goals. Postoperatively, elderly patients should be closely monitored for any acute changes in neurological status that may evidence intracavitary hematoma or elevated intracranial pressure. Such changes may require imaging, surgical evacuation, or treatment with steroids/mannitol.

In addition to prolonged survival and improved quality of life, another key benefit of surgical resection in elderly GB patients is the opportunity to collect tumor tissue for molecular diagnosis and matching with applicable targeted therapies. Some have postulated that distinct molecular or epigenetic differences found in the tumors of elderly patients may be a contributing factor to poor survival [22, 23]. TP53 and CDKN1a/p16

alterations have been associated with reduced survival in those over 70 years of age [24]. IDH1 mutations carry a better prognosis, but are rarely found in elderly patients [25]. VGFR/EGFR expression is higher in recurrent GB patients above the age of 55 and could support the use of antibody therapies against these receptors (ARTE trial) [26]. One of the most helpful tests to date for elderly patients is MGMT promoter methylation status. Methylation of the MGMT promoter has been observed in 40–60% of elderly GB and can guide chemotherapeutic use and choice as it predicts favorable response to temozolomide [27, 28]. As we continue to learn more about the molecular makeup and evolutionary processes of GB, collection of multiple, spatially distinct tissue samples will become even more crucial for adequate diagnosis and individualized, targeted treatment planning [4]. Elderly patients should be included in many ongoing and future trials for targeted therapeutics and immunotherapies.

Role of Chemoradiotherapy

In younger GB patients, the standard of care after surgical resection is targeted radiotherapy (60 Gy–30 fractions of 2 Gy) plus concomitant and adjuvant (6 cycles) temozolomide. Many studies concerning adjuvant treatment in the elderly are focused on single modality therapy in an effort to minimize side effects or due to increased toxicity concerns [29–31]. Several studies have demonstrated that elderly patients with good performance status can tolerate and benefit from combination therapy [32, 33]. In particular, hypofractionated RT with concomitant and adjuvant TMZ seems to balance the risks and benefits of combined modality adjuvant therapy [34, 35]. In contrast, there are a few studies with conflicting results suggesting a single modality may be beneficial for select patients based on MGMT methylation status [31]. Specifics on various chemoradiotherapy regimens and their associated survival benefits is beyond the scope of this chapter. However, suffice it to say, elderly GB patients tend to benefit from chemoradiotherapy regimens that are as aggressive as is deemed appropriate based on postoperative recovery course, performance status, and personal treatment goals. It is also important to note that debulking has the potential of improving the efficacy of adjuvant therapies. In one study, radiation dose had a significant effect on survival and radiotherapy was more likely to fail in the biopsy group despite an earlier radiation start time after biopsy [15]. As with surgical decisions, the medical oncology team should consult with geriatricians whenever possible to provide the best care possible by tailoring multimodal therapies to each individual patient.

Conclusion

In conclusion, elderly glioblastoma patients present a particularly difficult treatment challenge for the neurosurgeon and neuro-oncologist. In some cases, the number and severity of comorbidities and poor preoperative performance status make cytoreductive surgery an impossibility. However, many elderly GB patients exist on a spectrum and require a comprehensive geriatric assessment to more adequately and holistically predict their ability to undergo and ultimately benefit from surgery.

Since maximum safe surgical resection leads to improved survival in elderly patients, age alone should not be used as a criterion to deny surgical services for older GB patients. In fact, because elderly patients make up such a large percentage of GB patients, a stronger effort to include this vulnerable population in clinical trials should be made. Neurosurgeons are well positioned to lead in this effort as neurosurgeons are often one of the first consults and points of contact for patients after detection of an intraaxial mass on imaging. Neurosurgeons should be prepared to offer surgical resection to appropriate elderly GB patients and to encourage enrollment in clinical trials whenever feasible. In this way, a consensus on standard of care for elderly GB patients may be reached in the future.

Box

What is known?

Maximal safe surgical resection improves overall survival for glioblastoma patients while advanced age is associated with poorer prognosis. Elderly glioblastoma patients are often excluded from gross total resection, the validated optimal surgical treatment, due to preoperative comorbidities or concern about potential postoperative complications.

What is new?

Recent studies that include elderly glioblastoma patients demonstrate that cytoreductive surgery improves quality of life, progression free survival (PFS) and overall survival (OS) in the elderly population. Despite the potential benefits, elderly patients often receive less aggressive surgical resection and suboptimal postoperative treatments. An underlying factor for the uncertainty regarding best treatment strategies is the fact that elderly patients are systematically excluded from clinical trials. Therefore, in the literature there is a lack of data to support management guidelines for this population.

What are the consequences for clinical practice?

Age alone should not be a criterion in the decision to offer surgical treatment to glioblastoma patients. Since all patients can potentially benefit from surgical resection, neurosurgeons must consider more holistic metrics such as a comprehensive geriatric assessment when making operative decisions. Additionally, a more concerted effort should be made to include elderly patients in ongoing and future clinical trials.

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A Restriction for the Surgical or Endovascular Treatment of a Ruptured Aneurysm in the Elderly?

5

Christian Mirian and Tiit Mathiesen

Introduction

Aneurysm treatment with clipping or coiling is indicated to prevent aneurysm re-rupture after aneurysmal subarachnoid hemorrhage (SAH). Any form of benefit of treatment requires active treatment to improve on natural history of the aneurysm. Primarily, morbidity and mortality of aneurysm treatment need to be lower than morbidity from re-rupture. For ruptured aneurysms, the risk of re-rupture within 6 months was reported at 40% for patients of all ages with a mortality of 78% [1]; and not less for elderly patients. Next to effects of initial bleeding, historical materials cite re-bleeding and surgical complications as main determinants of a bad outcome [2]. For subarachnoid hemorrhage, high age appears to increase treatment risk [3]. The highest mortality was seen in poor-grade patients over 75 who, however, were treated conservatively [4]. In addition, the expected remaining life-time for the age must be considered to assess potential benefit of preventing re-rupture, since competing risks are higher at a higher age. In contrast, several studies report favorable outcome after more aggressive management of aneurysms in an elderly population [5, 6].

Hence, precise information of how age affects outcome of aneurysm treatment would be necessary for practical decision-making. The rationale for treatment is unclear in advanced age, since a limited expected life-span affects long-term benefit of treatment and advanced age with potential health problems increase complications. This review was made to investigate published information on outcomes of treatment in elderly patients.

We were seeking information on outcomes of treatment in elderly patients with the primary intent to find data to support microsurgical or endovascular strategies in elderly patients.

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Methods

A Pub Med Search was made on 15th September, 2018 with the search terms" elderly patients", "age", "Intracranial aneurysm", "clipping", "coiling". English literature was searched and reference lists of selected papers were reviewed for additional articles. We retrieved 286 abstracts, that were screened for contents. In total, 31 articles were selected and after reading, 17 articles were deemed relevant and used for further analyses. The articles were used to extract data for meta-analytical investigation.

A random-effects model, which acknowledges the existence of different effects sizes underlying different studies, was used in this analysis. We adopted the "restricted maximum likelihood"-estimator in the random-effects model based on meta-analytic studies comparing bias and efficiency of meta- analytic variance estimators in random-effects models [7, 8].

I^2 quantifies the proportion of variance in study effect estimates, which is attributable to heterogeneity rather than chance. Thus, an I^2-value of 0% correlates with no inconsistency between studies.

Heterogeneity was quantified accordingly to Higgins et al., with "low", "moderate" and "high" corresponding to I^2-values of 25%, 50% and 75% [9]. The p-value for χ^2-test was computed to determine whether significant heterogeneity existed.

Statistical analyses were performed in R-Studio. This meta-analysis and its graphical content were made by using the "metafor"-package [10].

The primary outcome was: first, to establish the 1-year survival after treatment with either endovascular treatment or microsurgical clipping; and second, to quantify the proportion of patients achieving a favorable outcome after treated with either endovascular coiling or microsurgical clipping. A favorable outcome was defined in alignment with the vast majority of definitions applied within the individual studies, which comprised either a Glasgow Outcome Scale (GOS) equal to "good recovery (GR): none or minor physical or mental deficits that affects daily life" or "moderate disability (MD): independent, but cannot resume work/school or all previous activities" or a modified Rankin Scale (mRS) equal to "0: no symptoms", "1: no significant disability, despite symptoms; able to perform all usual duties and activities" and "2: slight disability; unable to perform all previous activities but able to look after own affairs without assistance".

We sought to include a set of covariates for a meta-regression analysis to explore this heterogenous group of patients and how these may have affected outcome. However, the only consistent covariates were mean age and the proportion of "poor prognosis" patients—although, different assessment schemes were used for determining poor prognosis; in alignment with the majority of the included studies, we defined "poor prognosis" as a NIS-SAH Severity Score greater than 7, a World Federation of Neurosurgical Societies (WFNS)-score of 4–5 or, a Hunt-Hess grade equal to 4 or 5. We calculated the fraction of "poor prognosis" patients per total cohort as surrogate marker for the baseline severity of the included patients.

We grouped data in decades based on the age mean for the specific cohort. Age groups were compared corresponding to a mean age between 60 and 69 year, 70 and 79 year, 80 and 89 year or older than 90 year and across all age groups.

Results

A total of 31 articles were read of which 17 were eligible for quantitative synthesis, comprising 3998 patients treated with endovascular coiling whereas 2461 patients underwent microsurgical clipping—see Table 5.1 for further information; the age distribution in studies addressing endovascular coiling (n = 15), two studies were allocated in the age group between 60 and 69 year [11, 26], 11 studies were allocated in the age group between 70 and 79 year [12–22], and one study was allocated in the age group between 80 and 89 year [25]. One study did not report the mean age [27]; whereas the age distribution in studies addressing microsurgical clipping (n = 8), four studies were allocated in the age group between 70 and 79 year [17–19, 23] and three studies were allocated in the age group between 80 and 89 year [23–25]. The last study did not report a mean age but comprised a range between 70 and 82 year [16].

Favorable Outcome

A random-effects model was used to produce a weighted proportion of patients achieving favorable outcome in each treatment (Fig. 5.1a, b). In total, 55% (95% CI: 45%; 65%) across all age groups achieved a favorable outcome after treatment with endovascular coiling (Fig. 5.1a); similarly, 56% (95% CI: 52%; 59%) of patients achieved favorable outcome after treatment with microsurgical clipping (Fig. 5.1b). Notably, the overall I^2-percentage was 87.2% and considered high. The χ^2-p-value for all studies combined was 0, indicating that highly significant heterogeneity was observed in the analysis of endovascular treatment. In quite contrast, the I^2-percentage and χ^2-p-value was 12.2% and 0.38, respectively, indicating low, non-significant heterogeneity, hence between-study consistency.

Figure 5.1c depicts a Funnel Plot (the proportion of patients achieving a favorable outcome in each individual study plotted against the standard error (an index of precision). The white funnel illustrate 95% confidence band corresponding to each standard error) of the random-effects model used for analysis of favorable outcome after endovascular coiling. The studies are spread out an only poorly contained within the funnel—which give arise to the large heterogeneity observed. It demonstrates the complexity and difficulty in encapsulating this patient group due to considerable differences in e.g. baseline patient characteristics or selective cohorts used for different studies.

Table 5.1 Study and patient characteristics

	Endovascular coiling					Microsurgical clipping				
Study	Mean age (range or SD)	Total	Favorable outcome	One year death	Baseline: Poor prognosis	Mean age (range or SD)	Total	Favorable outcome	One year death	Baseline: Poor prognosis
Duan et al. [11]	67.9 (±6.4)	416	267 (64.2%)	42 (10.1%)	11%	NA	NA	NA	NA	NA
Sedat et al. [12]	71.5 (65–85)	52	NA	12 (23.1%)	37%	NA	NA	NA	NA	NA
Johansson et al. [13]	71.5 (65–81)	62	24 (31%)	14 (22.6%)	34%	NA	NA	NA	NA	NA
Watanabe et al. [14]	74.1 (70–91)	51	33 (64.7%)	NA	33%	NA	NA	NA	NA	NA
Gu et al. [15]	75.0 (70–89)	96	77 (80.2%)	NA	26%	NA	NA	NA	NA	NA
Karamanakos et al. [16]	75.0 (70–81)	49	23 (46.9%)	22 (44.9%)	24%	NA (70–82)	96	58 (60.4%)	22 (22.9%)	18%
Bekelis et al. [17]	75.3 (±6.2)	2004	NA	821 (41.1%)	NA	73.5 (±6.8)	1206	NA	348 (36.3%)	NA
Proust et al. [18]	75.4 (±4.3)	30	11 (36.7%)	NA	30%	73.1 (±2.2)	34	16 (47.1%)	NA	38%
Park et al. [19][a]	75.9 (±4.9)	80	46 (57.5%)	NA	24%	74.3 (±6.8)	85	54 (63.5%)	NA	14%
Iosif et al. [20]	76.0 (71–84)	59	23 (39.0%)	NA	25%	NA	NA	NA	NA	NA
Jain et al. [21]	76.0 (72–89)	13	5 (38.5%)	NA	100%	NA	NA	NA	NA	NA
Luo et al. [22]	76.8 (71–87)	25	21 (84.0%)	1 (4%)	4%	NA	NA	NA	NA	NA
Horiuchi et al. [23]	NA	NA	NA	NA	NA	73.7 (±2.7)	449	239 (53.2%)	NA	27%
Horiuchi et al. [23]	NA	NA	NA	NA	NA	82.2 (±2.2)	89	45 (50.6%)	NA	20%
Horiuchi et al. [24]	NA	NA	NA	NA	NA	82.3 (80–94)	190	106 (55.8%)	NA	46%
Dasenbrock et al. [25]	84.9 (±3.5)	1010	543 (53.8%)	NA	24%	84.2 (±3.3)	288	169 (58.7)	NA	19%
Zheng et al. [26]	NA	35	18 (51.4%)	23 (66%)	NA	NA	24	13 (54.1%)	11 (45.8%)	NA
Wilson et al. [27]	NA	16	7 (43.8%)	NA	NA	NA	NA	NA	NA	NA
Subtotal		3998	1095/1942 (56.4%)	935/2643 (35.4%)			2461	700/1255 (55.8%)	381/1326 (28.7%)	

[a]Favorable outcome was included modified Rankin Scale between 0 and 3

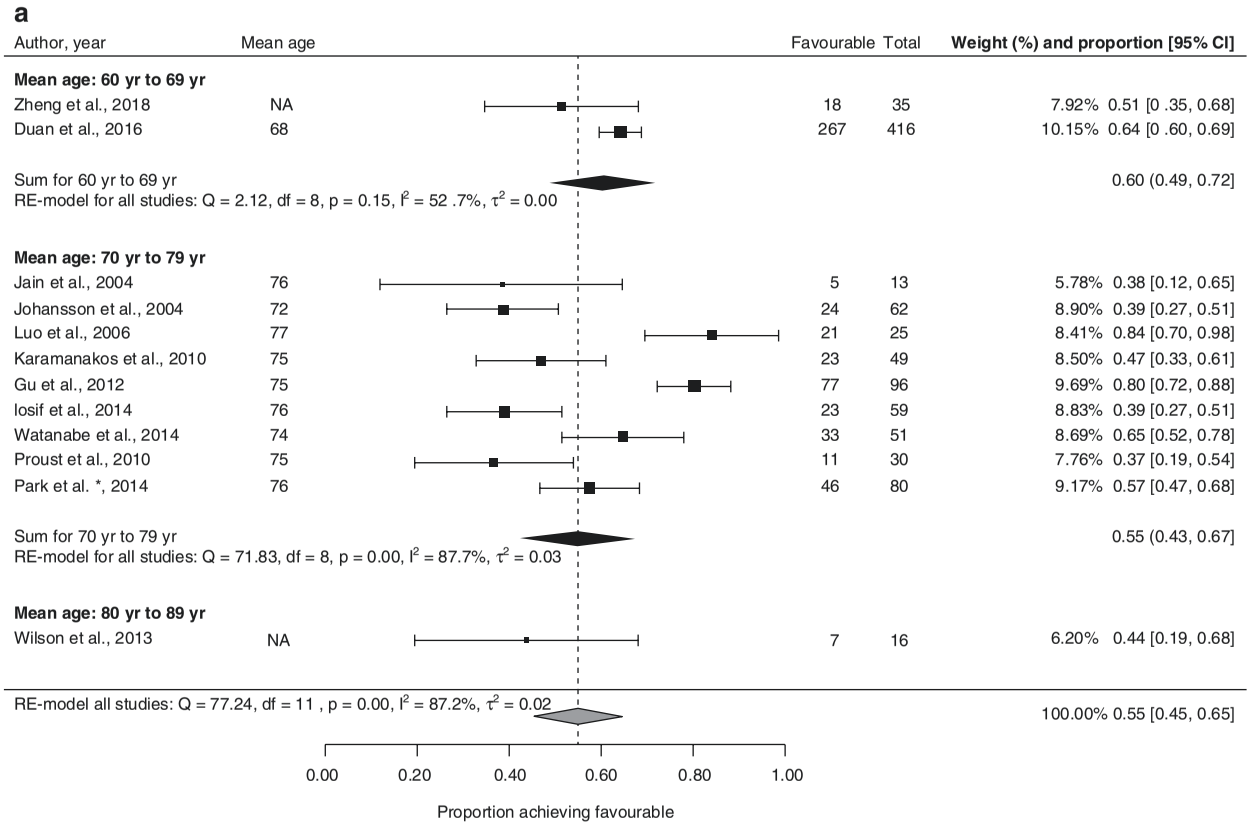

Fig. 5.1 (**a**) Favorable outcome after endovascular coiling. (**b**) Favorable outcome after microsurgical clipping. (**c**) A Funnel Plot computed based on the random-effects model used in (**a**); determining the proportion of patients achieving a favorable outcome among endovascular treated patients

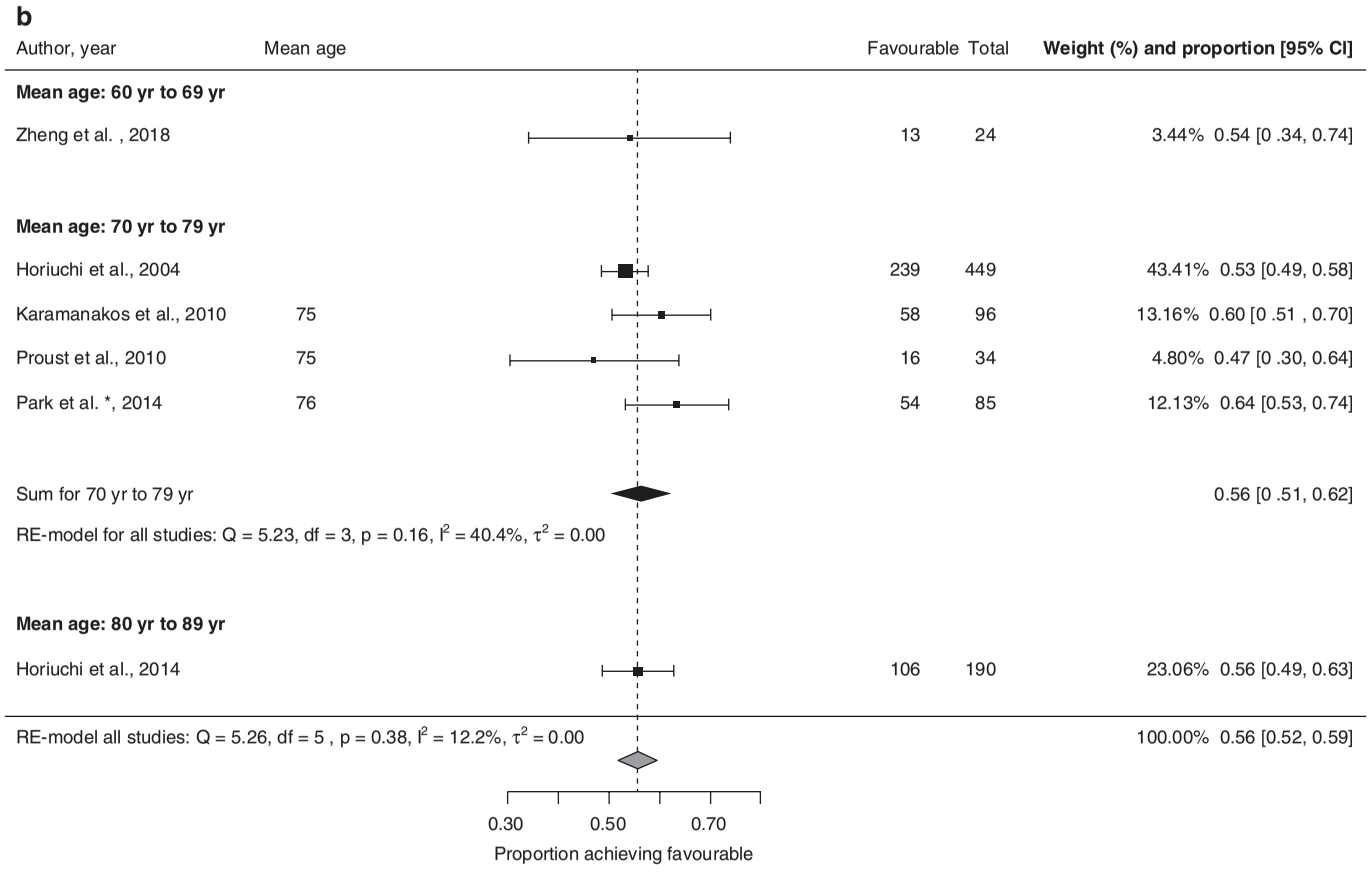

Fig. 5.1 (continued)

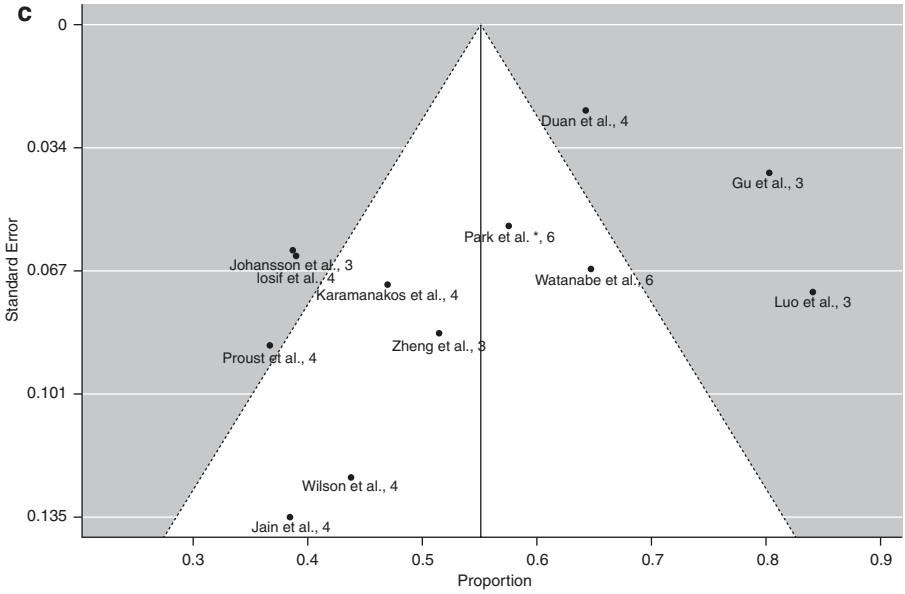

Fig. 5.1 (continued)

One-Year Mortality

Similarly, we used a random-effects model to determine the weighted proportion of patients being alive 1-year after treatment (Fig. 5.2a–d). Both models were associated with very high and significant heterogeneity at I^2-percentages of 98.8% and 95.7% for the endovascular coiling and microsurgical clipping, respectively, and χ^2-p-values of 0.

The proportion being alive after 1-year was 67% and 59% for endovascular (Fig. 5.2a) and microsurgical (Fig. 5.2b) treatment, respectively. Surprisingly, in both models the one study that comprised the (80–89 year)-age group suggest a better 1-year prognosis in this group compared to the (70–79 year)-age group [25]. Funnel Plots were computed for both models, and greatly visualizes the how scattered the studies are due to heterogeneous study groups.

A meta-regression including the proportion of baseline "poor grade" per total cohort did not significantly intercept, meaning that baseline surrogate marker for "poor grade" could not be demonstrated to alter the 1-year survival outcome.

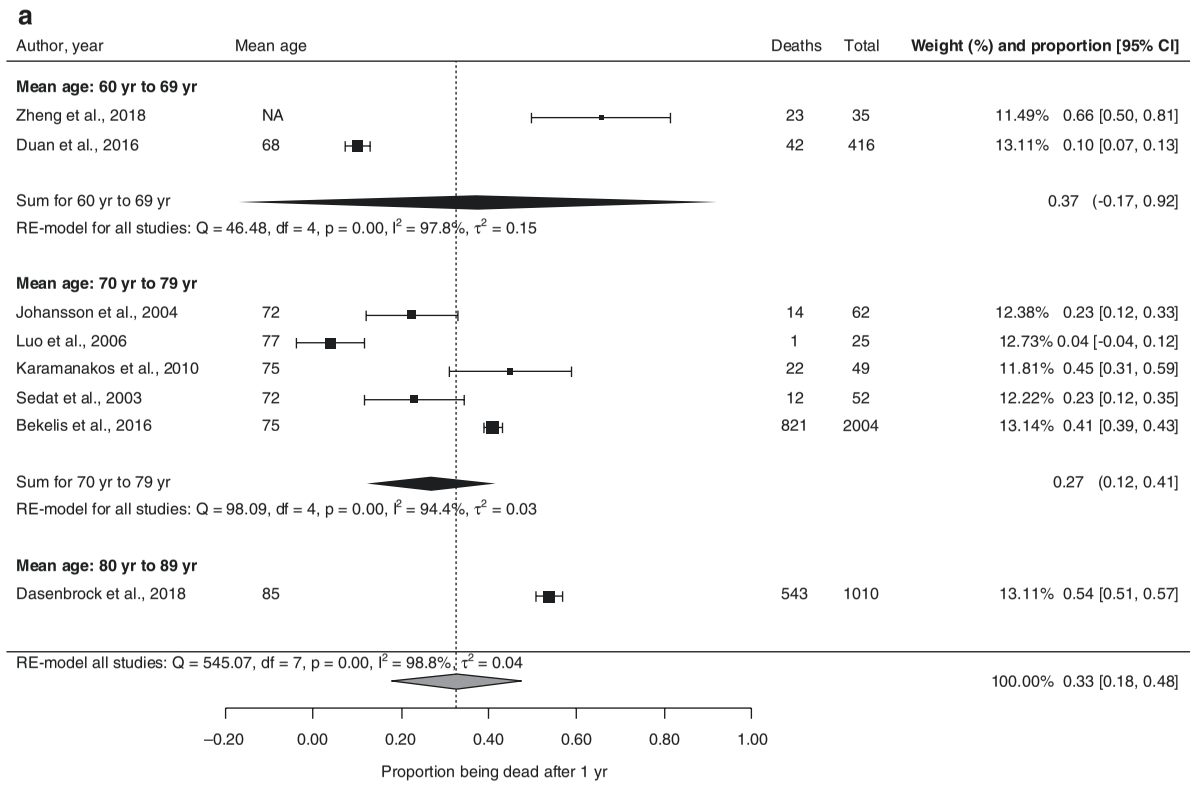

Fig. 5.2 (**a**) A Forest Plot illustrating 1-year survival after endovascular coiling. (**b**) A Forest Plot illustrating 1-year survival after microsurgical clipping. (**c**) A Funnel Plot computed based on the random-effects model used in (**a**); determining the proportion of patients being alive 1-year after endovascular treated patients. (**d**) A funnel plot computed based on the random-effects model used in (**a**); determining the proportion of patients being alive 1-year after microsurgical treated patients

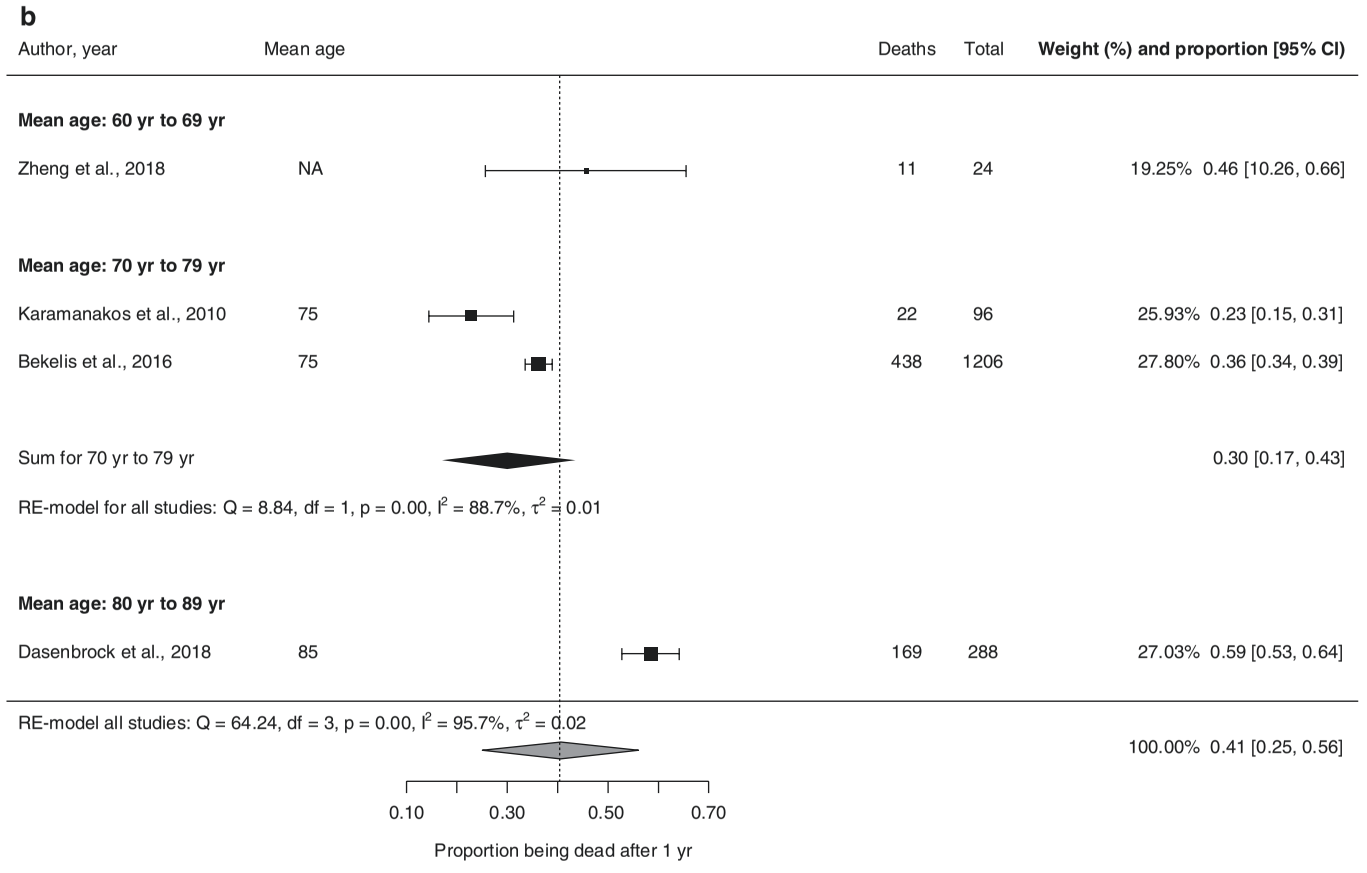

Fig. 5.2 (continued)

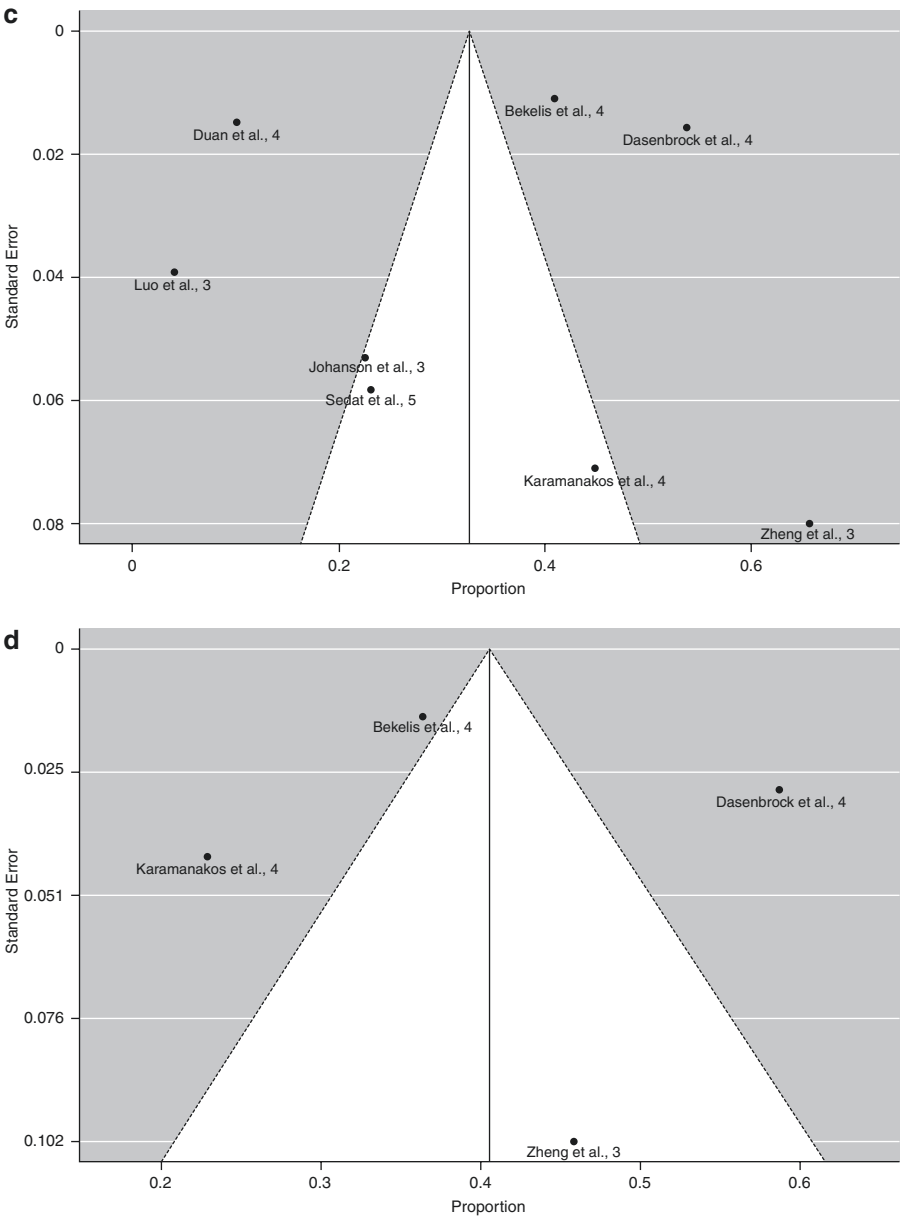

Fig. 5.2 (continued)

Level of Evidence

All studies represent retrospective reviews of cohorts, where patients were offered treatment at the discretion of physicians in charge or one represent a selected subgroup of patients at equipoise regarding better benefit of clipping or coiling. The quality per GRADE was considered very low, since selection bias regarding expected benefit was the basis of treatment allocation.

Discussion

Favorable outcomes were reported after clipping in 56% (95% CI: 52–59%) and after coiling in 55% (95% CI: 45–65%) after aneurysmal subarachnoid hemorrhages. In total, 1-year survival after clipping was 59% (95% CI: 44–75%) and after coiling 67% (95% CI: 52–82%). One study indicated higher mortality in patients aged 80–89, but a very high heterogeneity did not allow identification of a coherent pattern; we found a low heterogeneity only in the analysis of favorable outcome after clipping. The studies showed no difference between different age cohorts. Taken together, the studies indicate that patients offered treatments with either clip or coil for aneurysmal SAH were more likely to experience a favorable outcome than the opposite, although morbidity was high and can be expected to increase with age, although available studies do not allow a direct comparison of the results of the different treatments and conservative management. The patients that are already offered treatment will probably continue to be treated, since meta-analyses did not indicate any unexpectedly bad results from active treatment. The results can only be understood to show that personal knowledge and individual decision making was used for management of the patients and the coarse comparisons of quantitatively synthesized data on the meta-level failed to provide new insights because the included studies reflected treatment of heterogenous, highly selected patients. It is probable that the decision- making physicians had knowledge to offer clipping or coiling to patients they expected to benefit from active treatment from previous experience; these explicit parameters were not revealed in the analyzed studies. Hence, an algorithmic approach that is a prerequisite for meaningful meta-analyses was not identified in any included study and, subsequently, the results provided no information for an age- related algorithm for aneurysm-management.

We could thus summarize outcomes in the treated cohorts where treatment was offered per best knowledge and experience; whether the outcomes are desirable is a matter of values and evaluation from experience of what an expected alternative outcome with different or conservative treatment would have been. Neither mortality nor favorable outcome was compared to valid controls.

There is no obvious reason why age groups should be divided into decades. This was chosen in alignment with the included studies to apply some categorization suitable for statistical analysis. Age as a solitary criterion for treatment allocation seem arbitrary as a 60-year old with a high comorbidity index and poor performance status may have a significant shorter life expectancy contrarily to a healthy 90-year old with a good performance status. Further, we categorized the vast majority of studies based on the reported mean age, e.g. a mean of 75 year to the (70–79 year)-age group, although the age ranged between the seventh and ninth decade of life; the use of a mean age without supporting standard deviations is a major flaw, which was not possible to implement.

We believe that our finding of an absent age-relation reflects strict selection of patients with favorable prognoses; probably more so in the oldest patients. Other observations suggest that age is a relevant prognostic factor. One study on unruptured aneurysms [28] and two registry studies on hospital discharge cohorts [29, 30] indicated a higher mortality by a factor of 1.4 in patient over 65 compared to those younger, and morbidity appears to increase with age [3]. Not surprisingly, we conclude that age is probably related to worse outcomes for clipping and coiling after aSAH. Still, the available literature showed that selected patients appear to do well

with the treatments offered. Age in relation to management of intracranial aneurysms is complex, and individual decisions cannot be determined by findings in larger groups unless findings are unequivocal and can be known to apply to the individual patient. The available articles fail to provide such information. The articles either compare outcomes of older to younger patients and conclude that outcomes in older patients are worse than in younger.

However, there is no comparison to natural history, hence we rely on historical knowledge of natural history of ruptured and unruptured aneurysms. For the former, expected risk of death within a year of hemorrhage is sufficiently high to warrant coiling or clipping if this can be achieved at surgical mortality below 10–20%.

Conclusion

Today, the individual decisions to offer treatment reflect individual experience and expertise. Treatments will need to continue to be based on individual decision-making by experts and it is probably more worthwhile to collect treatment data in registries to analyze treatments to improve gradually, than to expect "high quality" information from prospective randomized trials: surgical decision-making handles a multitude of parameters other than age and it is not probable than a RCT can meaningfully control for these sufficiently to tailor individual algorithms for therapy.

Outcomes reflect populations with treatment selected already based on practical knowledge of individual risk and benefit. Hence, comparison between clipping and coiling was not relevant, while all studies showed that a substantial proportion of patients can be treated with limited morbidity and that morbidity appears to be lower than would be expected without treatment.

Box

What is known?

More than 40% of aSAH patients will suffer a re-hemorrhage within 6 months and up to 80% of them will die. Re-bleeding is an important potential cause of death in aSAH patients whose aneurysms remain unsecured which may be a proportionally higher risk for elderly patients.

What is new?

The literature search and analyses of articles did not reveal any relevant novel information, apart from an indication that a meta-analysis for the research-question may be futile. It was due to the complexity—manifested as large analytical heterogeneity—derived from competing risks such as comorbidities and other severe illness, different and inconsistent usage of assessment schemes, improved and advancements within the applied treatment techniques throughout the different study periods and patient inclusion and different primary study objectives yielding subsets of selective cohorts that may not be comparable.

What are the consequences for clinical practice?

Age should not be a solitary determinant of treatment allocation. Clinical practice should continue to comprise surgery or endovascular treatment of aneurysms in selected patients based on expert knowledge, multidisciplinary interaction and specialized patient assessment while long-term data can be gathered with use of registries.

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6 Subarachnoid Hemorrhage Due to Ruptured Intracranial Aneurysm: Clipping or Coiling

Rami O. Almefty and Robert F. Spetzler

Abbreviations

BRAT	Barrow Ruptured Aneurysm Trial
GOS	Glasgow Outcome Scale
ISAT	International Subarachnoid Aneurysm Trial
mRS	modified Rankin Scale

Introduction

Microsurgical clipping has a long-established benefit in preventing recurrent subarachnoid hemorrhage from a ruptured aneurysm. Since the advent of the detachable coil in 1990 [1], the endovascular treatment of intracranial aneurysms has emerged as a minimally invasive alternative to microsurgical clipping. With the development and widespread adoption of endovascular techniques, debate has ensued over the optimal treatment of intracranial aneurysms. This debate was intensified with the publication of the results from the International Subarachnoid Aneurysm Trial (ISAT) [2]. Despite flaws in methodology limiting their general applicability, the ISAT results have significantly affected practice across the world, resulting in the increasing use of endovascular techniques for the treatment of intracranial aneurysms [3, 4]. Unfortunately, existing studies have failed to adequately reveal the optimal strategy for the treatment of ruptured intracranial aneurysms; this chapter reviews the existing data on this subject.

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Methods

The PubMed Database was searched for "subarachnoid hemorrhage," "coiling," "clipping," and "randomized trial" in the English-language biomedical literature. Results were reviewed for studies involving randomized trials comparing the results of surgical clipping to those for endovascular coiling of ruptured intracranial aneurysms.

Results

Our search identified only four randomized trials that have been published in the English-language literature that compared microsurgical clipping with endovascular coiling for ruptured intracranial aneurysms. These are described below.

The International Subarachnoid Aneurysm Trial (ISAT)

The ISAT [2] was a multicenter randomized trial that enrolled patients with aneurysmal subarachnoid hemorrhages from 1994 until 2002. A key aspect of the ISAT design was that the aneurysm morphology had to be considered suitable for both microsurgical clipping and endovascular coiling by the study investigators. As a result, the study suffered from significant selection bias in that, despite screening almost 10,000 patients, it enrolled only 2143, with 1073 allocated to endovascular treatment and 1070 allocated to microsurgical clipping. The primary outcome that was studied was proportion of patients with a modified Rankin Scale (mRS) score of 3–6, corresponding to dead or disabled at 1 year. There was no significant difference between the two groups in terms of age, sex, or World Federation of Neurological Surgeons grade. There was a significant difference in time to treatment in the two groups, with more delayed treatment in the surgical group. Almost the entire cohort had aneurysms arising from the anterior circulation (97.3%), most of which were small (>90% under 1 cm).

For analysis of the primary endpoint in the ISAT study, 1-year follow-up was available for 801 patients in the endovascular group and for 793 in the clipping group. In the endovascular group, 190 of 801 patients (23.7%) had an mRS score of 3–6 whereas 243 of 793 (30.6%) patients in the microsurgical clipping group had an mRS score of 3–6. This finding corresponded to an absolute risk reduction of 6.9% and a relative risk reduction of 22.6%, significantly in favor of endovascular coiling ($P = 0.0019$). Preprocedural rebleeding occurred in 14 patients in the endovascular group and in 23 in the neurosurgical group, which was likely reflective of the increased time to treatment in the clipping group. At 1-year follow-up, postprocedural rebleeding had occurred in 26 patients in the endovascular group and in ten in the clipping group.

Barrow Ruptured Aneurysm Trial (BRAT)

The BRAT study [5] was designed in an effort to overcome some of the limitations of the ISAT trial that resulted from the high selection bias. The BRAT was based on an intent-to-treat analysis designed to test a real-world scenario of a "right of refusal." All patients who presented with spontaneous subarachnoid hemorrhage were eligible for enrollment with no anatomical exclusions and crossover was allowed. Enrollment occurred between 2003 and 2007, with 725 patients screened. Of those screened, 209 were assigned to clipping and 233 were assigned to coiling. Four patients assigned to clipping were crossed over to coiling and 75 patients assigned to coiling were crossed over to clipping. Results were interpreted on an intent-to-treat basis by initially assigned group. Similar to the ISAT, the primary outcome studied was number of patients with an mRS score >2.

For analysis of the primary outcome, 205 clipped patients and 198 coiled patients were available for follow-up. In the clipping group, 69 of 205 patients (33.7%) had an mRS score >2, which was significantly higher than the 46 of 198 patients (23.2%) in the coil group (P = 0.02). Two rebleeds occurred in the clip group prior to treatment. One in-hospital, post-treatment rebleed occurred in each group. No post-hospitalization rebleeds occurred in either group.

Outcomes of Early Endovascular Versus Surgical Treatment of Ruptured Cerebral Aneurysms: A Prospective Randomized Study

This study by Koivisto et al. [6] enrolled and randomly assigned 109 out of 242 patients with proven aneurysmal subarachnoid hemorrhage between 1995 and 1997 to surgical clipping (n = 57) or endovascular coiling (n = 52). The two groups did not differ significantly in age, sex, Hunt and Hess grade, Fisher grade, or site or size of aneurysm. The primary endpoints in the study included rebleeding, death, and clinical outcome based on Glasgow Outcome Scale (GOS) at 1 year. A good to moderate recovery was reported for 43 of 57 patients (75.4%) in the surgical group and for 41 of 52 patients (78.8%) in the endovascular group. There was no significant difference between groups in outcome or survival and no late rebleeds were reported in either group.

Outcomes of Endovascular Coiling Versus Surgical Clipping in the Treatment of Ruptured Intracranial Aneurysms

This study by Li et al. [7] enrolled 192 consecutive patients with acute aneurysmal subarachnoid hemorrhage between 2005 and 2009. Of the enrolled patients, 96 were randomized to endovascular treatment and 96 to surgical treatment. The two groups were matched demographically and by severity of subarachnoid hemorrhage. Data from 186 patients were available for analysis.

At 1-year follow-up, the mortality rates of 10.6% (10/94) in the endovascular group and 15.2% (14/92) in the surgical group were not significantly different. There was also no difference in good functional outcome defined as an mRS score of 2 or less in surviving patients, with 63 of 84 (75.0%) and 53 of 78 (67.9%) patients in the endovascular and surgical group, respectively, experiencing a good outcome. In the surgical group compared with the endovascular group, the rates of symptomatic vasospasm (37% vs 23%, respectively) and new cerebral infarctions (22% vs 13%, respectively) were significantly higher ($P < 0.05$). Significantly more aneurysms in the surgical group were completely occluded compared with those in the endovascular group (84% vs 65%, respectively; $P < 0.05$). Three rebleeds were reported in each group, which was not significantly different.

Level of Evidence

Despite the inherent strength in randomized trials, the existing studies comparing endovascular coiling to microsurgical clipping for aneurysmal subarachnoid hemorrhage have significant limitations that precluded our ability to make strong recommendations based on study results. The ISAT suffered from significant selection bias, with nearly 80% of patients excluded and the majority of patients harboring small aneurysms in the anterior circulation with good neurological grades, which limits the broad application of these results. The BRAT study, although all-inclusive, included patients with non-saccular aneurysms and had a high crossover rate. The studies by Li et al. [7] and Koivisto et al. [6] were underpowered because of low enrollment numbers. The results were reviewed in a systematic review, but given the heavily weighted influence of the ISAT results and the limitations of the analysis, it does not add significantly to the quality of the evidence [8]. Therefore, the level of evidence for clipping versus coiling is a Grade C (Table 6.1) [2, 5–7].

Table 6.1 Summary of findings

Author	Design	Patients (no.)	Good clinical outcome	Post-treatment rebleed (no. pt.)	Grade
Molyneux et al. [2]	Randomized trial[a]	Clip, 1070 Coil, 1073	Clip, 69.4% Coil, 76.3% P = 0.0019	Clip, 10 Coil, 26	C
Koivisto et al. [6]	Randomized trial[b]	Clip, 57 Coil, 52	Clip, 75.4% Coil, 78.8% NS	Clip, 0 Coil, 0	C
Li et al. [7]	Randomized trial[a]	Clip, 96 Coil, 96	Clip, 67.9% Coil, 75.0% NS	Clip, 3 Coil, 3	C
McDougall et al. [5]	Randomized trial[a]	Clip, 209 Coil, 233	Clip, 66.3% Coil, 76.8% P = 0.02	Clip, 1 Coil, 1	C

no. number, *NS* not significantly different, *pt.* patient
[a]Modified Rankin Scale score of 1–2 defined as good clinical outcome
[b]Glasgow Outcome Scale score used to assess clinical outcome

Patient Preferences

Superficially, endovascular treatment is much more appealing from a patient perspective because of its minimally invasive nature as a percutaneous procedure, whereas surgical clipping requires a scalp incision and craniotomy. Although surgical clipping is generally well tolerated, it requires a longer recovery period and patients experience more postoperative discomfort than with endovascular treatment. It is easy to be influenced by this immediacy effect and assume that all patients would prefer endovascular coiling. However, surgeons and patients must also consider that endovascular coiling is associated with lower complete occlusion rates and higher retreatment rates. Although retreatment for previously coiled aneurysms is safe [9] and rebleeding rates are low, these factors must be included in the risk profile for each procedure and the quality of life of the patient should be considered in terms of burden of follow-up, inconvenience of additional procedures, and psychological impact of a residual aneurysm (Table 6.2).

Discussion

Unfortunately, the existing data do not allow for strong conclusions to be made in regard to recommending clipping or coiling for ruptured intracranial aneurysms. Given their small size, the studies by Li et al. [7] and Koivisto et al. [6] contribute little to the debate. The ISAT [2] is the largest study to date and has had the most significant impact on current practice as, since its publication, treatment has shifted to a higher proportion of patients undergoing endovascular coiling than microsurgical clipping. However, this treatment shift is due to the inappropriately broad application of the ISAT findings. As mentioned earlier, the ISAT researchers found that patients treated with endovascular coiling had an improved functional outcome at 1 year. However, nearly 80% of patients screened were excluded from participation and 97% of the aneurysms that were treated were of the anterior circulation with the majority of

Table 6.2 Benefits and risks of clipping versus coiling for ruptured intracranial aneurysms

Type of treatment	Benefit	Risk
Coiling	• Prevents rebleed • Minimally invasive • Fast recovery • Rapidly advancing technology	• Procedure-related morbidity and mortality • Higher recurrence • Need for retreatment • Poorly applicable to some aneurysm morphology
Clipping	• Prevents rebleed • High complete obliteration rate • Durable • Most aneurysms are amenable to procedure	• Procedure-related morbidity and mortality • More invasive • Longer recovery • Postoperative hematomas and infections

aneurysms being small and the patients having a good clinical grade. Furthermore, the improved functional outcome in endovascular patients compared to microsurgical patients was lost on longer-term follow-up, whereas the increased risk of repeat hemorrhage and the need for retreatment persisted [10, 11]. A more appropriate conclusion based on the ISAT design and results is that, for a select group of patients with aneurysms who present with acute subarachnoid hemorrhage, short-term functional outcome is improved with endovascular coiling compared with microsurgical clipping, but with an increased rate of rehemorrhage and need for retreatment. In regard to the ISAT study design, it should be noted that enrollment occurred not long after development of the detachable coil and considerable progress has been made in endovascular experience, technique, and technology since that time.

The BRAT study [5] attempted to overcome some of the shortcomings of the ISAT trial by including all patients with spontaneous subarachnoid hemorrhage regardless of aneurysm morphology. The analysis was based on the intent to treat in order to represent the real-life scenario of "the right of first refusal" and allowed for crossover. As a result, many non-saccular aneurysms were included in the study and a high proportion of patients crossed over from endovascular coiling to surgical clipping. Based on the intent-to-treat analysis, the BRAT also found an improved short-term functional outcome in the coiling group. Again, this difference in outcome was not maintained on long-term follow-up with the need for retreatment again higher in the coiling group. At 6-year follow-up, no rebleeds were found in either group [12, 13]. When saccular aneurysms alone were analyzed using the BRAT data, there was no significant difference between the two treatment groups in functional outcome at any time period [14]. However, the same absolute difference in functional outcome existed as in the ISAT study, but the BRAT was underpowered to show a difference with only 362 patients in this analysis. At the 10-year follow-up for patients with saccular aneurysms in the BRAT, no significant difference in clinical outcomes were noted at any time period, despite clipping being statistically superior to coiling in terms of rebleeding, recurrence, and degree of obliteration [15].

The BRAT was a single-center study intended to be a feasibility study leading to a larger, multicenter trial. Given the existing studies' failure to reach a definitive conclusion about the best treatment approach for ruptured intracranial aneurysms, it is time to proceed with the larger trial for which the BRAT was intended as a prelude.

Conclusion

On the basis of the results of the ISAT and BRAT, we can conclude that for some aneurysms endovascular coiling has a short-term functional outcome benefit compared with that of microsurgical clipping. However, this difference must be weighed against an increased risk of retreatment and rehemorrhage after endovascular treatment. It should be noted that since these studies were published, considerable strides have been made in improving endovascular techniques initially and on retreatment and that further improvement is needed and is in progress for this technique.

At this point, patients with ruptured intracranial aneurysms are best considered on an individual basis based on their condition, their medical comorbidities, and

aneurysm size, location, and morphology. Aneurysms should be treated at centers with expertise in both modalities highlighted by the high crossover rate from coiling to clipping in the BRAT, despite having experienced endovascular surgeons performing the procedures in this study.

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Box

What is known?

Surgical clipping and endovascular coiling reduce the risk of rehemorrhage of ruptured intracranial aneurysms. Despite study limitations, the existing literature has shown improved short-term functional outcomes for patients with certain aneurysms treated with endovascular coiling and a more complete and durable aneurysm occlusion with surgical clipping.

What is new?

Endovascular treatment is rapidly advancing with refinement of technique and the development of new devices and strategies to improve the safety and efficacy of the treatment of aneurysms.

What are the consequences for clinical practice?

The existing data fail to definitely define an overarching optimal treatment strategy for ruptured intracranial aneurysms. Thus, each case must be individualized based on characteristics of the patient and the aneurysm. Patients with ruptured aneurysms are best treated at facilities with expertise in both open and endovascular techniques.

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7 Subarachnoid Hemorrhage Due to Ruptured Intracranial Aneurysms: The Scientific Base for Flow Diverters

Michelle F. M. ten Brinck and Joost de Vries

Introduction

Flow diversion is a relatively new technique used for the treatment of intracranial aneurysms. The introduction of flow diverters (FDs) dates back to 2007. Nowadays, several types of FDs are available on the market of neurointerventional devices. Indications for flow diverter use are unruptured large or giant saccular wide-neck or fusiform intracranial aneurysms. However, the number of published studies regarding the off-label use of FDs in the setting of acute aneurysmal subarachnoid hemorrhage (SAH) is increasing [1–4].

The main goal in treatment of ruptured intracranial aneurysms is to prevent aneurysm rebleeding. Subarachnoid hemorrhages, especially due to dissecting or blood blister-like aneurysms, are still therapeutically very challenging. The use of flow diverters in this situation has become an established off-label treatment option.

Flow diversion technology is based on two phenomena: it causes disruption of the fluid momentum into the aneurysm sac resulting in blood stasis and induction of thrombosis, and it serves as a scaffold that produces a remodeling effect on the vascular wall with neointimal growth. An advantage of this technique over, for example, (stent-assisted) coiling is that manipulations within the aneurysm sac are not needed, which may lower the procedural rupture risk. Also, the occlusion on long-term might be more durable when compared to coiling or stent-assisted coiling, which in turn decreases the need for and rate of retreatment. However, the fact that aneurysm occlusion caused by flow diversion is not achieved immediately could make these aneurysms more prone to re-rupture during the early post-procedural phase. Additionally, patients treated with flow diverters should be receiving dual antiplatelet therapy up to several months after FD placement. Therefore, patients in

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the acute SAH phase may have a higher risk of hemorrhagic complications since they are often subjected to additional procedures such as ventriculostomy or hematoma evacuation.

In 2017 a meta-analysis has been published regarding flow diversion for ruptured aneurysms [5]. The authors could only include 62 patients who were treated within 15 days. Another meta-analysis published in 2018 reported on outcomes of patients with ruptured aneurysms treated within 30 days [6]. However, after 30 days the risk of delayed cerebral ischemia is generally low and therefore patients treated with flow diverters at this interval may have better clinical outcomes compared to patients with acute SAH treated within 15 days. Furthermore, the risk of rebleeding is lower after 30 days (versus after 15 days) so theoretically there is a higher chance of patient selection with a more favorable clinical status.

Both authors of the previously mentioned meta-analyses concluded that flow diversion results into a high complete occlusion rate. No hard conclusions were drawn regarding clinical outcome and complication rate. Madaelil et al. reported a favorable clinical outcome for 79% of patients treated within 15 days and Cagnazzo et al. found a rate of good neurologic outcome of 83% with a treatment-related complication rate of 18%, which was 27% for ruptured posterior circulation aneurysms [5, 6].

These studies had a substantial overlapping study population and included several case series with $N < 5$, which are prone to selection and publication bias. Therefore, especially clinical outcome and complications of FD treatment in setting of acute SAH are still to be questioned. This chapter addresses the following: What is the rate of favorable clinical outcome, complications, and complete occlusion for aneurysmal SAH patients treated with any type of flow diverter within 15 days after last moment of aneurysm rupture?

Methods

Search Strategy and Article Selection

We conducted a systematic review of available literature of studies reporting on both the clinical and angiographic outcome of acute SAH patients treated with flow diverters. The PRISMA guidelines were followed for the set-up of the search, study selection, and data extraction process [7]. We conducted the search both in the PubMed and EmBase database.

We expected relevant literature to be scarce and of recent date. Since the addressing of MeSH terms in the PubMed database is subjected to delay, we tried to use a minimum amount of index terms and instead focused on free text.

The following search was designed with cooperation of a librarian experienced in systematic reviews and with the used databases: "*((((((((((aneurysm*)) AND rupture*)) OR subarachnoid hemorrhage OR SAH)) AND ((flow div* OR flowdiv* OR flow-div* OR pipeline OR silk OR surpass OR fred OR flow re-directing OR flow*

redirecting OR flow-redirection OR p64 OR derivo OR flow modulation OR tubridge)))))) AND "2010/01/01"[PDat] : "2018/12/31"[PDat]". This search was last run on 20 September 2018 in PubMed. This search with identical medical terms was adjusted to the style of EmBase (regarding amongst others Boolean operators) and was conducted on the same day in EmBase. According to the chapter guidelines we excluded articles published before 2010.

All retrieved articles from both searches were imported into Endnote X8.0 in which we screened for and removed all duplicates. Two authors (MtB, JdV) independently screened the title and abstract of all remaining articles and assessed their eligibility for full text screening. The used inclusion criteria were as following: Articles reporting on both clinical and radiological outcome of patients with recently ruptured aneurysms treated with flow diverters. Furthermore, complications had to be reported. The maximum treatment delay was 15 days after last moment of hemorrhage, so both patients with a first aneurysmal SAH as well as patients with aneurysm rebleeding were included. We chose 15 days as cut-off point since delayed cerebral ischemia (DCI) mostly occurs within this timeframe. Additionally, the goal of treatment is prevention of rebleeding and the rebleeding risk is especially high the first days after rupture. Therefore use of flow diverters as treatment modality within this period is of main interest.

Any type of flow diverters were included. Patients were also included in case treatment consisted of flow diversion plus additional coiling. The required minimum number of eligible patients per study was five or higher. We chose this number in order to exclude all case reports and series with a low number of patients since these studies have a substantial risk of publication bias and selective reporting. We deliberately did choose to not have a minimum or maximum follow-up time, neither a mandatory way reporting of complications, since preparing study of literature indicated that follow-up time and ways of reporting complications differed considerably.

Articles types that were excluded concerned all congress abstracts, posters and presentations, all reviews, commentary, and animal or in vitro articles, and articles without full text availability in either English or Dutch. Furthermore, we excluded all studies with such substantial duplication that it could not be said with certainty that five 'new' eligible patients were included. Studies which had a sufficient amount of eligible patients included, but only as minor part of the total study population and in which no clinical and/or radiological results were separately published for our subgroup of interest, were excluded as well. When information was reported on patient level, we calculated the outcomes of interest for this group and used only the subgroup with its inherent outcome rates.

Results of title/abstract screening by both authors were compared. Disagreement was not encountered. The authors performed full text screening and made their final selection of articles to be included in this review. In case data was unclear or missing and this data was crucial for either inclusion or exclusion, a mail was send to the corresponding author. If no reply followed, the concerning study was excluded.

Primary and Secondary Outcomes

Primary outcome was the rate of favorable clinical outcome, defined as either a modified Rankin Scale (mRS) score of 0–2 or a Glasgow Outcome Scale (GOS) score of 4–5, at last available moment of follow-up. Secondary outcomes were rate of complete occlusion, aneurysm rebleeding, permanent neurologic deficit caused by procedure-related complications, and all cause mortality. Complete occlusion was defined as either Raymond-Roy (RR) 1 measured on the RR scale or O'Kelly-Marotta (OKM) D, measured on the OKM scale. We also considered occlusion complete in case studies described this textually without using a scale. From previous studying of literature we learned that various ways of reporting complications are being used. Specific types and consequences of complications are often not pre-specified or mentioned. Therefore, we categorized all reported complications by type (ischemic/intracranial hemorrhagic/other; e.g. vessel dissection) and timing (intra-procedural, early post-procedural and late post-procedural). Early post-procedural complications occurred ≤30 days after treatment and late complications >30 days.

Data Collection

One author (MtB) extracted all pre-specified data items according to the PRISMA statement in a form: These items were number of participating centers and countries, names of participating centers, study type, inclusion period, number of total patients and aneurysms included in the study, number of patients and aneurysms eligible for our review, and description of data on patient or cohort level (in case of patient level, data was extracted in a separate file on patient level as well). Of all eligible patients the following baseline characteristics were extracted: Sex, age, initial clinical presentation (Hunt and Hess [HH] or World Federation of Neurosurgical Societies [WFNS] grade), treatment delay, and periprocedural antiplatelet regimen. Of all aneurysm we collected the type, size, location (anterior/posterior), type of used FDs, and other treatment modalities. Regarding the outcome we extracted the rate of complete occlusion (including used scale) with inherent follow-up time, clinical outcome (mRS or GOS) with inherent follow-up time, complication rate with separate reporting of type (amongst others rebleed) and timing of complications, and amount of complications leading to permanent neurologic deficit.

Bias Evaluation

Quality of each study was assessed according to the GRADE criteria [8].

Statistics

A meta-analysis (random-effects model) was performed to calculate the pooled estimated event rates, including 95% confidence interval, of favorable clinical outcome, complete occlusion, and all cause mortality. All calculations were performed using Comprehensive Meta Analysis V2 (Biostat Inc., Englewood, New Jersey, USA).

Results

Search Strategy and Process

The initial search in both EmBase and PubMed database yielded 730 studies eligible for title/abstract screening combined, after removal of duplicates. Subsequently, we performed full text screening of 72 articles. Fiftysix of these 72 studies have been excluded. The two main reasons for exclusion were either no/insufficient data of patients treated within 15 days being available or a number of eligible patients <5. One other study is submitted, but not yet published. However, the results of this study are available to us and therefore were included. We will use the asterisk [∗] as reference for this article. Ultimately, we included 17 studies in our review. See Fig. 7.1 for the search flow diagram which provides a more detailed overview of this process.

All but one study were retrospective case series. One study was presented as being prospective, however, in our opinion, the methods describe the process of a retrospective analysis of a prospectively kept registry [9].

Study Population

The total study population of our review consisted of 258 patients harboring 268 recently ruptured aneurysms (Table 7.1). Timing of treatment was questionable in two studies [10, 11]. Both corresponding authors have been contacted and confirmed that all patients were treated within 15 days (Table 7.2). There was duplication of patient population among four studies [11, 16, 20, 21].

Patient and aneurysm inclusion criteria varied considerably among studies. Some studies included several types of aneurysms [9, 10, 14, 16–18, 21], [∗], whereas others focused on a single aneurysm subtype [11–13, 15, 19, 20, 22–24]. A substantial variance in initial clinical presentation was observed. Altogether, 66/249 (27%, range 0–64%) patients presented with either a WNFS or Hunt and Hess score of 4–5. This resulted in a heterogeneous study population. For example, when comparing the study of Aydin et al. (nine patients) versus Maus et al. (14 patients), they had, respectively, 81% versus 0% anterior circulation aneurysms included [12, 19]. In the study of Aydin et al. patients were treated after a minimum of 5 days, while in Maus' et al. his study, all patients were treated within 12 h after hospital admission.

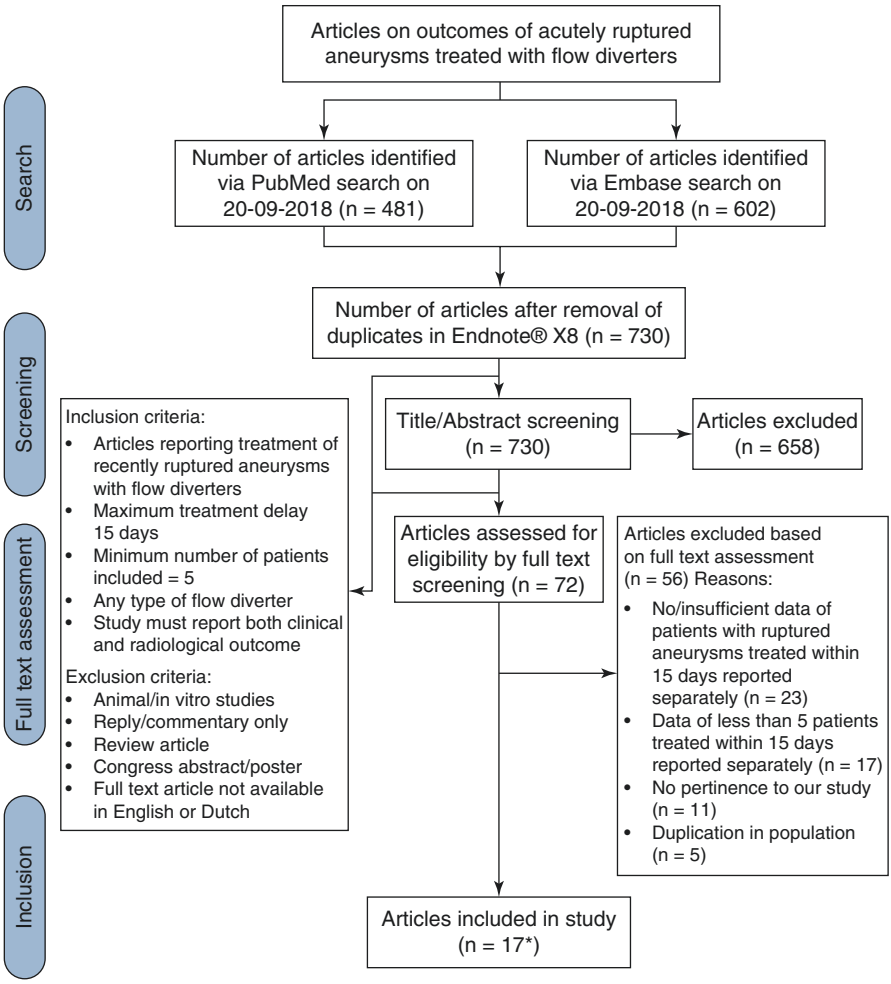


Fig. 7.1 Flowchart of search and selection process. ∗17 and 56 add up to 73; This is due to the fact that we added results of one extra article which is submitted for publication, but not yet published

In the majority of studies a flow diverter was used only if no other treatment options were considered feasible. Several series had some patients included which were treated by a flow diverter plus additional coiling [9, 10, 14–19, 21, 24], [∗]. Treatment of blood blister-like aneurysms in the setting of acute SAH were reported most frequently; 146 times (54%), followed by dissecting (n = 57, 21%), saccular (n = 45, 17%) and fusiform (n = 20, 8%) aneurysms. Most aneurysms were located in the anterior circulation (n = 200, 75%, range 0–100%). It was not possible to calculate either a pooled median or mean treatment delay due to the heterogeneity in ways of reporting.

Table 7.1 Pooled study baseline characteristics and outcomes

Pooled variables	Number (%)	Number of articles
Total population		
N eligible patients	258	**17**
N. eligible aneurysms	268	**17**
Proportion unfavorable HH/WFNS grade at presentation	66/249 (27)	16
Aneurysm type		17
• Blood blister-like	146 (54)	
• Saccular	45 (17)	
• Fusiform	20 (8)	
• Dissecting	57 (21)	
Aneurysms located in posterior circulation	**200 (75)**	**17**
Favorable clinical outcome (mRS 0–2, GOS 4–5)	179/253 (71)	17
Complete occlusion	183/202 (91)	17
Complication rate	62/257 (24)	17
• Leading to permanent neurological deficit in N patients	29/206 (14)	15
Rebleeding rate	9/268 (3)	16
All cause mortality rate	38/258 (15)	17

GOS Glasgow Outcome Scale, *mRS* modified Rankin Scale, *N* number

Primary and Secondary Outcomes

Overall, we found an estimated favorable clinical outcome rate of 75% (179/253; 95%C.I. 63–83% (Fig. 7.2a). All studies used either the mRS or GOS scale for reporting clinical outcome. The median/mean clinical follow-up time of at least 12 studies did not exceed 12 months. Furthermore, a distinction can be made between larger and smaller studies. Three studies outnumber the others [16, 20], [∗]. We will name those studies as the bigger ones. It must namely be noted that the pooled favorable clinical outcome rate of these three bigger ones combined was 60% (60/100) versus 82% (47/57) for studies with patient N < 10 (n = 7).

The pooled mortality rate was 17% (38/258; 95%C.I. 13–23%), ranging between 0 and 50% (Table 7.3; Fig. 7.2a). Again, there is a substantial difference in all cause mortality rate for the three bigger ones versus studies with ten or less patients included, with rates of respectively 18% (19/105) versus 5% (3/57).

Combining the results of all studies, complications were reported for 62/257 (24%, range 0–50%) patients. For the three bigger ones the complicate rate was 32% (34/105) versus 18% for studies with a patient number smaller or equal to ten. The total number of reported ischemic, hemorrhagic, and other type of complications was 32, 29, and 10, respectively. The rate of rebleeding was 3% (9/268), ranging from 0 to 33%. Most complications occurred within the early post-procedural phase, followed by the intra-procedural phase. 29/206 (14%, range 0–33%) patients had permanent deficit caused by complications (Table 7.4). However, detailed clinical consequences of complications were not always provided.

Table 7.2 Study characteristics and baseline characteristics per study

Study name	Design	No. participating centers	Inclusion period (mm-yyyy)	Total N of patients in study	N of eligible patients// aneurysms	Female sex (%)	Unfavorable HH (4, 5)/ WFNS (4, 5) (N, %)	An. anterior circulation (N, %)	An. type	An. mean size (mm)	Mean treatment delay (days)
Aydin et al. [12]	R	3	01-2009 to 01-2013	11	11//11	82	1 (9)	9 (82)	11 × BBL	3	10
Ten Brinck (2019)[a]	R	6	03-2012 to 12-2017	44	44//44	64	14 (32)	24 (55)	13 × FUS 11 × SAC 11 × DIC 9 × BBL	9	3
Cerejo et al. [13]	R	1	06-2011 to 06-2016	8	7//7	71	2 (29)	7 (100)	7 × BBL	3	6
Chalouhi et al. [14]	R	2	01-2012 to 01-2014	20	16//16	88	0 (0)	11 (69)	12 × SAC 4 × DIS	7	4
Chan et al. [15]	R	1	12-2010 to 02-2013	8	8//8	63	2 (25)	0 (0)	8 × DIS	3	3
Goertz et al. [10]	R	3	02-2016 to 03-2018	10	10//11	70	3 (30)	9 (82)	4 × SAC 3 × BBL 3 × DIS 1 × FUS	4	All within 24 h after hospital admission[b]
Lin et al. [16]	R R	5	2011–2013	26	18^3//18	UN	6 (33)	15 (83)	8 × BBL 6 × DIS 2 × SAC 2 × FUS	7	UN
Linfante et al. [11]	R	2	11-2013 to 11-2015	10	10^3//10	UN	1 (10)	10 (100)	10 × BBL	2	UN
Lozupone et al. [17]	R	1	01-2009 to 02-2005	17	16//16	69	6 (38)	10 (63)	9 × DIS 7 × BBL	5	4

Mahajan et al. [18]	R	1	06-2016 to 03-2018	16	15//15	UN	1 (7)	13 (87)	9[c] × SAC 1 × FUS 5 × BBL	4	5
Maus et al. [19]	R	3	11-2011 to 11-2017	15	14//14	36	9 (64)	0 (0)	14 × DIS	6	All within 12 h after hospital admis-sion[b]
McAuliffe and Wenderoth [9]	P[a]	3	08-2009 to 08-2010	11	6//6	67	2 (33)	3 (50)	2 × SAC 2 × FUS 2 × BBL	17	3
Mokin et al. [20]	R	14	11-2011 to 04-2017	43	43^3//45	67	14 (33)	45 (100)	45 × BBL	2	UN
Natarajan et al. [21]	R	1	06-2011 to 06-2016	11	11^3//14	73	4 (36)	11 (79)	5 × SAC 1 × FUS 6 × BBL 2 × DIS	5	3
Parthasarathy et al. [22]	R	1	05-2014 to 07-2015	9	7//7	57	0 (0)	7 (100)	7 × BBL	2	5
Ryan et al. [23]	R	1	10-2013 to 11-2016	13	13//16	85	2 (15)	16 (100)	16 × BBL	2	3
Yang et al. [24]	R	1	06-2010 to 01-2017	13	9//10	67	UN	10 (100)	10 × BBL	4	6

An. aneurysm, *BBL* blood blister-like, *DIS* dissecting, *FUS* fusiform, *HH* Hunt and Hess, *N* number, *P* prospective observational study, *R* retrospective analysis, *SAC* saccular, *UN* Unknown/Unclear, *WFNS* World Federation of Neurosurgical Societies

[a]Submitted, not yet published

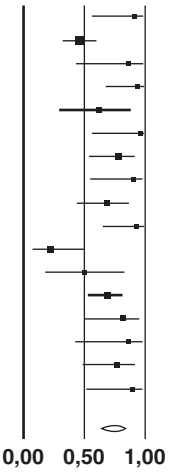
[b]Corresponding authors of both articles were mailed and confirmed all patients were treated within 15 days after last moment of hemorrhage

[c]Four of these aneurysms were described as 'fusisaccular'

a

Study name	Event rate	95% C.I. Lower limit	95% C.I. Upper limit	Event/total
Aydin 2015	0,909	0,561	0,987	10/11
ten Brinck 2019	0,455	0,315	0,601	20/14
Cerejo 2017	0,857	0,419	0,980	6/7
Chalouhi 2015	0,938	0,665	0,991	15/16
Chan 2014	0,625	0,285	0,875	5/8
Goertz 2018	0,955	0,552	0,997	10/10
Lin 2015	0,778	0,535	0,914	14/18
Linfante 2017	0,900	0,533	0,986	9/10
Lozupone 2018	0,688	0,433	0,864	11/16
Mahajan 2018	0,933	0,648	0,991	14/15
Maus 2018	0,214	0,071	0,494	3/14
McAuliffe 2012	0,500	0,168	0,832	3/6
Mokin 2018	0,684	0,522	0,811	26/38
Natarajan 2017	0,818	0,493	0,954	9/11
Parthasarathy 2018	0,857	0,419	0,980	6/7
Ryan 2017	0,769	0,478	0,924	10/13
Yang 2017	0,889	0,500	0,985	8/9
Total	0,745	0,632	0,833	179/253

Event rate and 95% CI

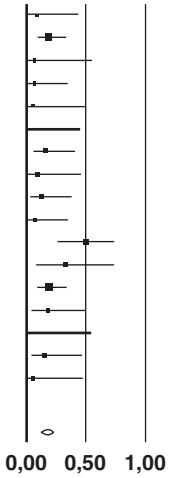


$I^2 = 0\%$

b

Study name	Event rate	95% C.I. Lower limit	95% C.I. Upper limit	Event/total
Aydin 2015	0,091	0,013	0,439	1/11
ten Brinck 2019	0,182	0,094	0,323	8/44
Cerejo 2017	0,063	0,004	0,539	0/7
Chalouhi 2015	0,063	0,009	0,335	1/16
Chan 2014	0,056	0,003	0,505	0/8
Goertz 2018	0,045	0,003	0,448	0/10
Lin 2015	0,167	0,055	0,409	3/18
Linfante 2017	0,100	0,014	0,467	1/10
Lozupone 2018	0,125	0,031	0,386	2/16
Mahajan 2018	0,067	0,009	0,352	1/15
Maus 2018	0,500	0,260	0,740	7/14
McAuliffe 2012	0,333	0,084	0,732	2/6
Mokin 2018	0,186	0,096	0,330	8/43
Natarajan 2017	0,182	0,046	0,507	2/11
Parthasarathy 2018	0,063	0,004	0,539	0/7
Ryan 2017	0,154	0,039	0,451	2/13
Yang 2017	0,050	0,003	0,475	0/9
Total	0,171	0,125	0,231	38/258

Event rate and 95% CI



$I^2 = 0\%$

Fig. 7.2 (**a**) Meta-analysis of favorable clinical outcome rate. (**b**) Meta-analysis of all cause mortality rate

Table 7.3 Outcomes per study

Study name	Complete occlusion (n/n, %)	Scale occlusion	Median/Mean angiographic FU time (months)	Favorable clinical outcome (n, %)	All cause mortality (n/n, [%])	Median/Mean clinical FU time (months)	Rebleeding (n, %)
Aydin et al. [12]	9/9 (100)	RR	6	10 (91)	1/11 (9)	UN	0 (0)
Ten Brinck (2019)[a]	27/29 (93)	RR	16	20 (46)	8/44 (18)	7.6 (mean)	5 (11)
Cerejo et al. [13]	6/7 (86)	NA	UN	6 (86)	0/7 (0)	12	0 (0)
Chalouhi et al. [14]	11/12 (92)	NA	5	15 (94)	1/16 (6)	5	0 (0)
Chan et al. [15]	8/8 (100)	NA	5	5 (63)	0/8 (0)	12	0
Goertz et al. [10]	9/10 (90)	OKM	8	10 (100)	0/10 (0)	8	0 (0)
Lin et al. [16]	15/16 (94)	NA	UN	14 (78)	3/18 (17)	UN	1 (6)
Linfante et al. [11]	9/9 (100)	RR	15	9 (90)	1/10 (10)	3	
Lozupone et al. [17]	12/14 (86)	NA	6–12 months	11 (69)	2/16 (13)	6–12 months	0 (0)
Mahajan et al. [18]	13/14 (93)	OKM	3–6 months	14 (93)	1/15 (7)	3–6 months	0 (0)
Maus et al. [19]	6/6 (100)	OKM	7	3 (21)	7/14 (50)	7	0 (0)
McAuliffe and Wenderoth [9]	3/4 (75)	NA	6	3 (50)	2/6 (33)	Up to 6 months	2 (33)
Mokin et al. [20]	28/32 (88)	NA	4	26/38 (68)	8/43 (19)	3	1 (2)
Natarajan et al. [21]	9/9 (100)	NA	24	9 (82)	2/11 (18)	23	0 (0)
Parthasarathy et al. [22]	6/7 (86)	NA	6	6 (85)	0/7 (0)	UN	0 (0)
Ryan et al. [23]	5/9 (56)	NA	UN	10 (77)	2/13 (15)	UN	0 (0)
Yang et al. [24]	7/7 (100)	RR	6–9 months	8 (89)	0/9 (0)	22	0 (0)

[a]Submitted, not yet published

Table 7.4 Complications per study

Study name	Complication rate (n/n, %)	Type[a]			Intra-procedural	Post-procedural		Leading to permanent deficit in N patients (n/n, %).
		Ischemic	Hemorrhagic	Other		<30 days	>30 days	
Aydin et al. [12]	1/11 (9)	1	0	0	0	1	0	1/11 (9)
Ten Brinck (2019)[b]	20/44 (45)	9	10	6	5	18	2	12/44 (27)
Cerejo et al. [13]	3/7 (43)	2	1	0	0	3	0	2/7 (29)
Chalouhi et al. [14]	1/16 (6)	0	1	0	1	0	0	1/16 (6)
Chan et al. [15]	1/8 (13)	1	1	0	0	2	0	UN
Goertz et al. [10]	2/10 (20)	1	0	1	1	1	0	1/10 (10)
Lin et al. [16]	5/18 (28)	3	2	0	2	3	0	2/18 (11)
Linfante et al. [11]	0/9 (0)	0	0	0	0	0	0	0/9 (0)
Lozupone et al. [17]	4/16 (25)	1	2	1	2	2	0	2/16 (13)
Mahajan et al. [18]	1/15 (7)	1	0	0	1	0	0	0/15 (0)
Maus et al. [19]	4/14 (29)	3	1	0	4	1	0	1/14 (7)
McAuliffe and Wenderoth [9]	3/6 (50)	2	3	0	2	2	0	2/6 (33)
Mokin et al. [20]	9/43 (21)	5	3	1	7	1	1	UN
Natarajan et al. [21]	2/11 (18)	2	1	0	2	1	0	1/11 (9)
Parthasarathy et al. [22]	0/7 (0)	0	0	0	0	0	0	0/7 (0)
Ryan et al. [23]	5/13 (39)	1	3	1	2	3	0	3/13 (23)
Yang et al. [24]	1/9 (11)	0	1	0	0	0	1	1/9 (11)
Total pooled	62/257 (24)	32	29	10	29	38	4	29/206 (14)

[a]The total amount of complications presented per subtype may exceed the number mentioned in the complication rate. This is due to the fact that some patients had multiple complications

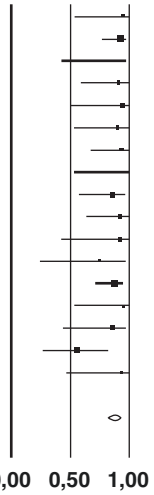
[b]Submitted, not yet published

Reporting of complications was performed in various ways and therefore these rates were hard to interpret. Chalouhi et al. specifically mention that they report all complications regardless of their clinical significance [14]. Mahajan and Aydin et al. only globally mention that they report complications [12, 18]. Goertz et al. report a chemotoxic contrast reaction as complication. Mokin et al. and Yang et al. report slow flow/flow stasis as complication [20, 24]. On the contrary, Parthasarathy et al. specifically describe that they only report hemorrhagic and thrombo-embolic complications and therefore we cannot be sure if the previously mentioned types of complications have occurred in their study [22].

The complete occlusion rate ranged between 56 and 100%. The pooled complete occlusion rate was 88% (183/202; 95%C.I. 82–92%) (Fig. 7.3). For both the three studies with most patients with available follow-up imaging as well as all studies with angiographic results for <10 patients the complete occlusion rate was 91% (70/77 versus 77/85).

Some studies assessed the grade of occlusion by using a scale (Raymond-Roy or O'Kelly-Marotta), however half of the articles only used a global description. Studies that did not use the RR or OKM scale did not report a higher pooled complete occlusion rate. Only four studies used angiographic follow-up with a median/mean follow-up time of 12 months or more (Table 7.3) [13, 15, 21, 24].

Study name	Statistics for each study				Event rate and 95% CI
		95% C.I.			
	Event rate	Lower limit	Upper limit	Event/total	
Aydin 2015	0,950	0,525	0,997	9/9	
ten Brinck 2019	0,931	0,762	0,983	27/29	
Cerejo 2017	0,857	0,419	0,980	6/7	
Chalouhi 2015	0,917	0,587	0,988	11/12	
Chan 2014	0,944	0,495	0,997	8/8	
Goertz 2018	0,900	0,533	0,986	9/10	
Lin 2015	0,938	0,665	0,991	15/16	
Linfante 2017	0,950	0,525	0,997	9/9	
Lozupone 2018	0,857	0,573	0,964	12/14	
Mahajan 2018	0,929	0,630	0,990	13/14	
Maus 2018	0,929	0,423	0,996	6/6	
McAuliffe 2012	0,750	0,238	0,996	3/4	
Mokin 2018	0,875	0,711	0,952	28/32	
Natarajan 2017	0,950	0,525	0,997	9/9	
Parthasarathy 2018	0,857	0,419	0,980	6/7	
Ryan 2017	0,556	0,251	0,823	5/9	
Yang 2017	0,938	0,461	0,996	7/7	
Total	0,879	0,821	0,920	183/202	



$I^2 = 0\%$

Fig. 7.3 Meta-analysis of complete occlusion rate

Quality of Evidence

Only studies providing (very) low quality of evidence were included. See Table 7.5 for the GRADE classification of each study.

Discussion

Benefits

- Placement of a flow diverter requires no manipulation within the aneurysm sac. This might lower the risk of intra-operative rupture.
- Durable occlusion (compared to bare and stent-assisted coiling) and less recanalization on long-term, therefore less retreatment is required, which in turn might decrease the amount of complications.
- Can be used for some types of aneurysms (e.g. blood blister-like) which are not always amenable to other (e.g. stent-assisted coiling or clipping) treatment modalities.

Table 7.5 Quality of evidence

Study name	Patient N	Precision issues	Study quality[a] (GRADE)
Aydin et al. [12]	11	Serious	⨁◯◯◯ Very low
Ten Brinck (2019)[b]	44	Serious	⨁⨁◯◯ Low
Cerejo et al. [13]	7	Very serious	⨁◯◯◯ Very low
Chalouhi et al. [14]	16	Very serious	⨁◯◯◯ Very low
Chan et al. [15]	8	Very serious	⨁◯◯◯ Very low
Goertz et al. [10]	10	Very serious	⨁◯◯◯ Very low
Lin et al. [16]	18	Very serious	⨁◯◯◯ Very low
Linfante et al. [11]	10	Very serious	⨁◯◯◯ Very low
Lozupone et al. [17]	16	Very serious	⨁◯◯◯ Very low
Mahajan et al. [18]	15	Very serious	⨁◯◯◯ Very low
Maus et al. [19]	14	Very serious	⨁◯◯◯ Very low
McAuliffe and Wenderoth [9]	6	Very serious	⨁◯◯◯ Very wow
Mokin et al. [20]	43	Serious	⨁⨁◯◯ Low
Natarajan et al. [21]	11	Very serious	⨁◯◯◯ Very low
Parthasarathy et al. [22]	7	Very serious	⨁◯◯◯ Very low
Ryan et al. [23]	13	Very serious	⨁◯◯◯ Very low
Yang et al. [24]	9	Very serious	⨁◯◯◯ Very low

[a]Observational studies start at 'low'. Due to already solely the issues regarding the precision (amongst others number of participants or events) all these studies must be judged to be of (very) low quality. We did not provide overview of other points of assessment (directness, publication bias) since this would also only yield serious/very serious issues and not change the final outcome of (very) low quality

[b]Submitted, not yet published

Risks

- No achievement of complete immediate occlusion and therefore a possible higher rate of rebleeding compared to e.g. clipping or stent-assisted coiling (when immediate occlusion is achieved with those techniques).
- Need for dual antiplatelet therapy may lead to a higher risk of hemorrhagic complications
- Possible high risk of periprocedural thromboembolic complications since acute SAH patients are in a hypercoagulable state.

At first sight, the rates of favorable clinical outcome, mortality and complete occlusion seem to not differ so much from results of two published meta-analysis regarding the use of flow diverters in the acute phase after subarachnoid hemorrhage. Based on the published clinical and angiographic outcome, we could consider the use of flow diversion in this setting a relatively effective option. However, reporting of complications was not specific enough to be able to draw conclusions regarding the safety.

Quality of Evidence and Bias

Published studies regarding the use of flow diverters in the acute subarachnoid hemorrhage phase provide evidence of only (very) low quality. For other reviews, stricter inclusion criteria such as only prospective studies or a minimum patient number of 50 per study are being used [25]. If we would have applied these criteria to the result of our literature search, then we would have had 0 studies to include.

Both the internal and external validity of the studies we included are limited. Selection and publication bias seem to be the main forms of present bias. In hardly any study, a concrete statement regarding the rationale behind both patient selection criteria and timing of treatment is included in the introduction/methods section. This results in very heterogeneous patient and aneurysm populations.

Smaller case series do not always concern consecutive patients, but often a selected subgroup with favorable outcomes. Mahajan et al. do for example not clearly describe how the final study population was selected [18]. Presence of selective reporting and publication bias is also nicely illustrated by the fact that both the rate of favorable clinical outcome and all-cause mortality were significantly lower when results of only the three biggest studies were pooled compared to results of studies with ten or less patients included. Differences in these rates were 22% and 13%, respectively.

Although the bigger series included in this review have less favorable results, even their results should be appraised critically. It has been shown that self-assessment of occlusion and clinical outcome can lead to overestimation of rates of complete occlusion and favorable outcome compared to when results are performed by an independent core-laboratory. Differences can be up to 26% [26].

Besides publication bias, also funding (bias) may have played a role: Several studies specifically mention the type of used flow diverter, both in study title and

conclusion [10, 11, 14–16, 18]. Authors involved in almost all these papers have some financial connection to the industry. To be clear, this does not necessarily mean that those results are altered or untrustworthy. However, it is more likely that in case results of small case series (such as published) would have been more negative, these results would never have been submitted/published (with emphasis on the used type of device). Funding may therefore unconsciously 'empower' publication bias.

Complications

The differences in complication rates between studies can partially be explained by characteristics of the included study population. Aneurysms in the posterior circulation seem to be associated with a higher complication risk [27]. Also, studies with a higher percentage of included patients with poor WFNS/HH grade at presentation are more likely to find worse clinical outcomes [28].

During full text reading and data extraction it became clear that reporting of complications was performed in various ways. Performing a meta-analysis was not appropriate.

Type of reported complications were not pre-specified in most studies. Most studies globally described that 'all complications' were being reported. Some studies specified this further into types (e.g. ischemic/hemorrhagic) or based on timing (early/delayed). However, in most studies it was not clearly defined what was considered as a complication and what type of complications were reported.

Furthermore, some authors reported the treatment-related mortality rate without specifying cause of death for cases they classified as disease-related deaths. It was not always clear whether or not a complication, and perhaps death, was treatment or disease-related. We recommend presenting both the all-cause mortality and treatment-related death rate. A detailed description of cause of death should be provided for cases with disease-related death in order to make verification possible. This also applies to permanent neurologic deficit caused by (treatment-related) complications.

Future Research

Since the true complication rate and rate of unfavorable clinical outcome may be higher than sketched by results of previously published meta-analysis, future research is required.

Patient and aneurysm characteristics, thus the indication for FD treatment in the acute SAH phase, are a key aspect which should be addressed more often. Interesting knowledge would be the rate of patients that have been up for discussion for FD treatment in the acute SAH phase, but have been assigned to other treatment modalities or no treatment. Flow diversion is often regarded as a 'last resort' treatment option in the acute SAH phase. If complications are anticipated by the multidisciplinary team, it could be decided not to treat a patient. However, in case those patients would be treated anyway, which could be advocated when flow diversion is the only feasible option, a poor outcome is more likely to be the result.

Furthermore, authors should improve homogeneity of reporting of complications. They should clearly state what is considered a complication and also explicitly state whether all complications, regardless of their clinical significance, were reported or only the ones with clinical sequelae. Only when we have a full transparent overview of all complications and patients' clinical outcome, we can make more valid comparisons with other treatment modalities and be able to select a defined subgroup that can possibly profit from FD treatment in the acute SAH phase.

Conclusion

Only (very) low quality evidence is available regarding the use of flow diverters for patients in the acute aneurysmal SAH phase, defined as 15 days after last moment of hemorrhage. The rate of complete aneurysm occlusion is probably overestimated, but seems to be fairly high. However, the true rate of favorable clinical outcome may be lower than rates found by published meta-analyses. Smaller studies, which are more prone to selection and publication bias, tend to show more positive outcomes, which in turn distorts the final outcome when included in a meta-analysis. This also applies to the complication rate. When no other treatment options are deemed feasible, flow diversion can be considered in a selected subgroup. However, one must always consider the possible (high risk of) complications inherent to the use of flow diversion treatment in this setting. Additional research is required and should focus on the indication for intended use of flow diverters in the acute SAH setting and a homogeneous way of reporting complications and clinical outcome.

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Box

What is known?

Flow diversion as treatment for recently ruptured aneurysms seems to yield a high complete occlusion rate. Two meta-analysis about this topic, with overlapping study population but different inclusion criteria, reported fairly high rates of favorable clinical outcome. Reporting of (treatment-related) varies considerably among published studies.

What is new?

Only (very) low quality evidence regarding the use of flow diverters in the acute SAH phase is available. Publication and selection bias seem to be important types of bias distorting the final results of meta-analyses, with larger series tending to report especially more negative results regarding clinical outcome.

Consequences for clinical practice

Flow diversion should be considered last resort option in the treatment of recently ruptured aneurysms. When no other treatment option is deemed feasible, the use of FDs can be considered. However the high rate of complications should be kept in mind. Rationale behind choice for FD treatment in this setting should be documented properly and should be subject of future research.

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Controversies in Deep Brain Stimulation Surgery: Micro-Electrode Recordings

8

Jeroen Habets, Bethany Isaacs, Saman Vinke, and Pieter Kubben

Introduction

Deep brain stimulation (DBS) of the subthalamic nucleus (STN) was first applied as a neurosurgical intervention technique for Parkinson's disease (PD) in the 1990s and has since become a widely accepted practice. Bilateral STN-DBS has been proven to be significantly improve levodopa-responsive parkinsonian symptoms and quality of life compared to best medical treatment alone [1, 2]. DBS is generally considered in patients only when pharmacological treatment does not respond in sufficient effect any longer or leads to unacceptable adverse effects. Stimulation of the subthalamic nucleus (STN) is the most common practice since it results in more time in well-treated 'ON-condition', though the internal segment of the globus pallidus (GPi) is also a possibility [3, 4]**.** While DBS of the STN specifically is effective for a majority of patients in relieving the motor related symptoms of PD, a fraction of patients will fail to witness such beneficial effects. Moreover, DBS patients may develop a number of side effects spanning a range of domains, from

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speech and gait impairments to cognitive decline and impulse control disorders, as well as psychiatric and emotional disturbances.

The first two concepts here are a product of accurate target identification and verification, which can be achieved via pre-operative magnetic resonance imaging (MRI) and or intraoperative microelectrode recordings (MER). This chapter will attempt to determine whether MRI with or without additional intraoperative MER-guidance is most effective method for target identification and verification in DBS via a structured literature review. Additionally, we will discuss some advantages, caveats and outstanding complications for both methods. In this chapter we will focus on STN-DBS for PD.

Originally, MER was seen as the golden standard for anatomical verification of a target. In this method, the leads are placed in the brain based on standard atlas coordinate applied on a preoperative MRI of the patient. Through macro-stimulation of functionally distinct portions of the STN along with behavioural and clinical tests, MER can spatially map out the optimal location for DBS lead placement [5].

However, the verification via MER requires that the patient be awake and tested during DBS implantation. The patient's awake response on the intra-operative stimulation regarding motor symptoms and adverse effects can influence the final lead placement. Moreover, MER signals will be influenced by general anaesthesia. This is time consuming, stressful and causes a lot of anxiety for patients. Originally controversial, but steadily gaining popularity is the use of pre-operative MRI for targeting and intra operative MRI or CT for identifying lead location, rather than MER. This approach allows the patient to be under general anaesthesia, and has been shown to be equally as effective as MER [6–8]. Despite of many studies, some contradictions stay unsolved. For example, on the one hand supporters of MER suggest optimal final lead placement can deviate from the (MRI or atlas based) planned target by using intraoperative MER [9]. While, on the other hand opponents of MER suggest image-guided and verified surgery can reduce intra-operative brain-shift and accompanying lead inaccuracy, especially in the second placed lead [10].

Relatedly, the overall success of traditional target identification and implantation still will depend on a number of factors; namely the existing knowledge of the anatomy of the STN and surrounding structures, counteracting intra operative brain shift and the use of multiple leads for MER. Furthermore, modern technical advances offer new possibilities which might positively influence the outcome of lead placement and clinical outcome, however they are bring their own considerations. Some of them are pre-operative ultra-high field MRI, multimodal image techniques such as diffusion and functional MRI, personalized stimulation parameters and calculation of surrounding tissue activated outside of the target by stimulating with directional steering leads.

The following chapter therefore consists of a literature review of *DBS of the STN in PD patients using both, or either MRI and MER*, as well as papers discussing the aforementioned factors which are deemed essential for successful DBS, though remain subject to personal preference.

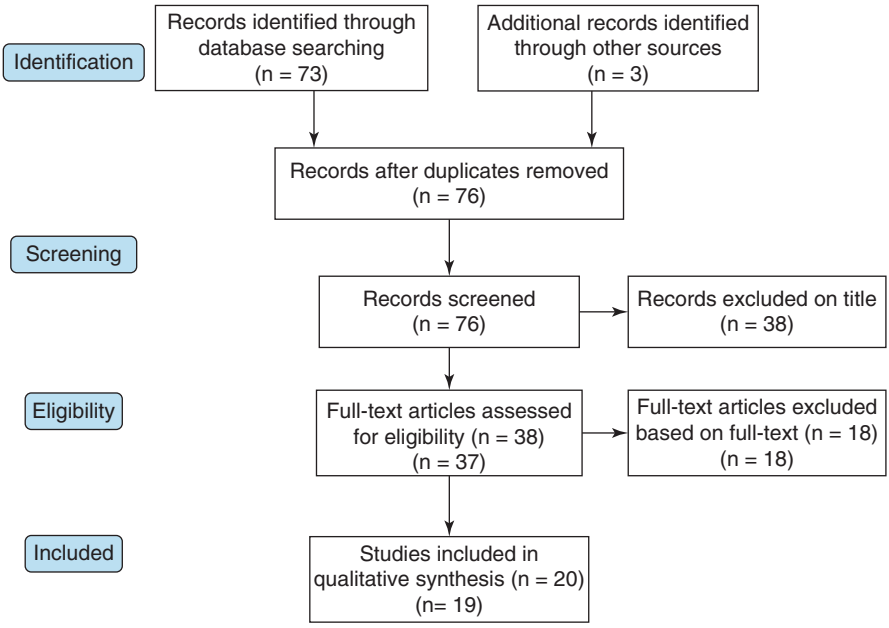
Methods

To collect relevant and recent literature we performed a literature search in the Pubmed database with the search string: "((micro electrode recording) OR (micro-electrode recording) OR MER) AND (MRI OR MR OR (magnetic resonance imag*)) AND (DBS OR (deep brain stimulation)) AND (STN OR (sub thalamic nucleus) OR (subthalamic nucleus))" on 18-07-2018, with a limitation of publication date within 10 years, which gave us 73 potential articles. We included three papers from cross-references.

We excluded 38 papers based on title. From the 38 full-articles, we excluded 18 articles because they had non-human subjects, described alternative methods besides conventional MRI-guided or MER-guided stereotactical DBS surgery, used non-STN targets or were non-original articles.

We included 20 articles for the qualitative evaluation we describe in this paper. Included articles are rated following the GRADE criteria for quality of evidence (https://bestpractice.bmj.com/info/us/toolkit/learn-ebm/what-is-grade/). Since this literature is very heterogenic, we did not perform a quantitative meta-analysis on clinical outcome, e.g. UPDRS or quality of life sores, or on anatomical outcome, e.g. millimetres deviation per MR-field strength or percentage of central MER-recordings used for final lead-implantation.

PRISMA Flow Chart



Results

We formatted the results section as two tables, comparing the included literature which is arguing in favour and against the additional use of intraoperative MER. Besides, we give an overview of current literature on the role for new techniques and modalities in improving MRI-guided targeting. Since different endpoints are used as outcome parameters in the literature, and most studies use different methodologies, we give a comprehensive, tough understandable, overview of the current opinions and evidence on this topic. We tried to summarize the concluding decisive of the authors in comparable arguments in order to enable a quick comparison of the actual opinions.

In favour of MER-guided targeting, using 1.5- or 3-Tesla MRI

References	Study design	Arguments
Amirnovin et al. [11]	Comparing 1.5T-MRI coordinates with final placement based on MER and intraoperative testing	– 58% of locations changed based on MER and testing
Temel et al. [12]	STN DBS with single (n = 32) vs. multiple (n = 23) intraoperative MER electrode recordings	– Multiple MER trajectories lead to better postoperative rigidity and tremor without more complications – Multiple MER trajectories induced mild declines in memory function
Bour et al. [9]	Comparing central MER trajectory (based on 1.5T-MRI) with final electrode trajectory	– Final trajectory was according MRI in 50%, final depth was within 1 mm range of MRI-target in 57% – 64% of final channels was channel with best MER activity
Schlaier et al. [13]	Comparing posterior STN-border based on 1.5T-MRI vs. MER	– 44% of MER STN volumes were larger than the MRI STN volumes – 46% of MER STN being incompatible with the MRI STN
Reck et al. [14]	Comparing DBS STN surgeries with 1.5T-MRI targeting and MER-guidance with (n = 32) vs. without (n = 10) intraoperative stimulation	– Significant better UPDRS III outcome in MER vs. non-MER – In 27% MER-guidance lead to trajectory adjustment
Schlaier et al. [15]	Comparing 1.5T-MRI defined STN vs. location defined as STN based on MER	– 16/42 active contact points beyond MRI defined STN borders
Longhi et al. [16]	Comparison of accuracy of 1.5T- vs. 3T-MRI in predicting final electrode location	– 1.5T: 2/12; 3T: 21/28 – Better clinical performance in 3 T group – MER to determine lead deepness and prevent adverse effects
Rabie et al. [17]	Direct targeting based on 3T-MRI vs. indirect targeting based on stereotaxic atlases and comparing MRI-coordinates with final implantations	– Significant different Euclidian distances between 3 T-MRI coordinates and final coordinates based on MER and intra-operative testing – MER has increased spatial resolution
Nowacki et al. [18]	Comparing targeting accuracy of 3T-MRI in 78 MER-verified implanted DBS electrodes	– Average difference between STN crossing lengths: 0.28 mm – In 43% the deviation was more than 1 mm

References	Study design	Arguments
Lozano et al. [19]	Evaluation of 100 consecutive DBS STN surgeries: comparing direct and in-direct targeting (1.5T-MRI) and MER-guided target adjustments	– 18% corrected based on MER in first side, 20% corrected in second side – Intraoperative electrophysiology or MRI is needed next to MRI-targeting

In favour of MRI-guided targeting, without additional MER, using 1.5- or 3-Tesla MRI

Reference	Study design	Arguments
Foltynie et al. [20]	Description of cohort one-year after 1.5T-MRI-guided STN DBS, without additional MER (n = 79)	– Mean UPDRS during off-medication: 28 points, 52% – Dyskinesia severity from 3.2 to 1.6 points (UPDRS IV) – Mean levodopa reduction 39% – Mean DBS: 3.0 V, 60 microseconds, 139 Hz
Nakajima et al. [6]	Comparison of two cohorts: local anaesthesia with MER and clinical testing (n = 68) vs. general anaesthesia without MER or intraoperative stimulation (n = 14)	– Comparable improvement of UPDRS-III (general: 52.8% vs. local: 50.8%) and LED reduction (general: 50.8%, local: 60.2%) – No comparison on DBS settings
Aviles-Olmos et al. [21]	Same cohort as Foltynie et al. [20]; 5 year followup (n = 41) and 8 year followup (n = 12)	– Off-medication UPDRS improvement remained 70% for tremor, 50% for rigidity and bradykinesia improvement decreased from 46% to 23%
Liu et al. [22]	Comparison of two retrospective cohorts: implantation without MER based on 1.5T T2 MRI (n = 61) vs. implantation with MER guidance (n = 76)	– Similar improvement after 1 year in off-medication UPDRS (resp. 65% vs. 66%) and quality of life (resp. 44% vs. 50%); similar levodopa reductions
Brodsky et al. [23]	Comparison of two cohorts (STN subgroups): asleep implantation without MER (n = 7) vs. awake implantation with MER (n = 18)	– No significant difference in UPDRS II and III improvement, no subscores for STN/GPi seperately – Asleep cohort was superior on quality-of-life, cognition and communication/speech outcomes
Lee et al. [24]	Evaluation of 45 consecutive DBS STN surgeries: either asleep without MER and intraoperative testing, or MER-guided DBS with intraoperative testing	– Side effect thresholds during initial programming were slightly lower in the MER group – No significant difference in the reduction of clinical symptoms or medication dosage was observed

Studies using alternative MRI techniques as ultra-high field MRI and susceptibility weighted sequences

Reference	Study design	Arguments and conclusions
Polanski et al. [25]	Comparing 182 MER trajectories from 42 STN's vs. T2, FLAIR and SWI 3T-MRI	– Recommendation for SWI MRI based on sensitivity, specificity and negative pred. value – Reserved to advise DBS without MER
McEvoy et al. [26]	Comparing 3T MRI SWI STN-SN border on coronal plane with MER activity in 7 DBS STN surgeries	– SWI MRI demonstrates reliable STN delineation
Verhagen et al. [27]	Comparing dorsal and lateral STN borders on 1.5T, 3T and 7T T2 MRI vs. computational MER-STN model	– 7T decreased variance between dorsal + lateral MRI and MER borders – 3T and 7T STN borders more dorsal than MER – 7T SWI should be explored besides 7T T2

Reference	Study design	Arguments and conclusions
Bot et al. [28]	Comparing STN targeting based on T2 and SWI 1.5T and T2 3T with MER STN activity	– MER STN activity in 84% of MRI target trajectories – 1.5T SWI inferior to 1.5T T2
Bus et al. [29]	Compare STN activity in MER trajectories (visualized with intra-operative CT) vs. 3T T2 and SWI MRI	– Low correspondence of ventral and dorsal MRI STN borders with MER STN activity – 3T SWI MRI decreases false-positive MRI-based STN targets – Only 42% of central SWI-based trajectories targeted final electrode placement

Discussion

While advancements in MRI acquisition and analysis techniques such as ultra-high field and diffusion tractography have greatly advanced and have the potential to be used for neurosurgical purposes like DBS, their application within the clinics has been severely limited [30–32]. The combined literature fails to provide a single favourable approach for DBS targeting. This is in part due to the differences in both the method and the outcome determinant. For instance, some studies report differences in the planned target in relation to the actual location as determined on CT, or by the deviation identified with MER. Others determine treatment efficacy by differences in pre and post-operative LED response and UPDRS scores. The manufacturers of both software and hardware used for surgical planning (e.g. Medtronic, Abbott, Boston Scientific) differs across DBS centres, as do the number of MER test electrodes used, types of MRI (e.g. 1.5T, 3T, 7T), vendors (e.g. Siemens, Phillips, GE), sequences and scan parameters (e.g. contrasts, voxel size). The number of patients also differs greatly across studies, which is a threat to statistical power in group-based analyses. Different surgeons can even be a confounder in such cross comparisons.

Some studies suggest that intraoperative MER can significantly improve the outcome of DBS of the STN [33]. Whereas others will argue that while targeting through standardized atlases are unreliable, the addition of MER fails to significantly improve STN DBS [34]. Following the trend of individualized and personalised medicine, direct targeting is certainly preferred over indirect targeting in MRI, though this does not necessitate that MER is no longer required. Instead, the increasing success of DBS will most likely depend on implementation of advanced MRI techniques within the clinics. Relatedly, advancements in lead and electrode hardware, such as the use of directional steering might play a role in the elimination of MER in DBS surgeries [35].

Regardless, the clinical relevance attributed to MER by many authors cannot be neglected. On one hand, it enables to measure nucleus specific neuronal activity, for example, the beta activity of the STN which can be helpful in identifying the dorsolateral boarders, reflecting the motor portion of the target. Additionally, MER allows for direct behavioural testing, optimization of stimulation parameters and assessment of potential side effects, which in theory collectively result in minimizing the occurrence of post-operative side effects and maximising clinical benefit [36]. Obviously, the

latter is no insurance for the absence of adverse effect though. However, identification of specific nuclei and their subcomponents through MER was only necessary due to the limitations of conventional MRI techniques, which traditionally lacked the contrast and spatial resolution required for the desired level of anatomical accuracy [25, 37, 38]. Moreover, DBS surgeries still heavily rely on the application of standardized coordinates and atlases, referred to as indirect targeting. Such an approach is erroneous given the well documented heterogeneity of deep brain structures. For instance, the STN is known to shift in the lateral direction with age as well as decrease in volume with disease; such alterations are not captured with stereotaxic atlases which can lead to suboptimal placement of electrodes.

However, the application of ultra-high field MRI and advanced multi modal approaches has the potential to revolutionize current practices. The increased signal and contrast offered by UHF MRI allows for sharper and more accurate visualisation of deep brain structures within a clinically feasible time frame [39–46]. The combination of diffusion tractography and functional MRI allow for the identification of both functional and structural networks which can provide additional information in relation to optimal DBS placement, which can additionally be used to inform on the potential volume of tissue activated and with connected networks, which is useful for predicting clinical outcomes. Relatedly, novel contrasts that exploit the paramagnetic properties of iron rich basal nuclei such as susceptibility-based contrasts and quantitative maps can be used to better visualize such DBS targets on 7T compared to 3T [22, 47–53].

Moreover, low field strength intra operative MRI (iMRI) can be used to monitor in real time the location of DBS leads. Although that low field strength MRI is notorious for suboptimal visibility of the STN, there are positive reports on the use of iMRI during DBS. Improved motor symptoms comparable to MER-guided DBS are reported for DBS using 1.5-T-iMRI techniques [54]. Reliance purely on radiological and neuroimaging techniques in theory leads a reduction in the additive surgical risks of MER usage, decreased operation time and increased perioperative patient wellbeing since surgery can be performed under general sedation and pre-operative dopamine-withdrawal can be excluded [55, 56]. The statement whether major surgical risks such as bleeding will decrease is debatable, since the use of multiple MER trajectories did not increase surgical risks compared to the use of a single MER trajectory [12]. However, leads placed in a single penetration, in a faster time frame, when based on MRI, can potentially limit the occurrence of brain shift by reducing CSF loss [24]. Further, a cost analysis showed MER more than doubles the price of a bilateral STN DBS surgery in the United States [57].

However, the use of UHF MRI in DBS should be applied with caution. Firstly, the deep brain structures like the STN are located in the middle of the brain, which means that the signal to noise ratio is substantially lowered compared to the cortex [44, 58–60]. This is important when considering the requirement of acquiring scans in a clinically feasible window especially for PD patients, given the potential for accumulative movement artifacts, though methods do exist for motion correction [61]. Secondly is the requirement of post processing techniques and expertise outside of a standard clinical setting, which is especially true for tractography and functional MRI [62]. And thirdly, the

absolute requirement of an accurate co-registration between pre, intra and post-operative MRI-MRI and or MRI-CT. Therefore, error can occur during the initial targeting on MRI and transformation to a stereotaxic coordinate system on CT, and during the intra and post-operative MRI and or CTs acquired for lead localization. This argument exists still for 1.5 and 3T clinical scans though appears to be more difficult to account for at 7T. Suboptimal fusion can lead to geometrical errors of up to 3 mm [63]. If we rely purely on neuroimaging, these errors cannot be accounted for.

A reasonable conclusion would be that when MRI based targeting does not result in an intraoperative deviation significantly more than when based on targets are based on MER, MRI should be preferred [64]. This doesn't suggest that MRI is significantly better than MER but rather it is a viable and attractive alternative given MRI guided DBS allows the patient to be fully anesthetized, and eliminating the need for behavioural feedback and intra operative testing [54, 65–73]. What remains so far unanswered is whether direct targeting via MRI guided DBS reduces the risk of reimplantation compared to DBS preformed with MRI and or only MER.

Conclusion

Literature is inconclusive regarding the added value of intraoperative MER during DBS surgery. Studies in favour of this technique use different endpoints then studies which do not find added value. This chapter provided an overview of these various arguments. For the near future, we expect decision making regarding "awake MER" versus "asleep MRI-guided" DBS to be made on an individual patient level, taking in to account the clinical presentation, MR imaging characteristics, experience with directional steering, and patient preference. Clinical trials comparing both methods will be needed to address this issue further.

Summary Box

What is known?

Supporters of MER suggest optimal final lead placement can deviate from the MRI-based planned target by using intraoperative MER**.** Opponents of MER suggest image-guided and verified surgery leads to satisfying post-operative results and can reduce intra-operative brain-shift and accompanying lead inaccuracy, especially in the second placed lead.

Technological developments in imaging and stimulating electrodes might influence this discussion.

What is new?

Available literature is still inconclusive regarding the added value of intraoperative MER during DBS surgery and consists of heterogenous studies using different endpoints.

Image guided and verified DBS surgery is not significantly better than DBS surgery using intra-operative MER but rather it is a viable and attractive alternative which allows the patient to be fully anesthetized.

Modern MRI techniques, for example ultra-high field imaging, are not used on a scale yet that they can contribute to the regular care in most hospitals.

What are the consequences for clinical practice?

Decision making regarding "awake MER" versus "asleep MRI-guided" DBS will vary per individual patient, taking in to account the clinical presentation, MR imaging characteristics and patient preference.

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Chiari Malformation: Posterior Fossa Decompression With or Without Duraplasty?

9

Alexander Perdomo-Pantoja, Rajiv R. Iyer, and Alan R. Cohen

Introduction

The term "Chiari malformation" describes a group of congenital hindbrain anomalies described by pathologist Hans Chiari at the end of the nineteenth century [1]. In the first of a series of articles, Chiari reported a 17-year old woman whose autopsy unveiled "elongation of the tonsils and medial divisions of the inferior lobules of the cerebellum into cone-shaped projections which accompany the medulla oblongata into the spinal canal" [2]. Since this 1891 report, the classification system of Chiari malformations has evolved, along with a better overall understanding of the pathophysiology, clinical manifestations, and diagnostic workup for patients with Chari malformations. The etiology of Chiari I malformation (CIM) is still unknown, but it is thought to be due to a defect of the paraxial mesoderm that leads to underdevelopment of the occipital somites [3, 4]. Sgouros et al. [5] studied the deficient growth of the posterior skull base with computer-aided 3D analysis in 30 CIM patients, and found abnormal geometrical measurements of the entire skull base, and also a smaller posterior fossa volume that correlated with the presence of concurrent syringomyelia.

Currently, CIM is defined as a caudal displacement of the cerebellar tonsils below the foramen magnum by 3–5 mm. Elster and Chen considered that 5 mm is an adequate cut-off for unilateral tonsillar herniation, while a 3–5 mm cut-off is more suitable for the bilateral tonsillar herniation [6, 7] (Fig. 9.1). However, our understanding of this disease has been evolving in the recent years. It has become more apparent that CIM may not be a homogeneous entity, as possible subgroups of patients with different radiographic characteristics and outcomes have been postulated. Some of these proposed subcategories are the Chiari 0 malformation

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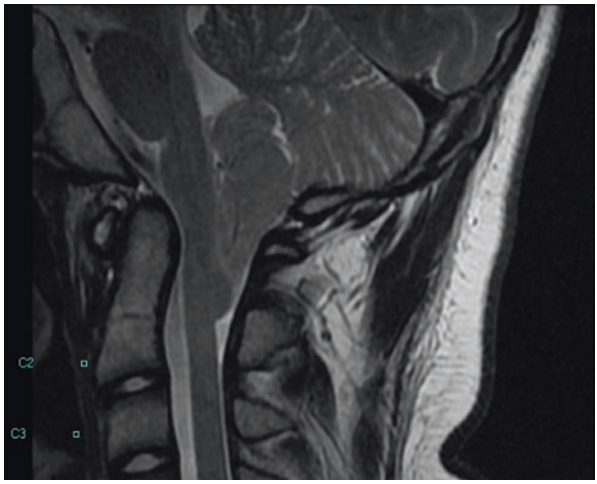


Fig. 9.1 Sagittal T2-weighted MRI scan showing findings compatible with CIM with descent of the cerebellar tonsils approximately 3 cm below the level of the foramen magnum. Normal appearance of the upper cervical spinal cord without evidence for syrinx

(crowding of the foramen magnum with tonsils in normal position), "Chiari 1.5 malformation" (caudal displacement of the brainstem and fourth ventricle through the foramen magnum), as well as "physiological" tonsillar ectopia in infants [1]. Brockmeyer and Spader [8] proposed the "Complex Chiari malformations" as a particular subgroup of pediatric patients, which features a Chiari 1.5 malformation, medullary kinking, retroflexed odontoid, abnormal clival-cervical angle, occipitalization of the atlas, basilar invagination, and syringomyelia. The widespread availability of magnetic resonance imaging (MRI) has also increased detection of CIM, with prevalence estimates reported to be around 0.77% [9]. There is also a female preponderance, with a female-to-male ratio of 3:1 [10]. According to Speer, around 215,000 individuals in the United States may be affected with CIM with or without syringomyelia [11].

The clinical spectrum of CIM can be age-related and can involve multiple aspects of the central nervous system (CNS) [3]. Occipital pressure-like headaches irradiating to the neck and shoulders are commonly seen in adults, but other associated clinical symptoms can also involve the visual system, vestibular system, lower cranial nerves, cerebellum, and sensory and motor tracts [10]. Headaches are often aggravated by Valsalva maneuvers, effort, straining, coughing and neck extension. Clinical presentation of CIM differs between infants and children over the age of 3 years [12]. Infants typically display oropharyngeal symptoms, sleep apnea, and other signs of cranial nerve dysfunction, whereas older children exhibit headaches worsened by Valsalva as well as progressive syringomyelia-related scoliosis [12, 13]. The diagnosis can often be made by correlating clinical manifestations with the radiological findings, with MRI the modality of choice for measurement of the tonsillar ectopia in relation to the McRae line drawn between the basion and opisthion [9].

Surgical intervention is the treatment of choice for symptomatic CIM, with the surgical goal being to restore normal cerebrospinal fluid (CSF) flow at the foramen magnum by anatomical expansion of this region. While posterior fossa decompression (PFD) is the treatment of choice for symptomatic CIM patients, much controversy

exists regarding specific surgical techniques needed to accomplish this goal [3]. Possible techniques include bony decompression alone, bony decompression with dural opening and duraplasty with autografts or allografts, dissection and opening of the arachnoid, cauterization and reduction of the cerebellar tonsils, syrinx management, and others [14]. While a variety of techniques have been described, an ongoing central debate exists regarding the need for duraplasty in addition to bony posterior fossa decompression for CIM. This topic has received great attention in both the pediatric and adult neurosurgical communities. Several systematic reviews and meta-analyses have attempted to address this topic, but a lack of a well-controlled randomized study has failed to establish one surgical technique as superior [14–17]. The continued ambiguity related to this topic warrants further investigation and begs the question regarding management of symptomatic CIM patients: should one perform a posterior fossa decompression with or without duraplasty?

Methods

We performed a systematic review and meta-analysis according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines [18] to analyze outcomes of CIM patients who underwent PFD with or without duraplasty. English-language clinical articles published from January 2000 to January 2018 were considered eligible. Inclusion criteria included peer-reviewed articles that compared PFD alone versus posterior fossa decompression with duraplasty (PFDD) with reported clinical outcomes and complications. Studies evaluating additional techniques or maneuvers (such as tonsillar reduction, or graft type) were excluded. Ongoing prospective trials, reviews, abstracts, expert opinions, commentaries, case series of <15 patients, and textbooks were also excluded.

The search strategy was planned along with a Johns Hopkins University Welch Medical Library Clinical Informationist, who performed the search based on the Peer Review of Electronic Search Strategies (PRESS) guidelines [19] utilizing the following databases: PubMed, Embase, Cochrane Library, CINAHL, Web of Science, Scopus, and Clinicaltrials.gov. The obtained references were imported to the Covidence platform (www.covidence.org, Melbourne, Australia), and underwent two-stage screening for study relevance by two independent reviewers (A.P. and R.I.), first by title and abstract, and then by full-text. Finally, the quality of the evidence of the articles selected was assessed by the same reviewers using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system [20], prior to data extraction.

Data extracted included the type of procedure (PFD alone vs. PFDD), age, sex, study design, the presence of a syrinx, follow-up duration, and various clinical outcomes.

All statistical analyses were performed using Comprehensive Meta-Analysis Software version 3 (Biostat, Englewood, NJ). Pooled patients from all included studies were categorized into PFD and PFDD subgroups. Next, particular outcomes were compared between both subgroups. Outcomes evaluated included clinical improvement, syringomyelia resolution, complications rate (CSF leak, aseptic meningitis,

wound infection, pseudomeningocele) and reoperation rate. Each outcome of interest was dichotomous and reported with Mantel-Haenszel (MH) odds ratios (ORs) and 95% confidence intervals (CIs). A fixed-effect model was applied and the assessment of the consistency (test of heterogeneity) of the meta-analysis was calculated using the Q and I^2-statistics. The I^2-statistic matches the actual percentage of total variation between studies that are considered to be due to real differences in event rates. I^2-values less than 25% were recognized as appropriate homogeneity for pooling, while 25–75% as moderate heterogeneity, and more than 75% as severe heterogeneity [21]. P values of <0.05 were considered statistically significant.

Results

Search Strategy and Selection Process

The PRISMA guideline (18)-based search and selection process is summarized in the flow diagram (Fig. 9.2). A total of 353 references were identified in the electronic databases listed. Twenty five were duplicates. The remaining 328 studies underwent initial screening based on the title and abstract. Two hundred and seventy three citations were excluded for lack of relevance for the aims of this study. Consequently, 55 articles underwent a full-text assessment for eligibility, with 46 of them being excluded for various reasons listed in the PRISMA workflow. Out of the 353 initial references, nine met the inclusion criteria and were included in this

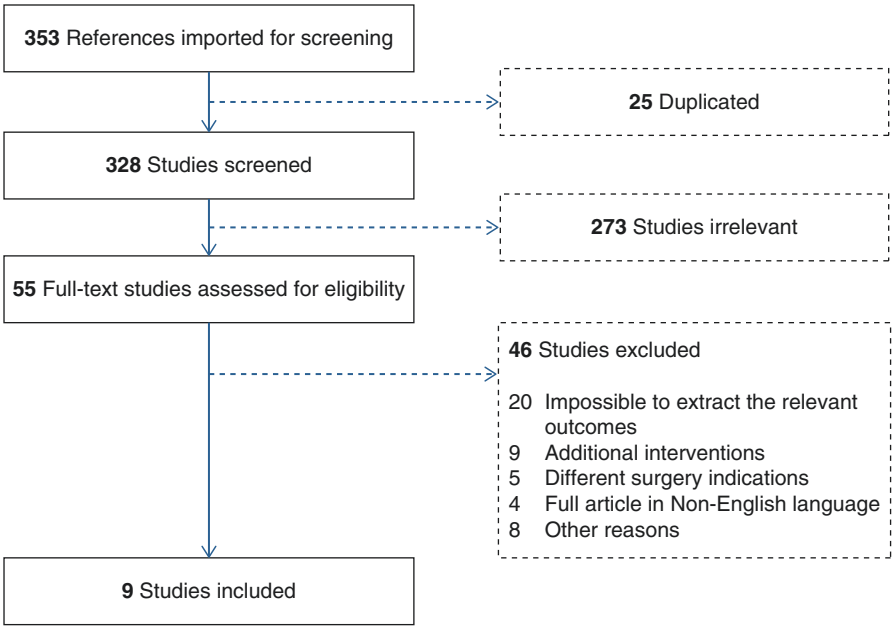


Fig. 9.2 PRISMA Diagram

meta-analysis. All references in which supplemental procedures were evaluated, such as arachnoid opening, tonsillar reduction or resection, etc.), were excluded. Studies that did not directly compare PFD to PFDD were excluded.

Characteristics of Included Studies

Of the nine studies reviewed, design types included seven retrospective studies, one prospective cohort study, and one randomized control trial (RCT). All studies presented surgical outcomes comparing both PFD and PFDD, with a total of 212 and 315 patients undergoing PFD and PFDD, respectively. Additional information, including age, gender and length of follow-up, are shown in Table 9.1.

Clinical Outcomes

Clinical Improvement

Six studies [22–24, 28–30] reported the number and proportion of patients who achieved post-operative clinical improvement in each subgroup (PFD vs. PFDD). Mutchnick et al. [27] did not report specific clinical outcomes after each type of intervention. Limonadi and Selden [26] presented outcomes with a 3-point scale and analyzed the results comparing averages. Jiang et al. [25] reported their outcomes using the Chicago Chiari Outcome Scale (CCOS) [31]. Therefore, it was not possible to homogeneously analyze post-operative clinical improvement in these three studies. Of the six studies with reported clinical improvement outcomes, 76 of 104 (73.1%) patients improved after PFD alone, and 158 of 197 (80.2%) improved following PFDD (mean difference = 1.45, 95% CI 0.82, 2.56, $p > 0.05$); heterogeneity test: $p = 0.67$, $I^2 = 0\%$ (Table 9.2A).

Syrinx Resolution

Post-operative syrinx status was reported in seven studies [23–26, 28–30]. Sixty nine of 91 (75.8%) patients in the PFD group and 125 of 135 (92.6%) in the PFDD demonstrated syrinx improvement (mean difference = 3.87, 95% CI 1.80, 8.32, $p < 0.05$); heterogeneity test: $p = 0.15$, $I^2 = 38.3\%$ (Table 9.2B).

Complications

All included studies reported post-operative complications rates [22–30]. Postoperative complications were present in 17 of 212 (8.0%) patients in PFD group, while 80 of 315 (25.4%) patients experienced complications in the PFDD group (mean difference = 3.87, 95% CI 2.21, 3.77, $p < 0.05$); heterogeneity test: $p = 0.50$, $I^2 = 0\%$ (Table 9.2C). We individually compared the following complications across study articles: CSF fistula, aseptic meningitis, wound infection and pseudomeningocele.

- *CSF fistula.* Eight articles reported post-operative CSF fistula prevalence [22–26, 28–30]. CSF leak was present in 2 of 156 (1.3%) patients undergoing PFD, and in 28 of 251 (11.2%) patients undergoing PFDD (mean difference = 4.96, 95% CI 1.95, 12.6, $p < 0.05$); heterogeneity test: $p = 0.32$, $I^2 = 14\%$ (Table 9.3A).

Table 9.1 Summary of studies included

Author	Study design	Procedure type (# patients)		Age (years)		Sex (M:F)		Postoperative hospital stay		Follow-up (years)	
		PFD	PFDD	PFD	PFDD	PFD	PFDD	PFD	PFDD	PFD	PFDD
Chen et al. [22]	Retrospective	33	70	40.7	40.6	9:24	23:47	13.06	12.97	1 month–1 year	
Erdogan et al. [23]	Retrospective	12	15	31.58	25.86	9:3	15:0	–	–	–	
Gurbuz et al. [24]	Retrospective	18	21	36		13:26		–	–	43 months	
Jiang et al. [25]	Prospective RCT	40	42	13.64	21	20:40	21:42	8.10	9.82	35.2 months	36.0 months
Limonadi and Selden [26]	Prospective cohort	12	12	7.6	10.8	7:5	6:6	3.0	3.75	15.7 months	14.8 months
Mutchnick et al. [27]	Retrospective	56	64	11.1		58:63		2.7	4	6 months	
Munshi et al. [28]	Retrospective	11	23*	38	29.6	4:7	7:14	–	–	9 months–8 years	
Romero and Pereira [29]	Retrospective	6	10	40.62		3:3	3:7	–	–	9 months–2 years	
Yilmaz et al. [30]	Retrospective	24	58	31	38.9	36:46		–	–	6 months	
Sum		212	315	–		–		–		–	

PFD posterior fossa decompression, *PFDD* posterior fossa decompression with duraplasty, *M* Male, *F* Female

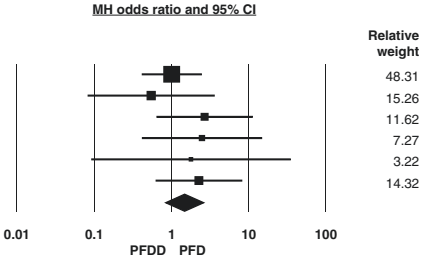
*Two of these patients initially underwent PFD (without duraplasty)

Table 9.2 Meta-analysis of clinical outcomes

A. Clinical Improvement

Author & year	MH odds ratio	Lower limit	Upper limit	Z-Value	p-Value	PFDD	PFD	Relative weight
Chen, 2017	1.014	0.412	2.499	0.031	0.975	49 / 70	23 / 33	48.31
Erdogan, 2010	0.550	0.082	3.682	-0.616	0.538	11 / 15	10 / 12	15.26
Gurbuz, 2014	2.705	0.638	11.458	1.351	0.177	17 / 21	11 / 18	11.62
Munshi, 2000	2.500	0.414	15.096	0.999	0.318	20 / 23	8 / 11	7.27
Romero, 2010	1.800	0.091	35.424	0.387	0.699	9 / 10	5 / 6	3.22
Yilmaz, 2011	2.281	0.623	8.351	1.245	0.213	52 / 58	19 / 24	14.32
	1.455	0.826	2.563	1.297	0.195			

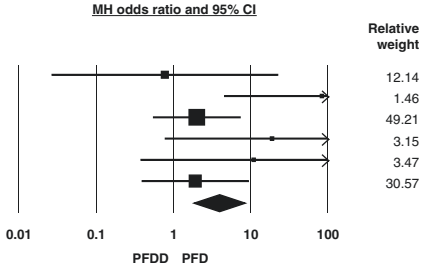
Heterogeneity: Q = 3.15, df (Q) = 5 (p = 0.67); I^2 = 0%



B. Syringomyelia Improved

Author & year	MH odds ratio	Lower limit	Upper limit	Z-Value	p-Value	PFDD	PFD	Relative weight
Erdogan, 2010	0.778	0.026	22.976	-0.145	0.884	10 / 11	4 / 4	12.14
Gurbuz, 2014	84.000	4.511	1564.257	2.970	0.003	12 / 13	1 / 8	1.46
Jiang, 2018	2.015	0.542	7.499	1.045	0.296	38 / 42	33 / 40	49.21
Munshi, 2000	19.000	0.769	469.213	1.800	0.072	9 / 9	3 / 6	3.15
Romero, 2010	11.000	0.373	324.521	1.389	0.165	5 / 5	2 / 4	3.47
Yilmaz, 2011	1.922	0.386	9.563	0.798	0.425	41 / 45	16 / 19	30.57
	3.877	1.806	8.320	3.477	0.001			

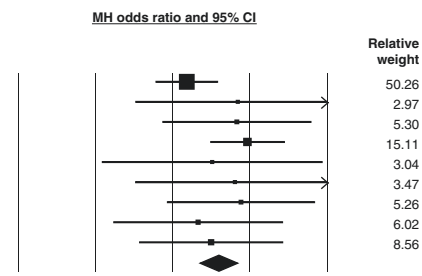
Heterogeneity: Q = 8.11, df (Q) = 5 (p = 0.15); I^2 = 38.3%



C. Complications

Author & year	MH odds ratio	Lower limit	Upper limit	Z-Value	p-Value	PDFF	PDF	Relative weight
Chen, 2017	1.529	0.598	3.913	0.886	0.376	23 / 70	8 / 33	50.26
Erdogan, 2010	7.000	0.327	150.063	1.244	0.213	3 / 15	0 / 12	2.97
Gurbuz, 2014	6.800	0.733	63.110	1.686	0.092	6 / 21	1 / 18	5.30
Jiang, 2018	9.333	3.049	28.569	3.913	0.000	24 / 42	5 / 40	15.11
Limonadi, 2004	3.261	0.120	88.347	0.702	0.483	1 / 12	0 / 12	3.04
Mutchnick, 2010	6.431	0.325	127.260	1.222	0.222	3 / 64	0 / 56	3.47
Munshi, 2000	7.692	0.840	70.457	1.805	0.071	10 / 23	1 / 11	5.26
Romero, 2010	2.143	0.169	27.103	0.589	0.556	3 / 10	1 / 6	6.02
Yilmaz, 2011	3.157	0.367	27.165	1.047	0.295	7 / 58	1 / 24	8.56
	3.874	2.214	6.777	4.745	0.000			

Heterogeneity: Q = 7.25, df (Q) = 8 (p = 0.50); I^2 = 0%



D. Reoperations

Author & year	MH odds ratio	Lower limit	Upper limit	Z-Value	p-Value	PFDD	PFD	Relative weight
Chen, 2017	0.089	0.004	1.916	-1.544	0.123	0 / 70	2 / 33	15.75
Erdogan, 2010	0.786	0.044	14.026	-0.164	0.870	1 / 15	1 / 12	4.87
Gurbuz, 2014	0.583	0.112	3.043	-0.640	0.522	3 / 21	4 / 18	17.32
Mutchnick, 2010	0.226	0.045	1.136	-1.805	0.071	2 / 64	7 / 56	33.93
Munshi, 2000	0.081	0.004	1.847	-1.576	0.115	0 / 23	2 / 11	15.31
Yilmaz, 2011	0.393	0.052	2.965	-0.906	0.365	2 / 58	2 / 24	12.82
	0.293	0.127	0.673	-2.891	0.004			

Heterogeneity: Q = 2.52, df (Q) = 5 (p = 0.77); I^2 = 0%

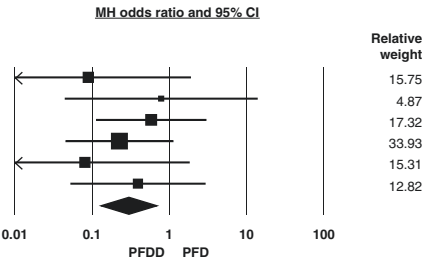
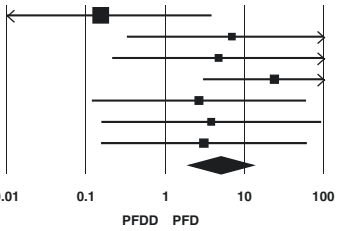


Table 9.3 Meta-analysis of complications

A. CSF fistula

Author & year	MH odds ratio	Lower limit	Upper limit	Z-Value	p-Value	PFDD	PFD	Relative weight
Chen, 2017	0.154	0.006	3.875	-1.137	0.255	0 / 70	1 / 33	38.11
Erdogan, 2010	7.000	0.327	150.063	1.244	0.213	3 / 15	0 / 12	8.16
Gurbuz, 2014	4.744	0.213	105.538	0.984	0.325	2 / 21	0 / 18	9.00
Jiang, 2018	24.000	2.997	192.172	2.994	0.003	16 / 42	1 / 40	12.00
Munshi, 2000	2.674	0.118	60.545	0.618	0.537	2 / 23	0 / 11	11.30
Romero, 2010	3.824	0.155	94.130	0.821	0.412	2 / 10	0 / 6	8.93
Yilmaz, 2011	3.090	0.154	62.133	0.737	0.461	3 / 58	0 / 24	12.50
	4.966	1.954	12.620	3.368	0.001			

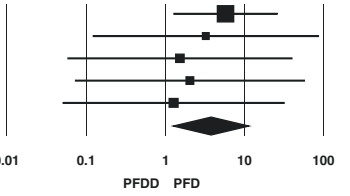
Heterogeneity: Q = 6.98, df (Q) = 6 (p = 0.32); I^2 = 14.0%



B. Aseptic meningitis

Author & year	MH odds ratio	Lower limit	Upper limit	Z-Value	p-Value	PFDD	PFD	Relative weight
Chen, 2017	5.775	1.258	26.504	2.255	0.024	19 / 70	2 / 33	46.49
Limonadi, 2004	3.261	0.120	88.347	0.702	0.483	1 / 12	0 / 12	10.38
Munshi, 2000	1.533	0.058	40.689	0.256	0.798	1 / 23	0 / 11	14.67
Romero, 2010	2.053	0.072	58.652	0.420	0.674	1 / 10	0 / 6	12.39
Yilmaz, 2011	1.278	0.050	32.487	0.149	0.882	1 / 58	0 / 24	16.07
	3.708	1.237	11.111	2.340	0.019			

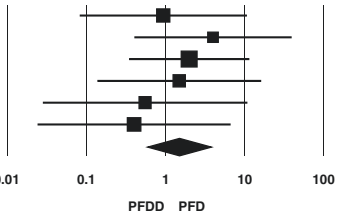
Heterogeneity: Q = 1.145, df (Q) = 4 (p = 0.88); I^2 = 0%



C. Wound infection

Author & year	MH odds ratio	Lower limit	Upper limit	Z-Value	p-Value	PFDD	PFD	Relative weight
Chen, 2017	0.941	0.082	10.765	-0.049	0.961	2 / 70	1 / 33	17.06
Gurbuz, 2014	4.000	0.404	39.583	1.185	0.236	4 / 21	1 / 18	11.27
Jiang, 2018	2.000	0.345	11.578	0.774	0.439	4 / 42	2 / 40	23.96
Munshi, 2000	1.500	0.138	16.323	0.333	0.739	3 / 23	1 / 11	15.20
Romero, 2010	0.556	0.028	10.933	-0.387	0.699	1 / 10	1 / 6	14.54
Yilmaz, 2011	0.404	0.024	6.728	-0.632	0.527	1 / 58	1 / 24	17.97
	1.472	0.584	3.710	0.819	0.413			

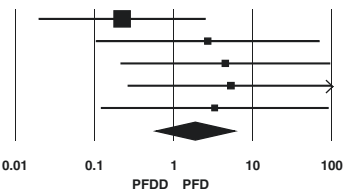
Heterogeneity: Q = 2.19, df (Q) = 5 (p = 0.82); I^2 = 0%



D. Pseudomeningocele

Author & year	MH odds ratio	Lower limit	Upper limit	Z-Value	p-Value	PFDD	PFD	Relative weight
Chen, 2017	0.225	0.020	2.571	-1.201	0.230	1 / 70	2 / 33	57.44
Gurbuz, 2014	2.707	0.104	70.647	0.598	0.550	1 / 21	0 / 18	10.72
Mutchnick, 2010	4.520	0.212	96.170	0.967	0.334	2 / 64	0 / 56	10.98
Munshi, 2000	5.308	0.261	107.814	1.086	0.277	4 / 23	0 / 11	11.61
Romero, 2010	3.316	0.120	91.601	0.708	0.479	1 / 10	0 / 10	9.26
	1.839	0.581	5.815	1.037	0.300			

Heterogeneity: Q = 3.84, df (Q) = 4 (p = 0.42); I^2 = 0%



- *Aseptic meningitis.* Five studies reported on post-operative aseptic meningitis [22, 26, 28–30]. Aseptic meningitis was observed in 2 of 86 (2.3%) patients undergoing PFD, and in 23 of 173 (13.3%) patients undergoing PFDD (mean difference = 3.70, 95% CI 1.23, 11.11, $p < 0.05$); heterogeneity test: $p = 0.88$, $I^2 = 0\%$ (Table 9.3B).
- *Wound infection.* Six studies described the proportion of patients who developed a wound infection [22, 24, 25, 28–30]. Seven of 132 (5.3%) patients who underwent PFD, and 15 of 224 (6.7%) patients who underwent PFDD experienced post-operative wound infections (mean difference = 1.47, 95% CI 0.58, 3.71, $p > 0.05$); heterogeneity test: $p = 0.82$, $I^2 = 0\%$ (Table 9.3C).
- *Pseudomeningocele*. Five studies reported the number of patients who developed post-operative pseudomeningocele [22, 24, 27–29], which was present in 2 of 128 (1.6%) patients undergoing PFD, and in 9 of 188 (4.8%) patients undergoing PFDD (mean difference = 1.83, 95% CI 0.58, 5.81, $p > 0.05$); heterogeneity test: $p = 0.42$, $I^2 = 0\%$ (Table 9.3D).

Reoperation

The reoperation rate was reported in six of nine articles [22–24, 27, 28, 30]. Across these studies, 17 of 154 (11.0%) PFD patients underwent reoperation, while 8 of 251 (3.2%) PFDD required additional surgery (mean difference = 0.29, 95% CI 0.12, 0.67, $p < 0.05$); heterogeneity test: $p = 0.77$, $I^2 = 0\%$ (Table 9.2D).

Quality Assessment (Level of Evidence)

Quality of evidence ratings were conducted based on the GRADE guidelines [20, 32–36]. The assessment of article quality was performed for each individual outcome listed above, evaluating limitations (including risk of bias) [32], inconsistency [33], indirectness [34], imprecision [35], and publication bias (Table 9.4) [36]. Given the dearth of RCTs comparing PFD and PFDD the overall quality of evidence rated low in the majority of outcomes evaluated.

Risk-Benefit Analysis of PFD Vs. PFDD

A summary of the advantages and disadvantages of PFD vs. PFDD for CIM is given in Table 9.5.

Discussion

In this report, we performed an evidence-based systematic review and meta-analysis evaluating outcomes for CIM patients undergoing PFD alone compared to PFDD. In order to most accurately compare PFD to PFDD for CIM, we conducted a wide search net to capture a high percentage of articles relevant to this topic and used stringent inclusion criteria for our subsequent meta-analysis. Based on our analysis,

Table 9.4 GRADE evidence profile

Quality assessment							Summary of findings					
							Number of patients			Absolute risk		
Outcomes	# and study design	Limitations	Inconsistency	Indirectness	Imprecision	Publication bias	PFD	PFDD	Relatively risk (95% CI)	Control risk	Risk difference (95% CI)	Quality
Clinical improvement	(6) RTP	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	76/104	158/197	1.09 (0.95–1.25)	730/1000	Not significant	(+)(+) Low
Syringomyelia improvement	(5) RTP, (1) PC, (1) RCT	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	69/91	125/135	1.22 (1.07–1.38)	758/1000	167 more per 1000 (72–270)	(+)(+) Low
Complications	(7) RTP, (1) PC, (1) RCT	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	17/212	80/315	3.16 (1.93–5.18)	80/1000	173 fewer per 1000 (110–232)	(+)(+)(+) Moderate
CSF fistula	(6) RTP, (1) PC, (1) RCT	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	2/156	28/251	8.70 (2.10–36.01)	13/1000	98 fewer per 1000 (52–144)	(+)(+)(+) (+) High
Aseptic meningitis	(4) RTP, (1) PC	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	2/86	23/173	5.71 (1.37–23.68)	23/1000	109 fewer per 1000 (38–170)	(+)(+)(+) (+) High
Wound infection	(5) RTP, (1) RCT	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	7/132	15/224	1.26 (0.52–3.01)	53/1000	Not significant	(+)(+) Low
Pseudomeningocele	(5) RTP	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	2/128	9/188	3.06 (0.67–13.94)	15/1000	Not significant	(+)(+) Low
Reoperation	(6) RTP	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	17/154	8/251	0.28 (0.12–0.65)	110/1000	78 more per 1000 (28–139)	(+)(+) Low

RTP Retrospective, *PC* prospective cohort, *RCT* randomized control trial, *PFD* posterior fossa decompression, *PFDD* posterior fossa decompression with duraplasty

Table 9.5 Risk-benefit analysis of PFD vs PFDD

	Benefits	Risks
PFD	• Similar clinical improvement rates compared with PFDD • Less invasive • Shorter hospital length of stay	• Increased reoperation rate
PFDD	• Increased syrinx resolution • Decreased reoperation rate	• Increased risk of CSF leak and aseptic meningitis

PFD posterior fossa decompression only, *PFDD* posterior fossa decompression with duraplasty, *CSF* cerebrospinal fluid

no clear-cut determination can be made regarding the superiority of one technique over the other. Our investigation suggests that there are particular benefits and shortcomings associated with PFD as well as PFDD, which should be taken into consideration when choosing to offer a patient one procedure over the other.

Outcomes

We compared the outcomes of patients undergoing PFD vs. PFDD with particular attention to four specific features: clinical improvement, syrinx regression, complications, and reoperation rate.

Clinical improvement was not statistically significant between PFD and PFDD (RR = 1.09, 95% CI 0.95, 1.25). All articles included were observational studies and of the three studies excluded for this measurement, two reported the clinical response using a separate scoring system that did not permit homogeneous comparison. The typical measurement of clinical outcome is with a post-operative scale with three possible outcomes: improved, unchanged or worsened. Limonadi and Selden [26] adapted this scale to include an additional category as follows: Resolved, 2; improved, 1; unchanged, 0; and worsened, −1. Then, a score is assigned to each of the three principal presenting clinical findings and an average is calculated across them. On the other hand, Jiang et al. [25] assessed the clinical outcome using the CCOS, which also uses a four-point scoring system for four separate postoperative categories: pain symptoms, non-pain symptoms, functionality, and complications. The CCOS allows a more consistent scoring system for clinical outcomes in CIM surgery, but it has not yet been widely adopted. Notably, however, neither of these excluded studies demonstrated a significant difference in clinical improvement between PFD and PFDD groups, consistent with the rest of our analysis.

We found that syringomyelia regression or improvement was significantly better in the PFDD group (RR = 1.22, 95% CI 1.07, 1.38). The true effect of the addition of a duraplasty in syringomyelia regression is difficult to determine and will hopefully be addressed by ongoing prospective, randomized trials. However, it has been suggested that PFDD provides increased expansion of the posterior fossa and allows for better restoration of CSF flow at the craniocervical junction [28]. In fact, some authors consider the presence of syringomyelia as strict criteria to perform duraplasty in addition to PFD alone [26, 27]. Nonetheless, syrinx regression occurs in some CIM patients after PFD alone, which warrants further investigation of this topic in prospective randomized trials. In addition to the presence of a syrinx, the degree of tonsillar herniation can also

affect CSF flow dynamics at the foramen magnum and has also been a contributing factor in the decision to perform PFDD opposed to PFD alone. In a retrospective study of 82 CIM patients, Yilmaz et al. [30] stratified patients preoperatively using a three-tier system according to the degree of tonsillar descent. Grade 1 patients are defined as having tonsillar descent more than 5 mm below the foramen magnum, grade 2 with tonsillar descent reaching the C1 arch, and grade 3 with tonsillar descent is beyond the C1 arch. The authors reported a decrease in syrinx size and clinical improvement in grade 3 patients undergoing PFDD compared to PFD. On the other hand, grades 1 and 2 did not show significant differences between the two procedures.

A higher rate of complications, especially CSF-related, has been reported in PFDD over PFD [14, 15]. In our study, we discovered a similarly higher complication rate in patients undergoing PFDD compared with PFD alone (RR = 3.16, 95% CI 1.93, 5.18). After more detailed evaluation of specific post-operative complications, we found that both CSF fistula (RR = 8.70, 95% CI 2.10, 36.01) and aseptic meningitis (RR = 5.71, 95% CI 1.37, 23.68) were significantly higher in PFDD patients, while wound infection (RR = 1.26, 95% CI 0.52–3.01) and pseudomeningocele (RR = 3.06, 95% CI 0.67, 13.94) were not significantly different. In a systematic review, Zhao et al. [14] compared the outcomes of different surgical techniques for CIM. Similar to the result of our analysis, they reported aseptic meningitis and CSF leak as predominant complications across all patients. These complications occurred with less frequency in their PFD alone group, although clinical improvement was significantly better with PFDD. Though we did not specifically address tonsillar reduction in this study, it is worth also mentioning that Zhao and colleagues found that the addition of tonsillar resection resulted in the highest complication rate amongst all surgical techniques.

The difference in the reoperation rate in favor of PFDD was another intriguing finding in this meta-analysis. Patients undergoing PFD alone had a higher risk to be reoperated on (RR = 0.28, 95% CI 0.12, 0.65), although the quality of available evidence regarding this topic was low. In PFD patients who underwent reoperation (17/154, 11%), the indications for repeat intervention were primarily related to a lack of resolution of clinical symptoms and syringomyelia. In the PFDD patients undergoing reoperation (8/251, 3.2%), five required additional decompression for the persistence of symptoms, while three required surgical repair of a CSF fistula. These results differ from a retrospective study by Shweikeh et al. [37], in which a higher reoperation rate was found in children with CIM who underwent PFDD, mainly due to post-operative CSF fistula formation. However, it should be noted that Shweikeh et al. [37] evaluated a specific subset of patients by using the national Kids' Inpatient Database (KID) with an average patient age of 10.3 years, and reported reoperations were principally related to early post-operative (procedure-related) complications rather than reoperations for failed symptom resolution at long-term follow-up. Further, this difference could be accounted for by heterogeneity in the PFDD population with respect to intradural work performed, as some patients underwent tonsillar reduction while others did not.

Implications for Clinical Practice

PFD vs. PFDD for CIM patients is an ongoing debate in the neurosurgical community. Here, we discovered that there was no significant difference in outcome with

respect to post-operative clinical improvement, rate of wound infection, or pseudomeningocele occurrence between PFD and PFDD subgroups. Although the clinical response was similar between the groups, the rate of syrinx regression was higher in patients undergoing PFDD compared to PFD alone. And while the reoperation rate was higher in the PFD alone subgroup, complications as a whole, including CSF fistula and aseptic meningitis, were more frequent in patients undergoing PFDD.

It is clear from this analysis that no singular technique can be labeled superior for CIM patients. Hence, clinicians must weigh the risks and benefits of each procedure when making a decision to perform PFD or PFDD for CIM. PFD carries some advantages as a less invasive procedure with a lower complication rate. However, there is a higher probability that a repeat operation will be necessary for patients undergoing PFD alone. PFDD results in an increased probability of syrinx regression from our analysis. It would seem reasonable to perform PFDD in patients with syringomyelia, as well as a high degree of tonsillar herniation. However, threshold criteria for syrinx size and extent of tonsillar ectopia are not well understood and the fact that syrinx resolution occurs in some patients undergoing PFD alone indicates that further investigation is necessary with regards to this topic.

Conclusion

Overall, we determined from this meta-analysis that PFD and PFDD are both generally well tolerated, with some differences in the risks and benefits between these subgroups of patients. Clinicians evaluating CIM patients for surgery must take into account their clinical presentation, comorbidities, age, presence of a syrinx, extent of tonsillar descent, as well as patient/family preference before choosing one intervention over the other. Further, outcomes with respect to related topics such as graft choice, tonsillar cauterization, and arachnoid opening will require further investigation. Ongoing prospective randomized clinical trials are likely to help address some of these questions and shed more light on this controversial topic.

Box

1. What is known?
   PFD is associated with a higher rate of reoperation, while PFDD carries a higher risk of complications.
2. What is new?
   PFD and PFDD for CIM result in similar clinical outcomes, with certain drawbacks associated with each surgical option. The surgical procedure offered should be based on an individualized evaluation with each patient.
3. What are the consequences for clinical practice?
   It may be reasonable to offer PFD alone for CIM patients without syringomyelia or with less degree of tonsillar herniation, while PFDD may be more appropriate for patients with large degrees of tonsillar ectopia and moderate to severe syringomyelia.

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RETRACTED CHAPTER: Craniosynostosis: Endoscopically Versus Open Treatment

10

Hans Delye

Retraction Note to: Chapter "Craniosynostosis: Endoscopically Versus Open Treatment" in Hans Delye (ed.), Evidence for Neurosurgery https://doi.org/10.1007/978-3-030-16323-5_10

The author has retracted this chapter [1] because it contains material that has not been authorised for use. It is based on, and parts of it were translated from, the Dutch 'Richtlijn Behandeling en zorg voor craniosynostose 2019' (Draft Guideline for Care of Patients with the Diagnoses of Craniosynostosis, to be published by the NVPC, Netherlands Society for Plastic Surgery), Chapter 5: Chirurgische behandeling van unisuturale, niet-syndromale craniosynostose (pp 65–82), authored by Irene Mathijssen, Marie-Lise van Veelen and Hans Delye.

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Posterior Decompression for Cervical Spondylotic Myelopathy: Laminectomy, Laminectomy and Fusion or Laminoplasty

11

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Introduction

Degenerative cervical myelopathy (DCM) represents a spectrum of chronic atraumatic spinal cord injury that occurs secondary to compression from disc spondylosis, hypertrophy of the ligamentum flavum, or ossification of the posterior longitudinal ligament (OPLL), etc. [1]. While surgical management has been shown to arrest the progressive deterioration and provide neurological and functional improvement, the selection of surgical procedures pertaining to specific cases is subject to much controversy [2–4]. While the subject of anterior versus posterior spinal decompression has been repeatedly debated amongst the experts, this chapter

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will focus on posterior surgical options and anterior alternatives will not be further elaborated.

The posterior cervical decompression techniques have a long track record of success in halting the progression of DCM. Prior to the introduction of cervical instrumentation strategies, posterior cervical laminectomies (LA) were a common procedure utilized to treat multilevel compressions [5–7]. Although initially found to be clinically effective, the development of late neurological deterioration secondary to post-operative instability and kyphosis [8–11] has led to the drive for alternative procedures. Since its introduction, laminectomy and instrumented fusion (LF) has been gaining popularity among the options in cervical decompression procedures [12–15]. In the modern era, the use of lateral mass screws and titanium rods allowed us to move away from wiring and plating of the cervical spine and to increase the safety of these procedures [16–20]. However, despite the advantages, the added stability with instrumentation comes at a cost of significant loss of mobility and range of motion (ROM) in the cervical spine [21–23].

The cervical laminoplasty (LA) procedure was designed to increase the overall spinal canal diameter by partial opening and elevating the laminae while keeping the posterior elements intact [24]. While a number of techniques have been described in the literature, they are largely the variations of two common procedures known as the "open-door" and the "French door" [25–28]. Although the posterior elements are preserved in these surgeries, post-laminoplasty kyphosis has been described in the literature [29–33]. Therefore, it is generally not the surgical procedure of choice when severe preoperative kyphotic deformity is present. Additionally, since the procedure itself avoids fusion, the benefit of relative preservation of motion comes at a cost of postoperative neck pain [34, 35].

Furthermore, the drive to preserve motion and prevent instability while achieving adequate decompression in the cervical spine has let to the development of a minimally-invasive, mucle-preserving posterior approach utilized in skip laminectomy (sLA), where only selective laminectomies are performed. Since this technique was introduced by Shiraishi et al. in 1998, it has shown promising results as a non-instrumented alternative for posterior decompression [36–38].

Nowadays, it is generally accepted that a fusion procedure should accompany any cervical decompression in the presence of kyphotic deformity [5, 39]. However, controversy exists as to the optimal procedure for DCM in a lordotic cervical spine. The goal of this chapter is to systematically review and summarize the evidence in the literature on the comparative efficacy and safety of the common posterior cervical spine procedures.

Material and Methods

Generation of Key Questions

Key questions were formulated to address important clinical inquiries: (Q1) What is the efficacy of LA or sLA compared to LF based on clinically important changes in neurological and functional status? (Q2) What is the efficacy of LP compared to LA

or sLA based on clinically important changes in neurological and functional status? (Q3) What is the efficacy of LF compared with LP based on clinically important changes in neurological and functional status? (Q4) What is the safety profile of LA or sLA compared to LF? (Q5) What is the safety profile of LP compared to LA or sLA? (Q6) What is the safety profile of LF compared to LP?

Electronic Literature Search

The literature search was performed by an experienced librarian using Ovid MEDLINE, Embase, and Cochrane library databases. To ensure high sensitivities in our systematic review, appropriate search concepts were developed with relevant subject headings complimented by text word searches of titles and abstracts using relevant MeSH terms and synonyms. Appropriate truncations, adjacent operators, parentheses and Boolean operators were employed to ensure the inclusiveness as well as the precision of the search.

For the purpose of this chapter, only English language articles published after January 2000 were included. For inclusion into the review, articles must include adult human patients (age >18), diagnosed with DCM, surgically treated with either LP, LA, sLA, or LF. Studies must have a clear reporting of neurological and/or functional outcomes both preoperatively and postoperatively or describe the spectrum and incidence of complications. In order to present the highest quality of evidence in the literature, the selection was further limited to only randomized control trials (RCT) and comparative studies with $\geq$10 patients in each treatment group.

Two authors independently screened titles and abstracts for relevant articles pertaining to the scope of this chapter. Full manuscripts of the selected articles subsequently underwent extensive review by the same authors. When conflicting opinion on the inclusion and exclusion of articles arose, the issues were either resolved by discussion, or when necessary, the advice from a third author was sought. For each article selected, the references list was carefully reviewed for additional relevant articles to include.

Data Extraction

An exhaustive assessment of outcome scores was attempted to address Q1–3 in this review, but the overall paucity of generalized reporting algorithms hindered this effort. Therefore, owing to their relatively consistent appearance across studies, the Japanese Orthopaedic Association (JOA) and the modified JOA (mJOA) Score for the Assessment of Cervical Myelopathy along with the Neck Disability Index (NDI) were selected as the primary measures of neurological and functional outcomes. The Visual Analogue Scale (VAS), Ishihara's cervical curvature index [40], and neck range of motion (ROM) were included as secondary outcomes. For Q4–5, the spectrum and incidence of key intraoperative and postoperative complications of each procedure were evaluated.

Evaluation of Level of Evidence and Strength of Literature

Gradings of the level of evidence were independently performed by two authors for each published article based on the criteria suggested by the *Journal of Bone & Joint Surgery* and Agency for Healthcare Research and Quality (AHRQ) [41, 42]. The overall strength of evidence for each outcome of interest was determined based on the recommendations by Grading of Recommendation Assessment, Development and Evaluation Working Group [43–46] and the AHRQ [42].

Data Analysis

For Q1–3, in order to compare the clinical effectiveness of the procedures, the difference in means, standardized mean difference (SMD), and 95% confidence interval (CI) between the treatment groups were calculated based on the preoperative and postoperative data reported in the manuscript. Missing data were input using methods proposed by the Cochrane Handbook for Systematic Reviews of Intervention [47]. To address the effectiveness of an intervention, the suggested measure by Cohen [48] was used whereby an effect size of 0.2 is considered as "small", 0.5 as "medium" and ≥0.8 as "large". For Q4–5, the spectrum and incidence of complications were extracted from the studies. For each complication, relative risk or risk ratio (RR) and 95% CI were calculated. Statistical calculations were performed using the Comprehensive Meta Analysis Version 3.3.070 (Biostat, Inc. Englewood, NJ, USA) [49].

Results

The literature search resulted in 6344 articles after removal of duplications. Through exclusion based on title, abstract, and year of publication, 178 articles remained for full manuscript review. Electronic manuscripts were obtained, and careful review of the articles was performed. By applying our inclusion and exclusion criteria, 16 articles were finally selected for the systematic review plus three additional articles that were found through screening of the reference lists (Fig. 11.1). A total of two articles were found that addressed Q1 [50, 51], six articles addressing Q2 [36, 37, 50–53], 12 articles for Q3 [21–23, 50, 51, 54–60], two articles for Q4 [51, 61], four articles for Q5 [36, 37, 51, 62] and 11 articles for Q6 [21–23, 51, 54–56, 58–60, 63]. The list of all included articles as well as their level of evidence are presented in Table 11.1.

For Q1 and 2, due to the limited number of studies identified through the literature that specifically addressed these questions, a qualitative review is presented in this chapter. The summary of reported outcome scores, imputed values, calculated SMD and 95% CI for each comparison are presented in Table 11.2. For Q3, although an adequate number of articles were identified, due to high heterogeneity of the studies, the pooling of the data for meta-analysis

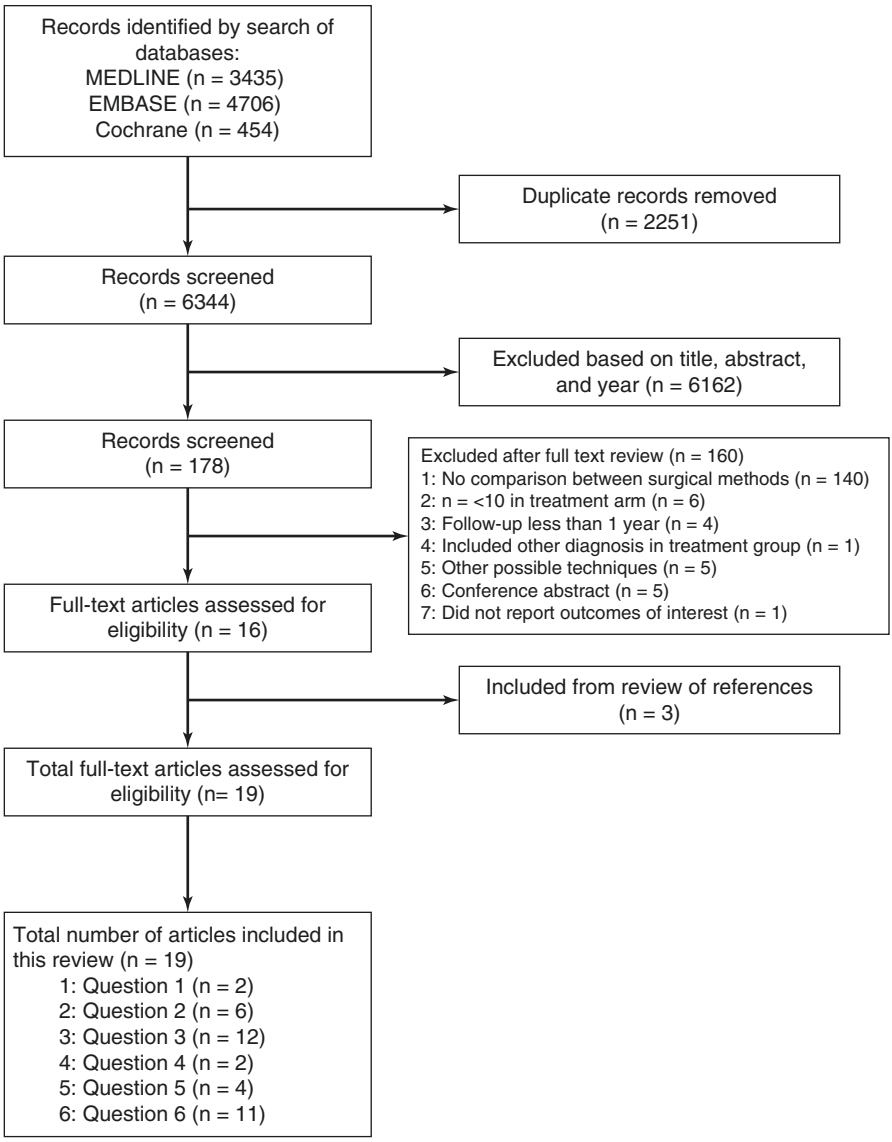


Fig. 11.1 Flowchart of literature search

was not performed. The calculated SMD and 95% CI for each outcome are presented in the form of forest plots (Fig. 11.2). For Q4 and 5, qualitative review of the literature is presented due to the limited number of studies. Results of calculated RR and 95% CI are summarized in Table 11.3. Finally, for Q6, due to the larger number of studies, a forest plot was used to present the summarized results (Fig. 11.3).

Table 11.1 Summary of the level of evidence for included studies

Author	Design	Randomization sequence generation[a]	Concealment of allocation[a]	Intention to treat analysis[a]	Blinding independent assessment	Co-intervention applied equally	Follow up (>80%)	Adequate Sample size	Controlling of confounders	Class of evidence	Risk of bias
Blizzard et al. [21]	Retrospective cohort							•	•	III	Moderately high
Chang et al. [52]	Prospective cohort							•	•	III	Moderately high
Della Pepa et al. [62]	Retrospective cohort							•		III	Moderately high
Du et al. [50]	Retrospective cohort							•	•	III	Moderately high
Fehlings et al. [54]	Prospective cohort					•		•	•	II	Moderately low
Heller et al. [22]	Retrospective cohort							•	•	III	Moderately high
Highsmith et al. [55]	Retrospective cohort							•	•	III	Moderately high
Lau et al. [56]	Retrospective cohort							•	•	III	Moderately high
Lee et al. [63]	Retrospective cohort							•	•	III	Moderately high
Lee et al. [51]	Retrospective cohort							•	•	III	Moderately high
Miyamoto et al. [57]	Retrospective cohort							•	•	III	Moderately high
Nurboja et al. [52]	Retrospective cohort							•		III	Moderately high

Shirashi et al. [36]	Prospective cohort						•	•	•	III	Moderately high
Stephens et al. [58]	Retrospective cohort							•	•	III	Moderately high
Woods et al [59]	Retrospective cohort					•	•	•	•	II	Moderately low
Yang et al. [23]	Retrospective cohort						•	•		III	Moderately high
Yehya et al. [61]	Randomized controlled trial	•						•	•	II	Moderately Low
Yuan et al. [60]	Prospective cohort							•	•	III	Moderately high
Yukawa et al. [37]	Randomized controlled trial						•	•	•	II	Moderately low

[a]Criteria applies only to randomized control trials

Table 11.2 Summary outcomes of laminectomy vs. laminectomy and fusion, laminoplasty vs. laminectomy, laminoplasty vs. selective/skip laminectomy

	Preoperative (mean ± SD)	Postoperative (mean ± SD)	Difference in score	Preoperative (mean ± SD)	Postoperative (mean ± SD)	Difference in score	Difference in mean	Standard mean difference	95% confidence interval	
									Lower limit	Upper limit
	Laminectomy			Laminectomy and fusion						
JOA/mJOA scores										
Du et al. [50]	n = 30, mean follow up 9.4 years (range 7.6–11.7)			n = 32, mean follow up 8.9 years (range 7.2–11.5)			−1.18	−0.92	−1.44	−0.40
	8.10 ± 1.18	13.07 ± 1.23	4.97	8.16 ± 1.11	14.31 ± 1.33	6.15				
NDI score										
Lee et al. [51][a]	n = 15, follow up >24 months			n = 21, follow up >24 months			−2.60	−0.30	−0.96	0.37
	18.30 ± 14.70	16.80 ± 3.10	1.50	17.90 ± 12.90	13.80 ± 11.20	4.10				
Ishihara index										
Du et al. [50]	n = 30, mean follow up 9.4 years (range 7.6–11.7)			n = 32, mean follow up 8.9 years (range 7.2–11.5)			−2.00	−0.35	−0.85	0.15
	16.10 ± 5.10	12.90 ± 6.10	−3.20	15.30 ± 4.70	14.10 ± 5.30	−1.20				
Lee et al. [51][a]	n = 15, follow up >24 months			n = 21, follow up >24 months			−0.90	−0.087	−0.75	0.58
	11.70 ± 8.80	7.70 ± 12.00	−4.00	8.40 ± 8.30	5.30 ± 8.90	−3.10				
VAS-neck										
Lee et al. [51][a]	n = 15, follow up >24 months			n = 21, follow up >24 months			0.20	0.091	−0.57	0.75
	2.80 ± 2.80	1.70 ± 1.70	1.10	2.90 ± 3.30	2.00 ± 2.50	0.90				
	Laminoplasty			*Laminectomy*						
JOA/mJOA scores										
Du et al. [50]	n = 36, mean follow up 9.2 years (range 7.3–11.4)			n = 30, mean follow up 9.4 years (range 7.6–11.7)			0.92	0.73	0.23	1.23
	8.08 ± 1.13	13.97 ± 1.28	5.89	8.10 ± 1.18	13.07 ± 1.23	4.97				

NDI score										
Lee et al. [51][a]	n = 21, follow up >24 months			n = 15, follow up >24 months			2.00	0.30	−0.37	0.96
	12.30 ± 5.60	8.80 ± 8.40	3.5	18.30 ± 14.70	16.80 ± 3.10	1.50				
Ishihara index										
Du et al. [50]	n = 36, mean follow up 9.2 years (range 7.3–11.4)			n = 30, mean follow up 9.4 years (7.6–11.7)			0.60	0.11	−0.37	0.60
	15.80 ± 4.30	13.20 ± 4.60	−2.60	16.10 ± 5.10	12.90 ± 6.10	−3.2				
Lee et al. [51][a]	n = 21, follow up >24 months			n = 15, follow up >24 months			−1.20	−0.13	−0.80	0.53
	10.90 ± 6.50	5.70 ± 6.40	−5.20	11.70 ± 8.80	7.70 ± 12.00	−4.00				
Nurboja et al. [52]	n = 75, mean follow up 96 months ±44			n = 34, mean follow up 58 months ±51			−0.3	−0.04	−0.45	0.36
	6.70 ± 12.20	0.70 ± 5.50[b]	−6.00	7.60 ± 16.80	1.90 ± 9.05[b]	−5.70				
VAS-neck										
Lee et al. [51][a]	n = 21, follow up >24 months			n = 15, follow up >24 months			−0.40	−0.17	−0.83	0.50
	3.40 ± 3.50	2.70 ± 2.80	0.70	2.80 ± 2.80	1.70 ± 1.70	1.10				
Nurboja et al. [52]	n = 48, mean follow up 96 months ±44			n = 33, mean follow up 58 months ±51			0.00	0.00	−0.44	0.44
	1.00 ± 5.00	1.00 ± 2.80[b]	0.00	2.00 ± 6.50	2.00 ± 1.70[b]	0.00				
	Laminoplasty			*Selective/skip laminectomy*						
JOA/mJOA scores										
Yukawa et al. [37]	n = 21, mean follow up 28 months ±10.1			n = 20, mean follow up 28 months ±10.1			−0.2	NA	NA	NA
	11.1 ± NR	14.4 ± NR	3.3	10.1 ± NR	13.6 ± NR	3.5				
NDI score										
Chang et al. [52]	n = 35, mean follow up 18.4 months ±6.9			n = 32, mean follow up 18.4 months ±6.9			0.60	0.10	−0.38	0.58
	17.90 ± 10.70	13.80 ± 4.10	4.10	18.30 ± 6.60	14.80 ± 7.40	3.50				

(continued)

Table 11.2 (continued)

	Preoperative (mean ± SD)	Postoperative (mean ± SD)	Difference in score	Preoperative (mean ± SD)	Postoperative (mean ± SD)	Difference in score	Difference in mean	Standard mean difference	95% confidence interval	
									Lower limit	Upper limit
	Laminectomy			Laminectomy and fusion						
Ishihara index										
Shiraishi et al. [36]	n = 51, mean follow up 43 months (range 24–66)			n = 43, mean follow up 30 months (range 24–41)			−5.9	NA	NA	NA
	16.0 ± NR	11.8 ± NR	−4.2	11.4 ± NR	13.1 ± NR	1.7				
VAS neck										
Chang et al. [52]	n = 35, mean follow up 18.4 months ±6.9			n = 32, mean follow up 18.4 months ±6.9			−0.40	−0.21	−0.69	0.28
	3.40 ± 2.30	2.70 ± 1.90	0.70	2.80 ± 2.50	1.70 ± 2.00	1.10				
ROM outcome										
Chang et al. [52]	n = 35, mean follow up 18.4 months ±6.9			n = 32, mean follow up 18.4 months ±6.9			8.10	0.89	0.39	1.39
	17.04 ± 9.19	15.05 ± 9.60	−1.99	20.00 ± 10.76	9.91 ± 8.54	−10.09				
Yukawa et al. [37]	n = 21, mean follow up 28.1 months ±10.1			n = 20, mean follow up 28.1 months ±10.1			−7.00	−0.71	−1.34	−0.08
	49.00 ± 10.70	35.80 ± 10.20	−13.20	43.40 ± 10.40	37.20 ± 9.50	−6.20				

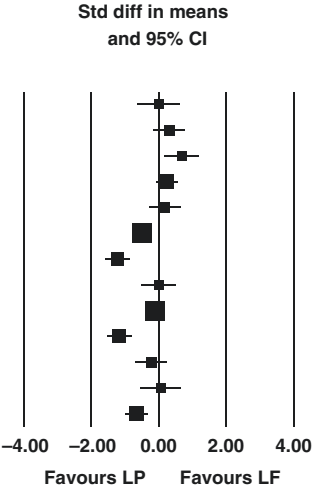
SD Standard deviation, *NR* Not reported, *NA* Not applicable

[a]Lee et al. [51]

[b]Missing standard deviation imputed based on methods recommended by Cochrane Handbook for Systematic Review

a

Study name	Outcome	Std diff in means	Lower limit	Upper limit
Yuan et al 2015	JOA	0.000	–0.637	0.637
Blizzard et al 2017	JOA	0.310	–0.159	0.779
Myiamoto et al 2014	JOA	0.683	0.162	1.203
Yang et al 2013	JOA	0.237	–0.095	0.569
Du et al 2013	JOA	0.199	–0.278	0.677
Fehlings et al 2017	mJOA	–0.492	–0.744	–0.240
Stephens et al 2017	mJOA	–1.231	–1.605	–0.856
Highsmith et al 2017	mJOA	0.000	–0.525	0.525
Fehlings et al 2017	NDI	–0.119	–0.367	0.129
Stephens et al 2017	NDI	–1.165	–1.536	–0.793
Blizzard et al 2017	NDI	–0.216	–0.684	0.251
Lee et al 2016	NDI	0.061	–0.544	0.666
Yang et al 2013	NDI	–0.655	–0.995	–0.316



b

Study name	Outcome	Std diff in means	Lower limit	Upper limit
Lee et al 2016	Ishihara Index	0.271	–0.337	0.879
Yang et al 2013	Ishihara Index	–0.083	–0.414	0.248
Du et al 2013	Ishihara Index	0.283	–0.195	0.762
Heller et al 2001	ROM	–1.559	–2.436	–0.681
Blizzard et al 2017	ROM	–2.193	–2.781	–1.605
Yang et al 2013	ROM	–2.521	–2.964	–2.079
Lau et al 2017	VAS Neck	0.435	0.077	0.792
Highsmith et al 2017	VAS Neck	1.217	0.645	1.788
Stephens et al 2017	VAS Neck	0.732	0.377	1.088
Blizzard et al 2017	VAS Neck	0.270	–0.199	0.738
Lee et al 2016	VAS Neck	0.075	–0.530	0.680
Yang et al 2013	VAS Neck	–1.050	–1.403	–0.698

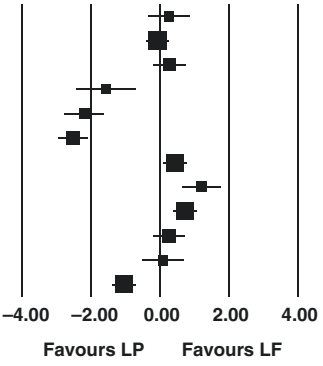
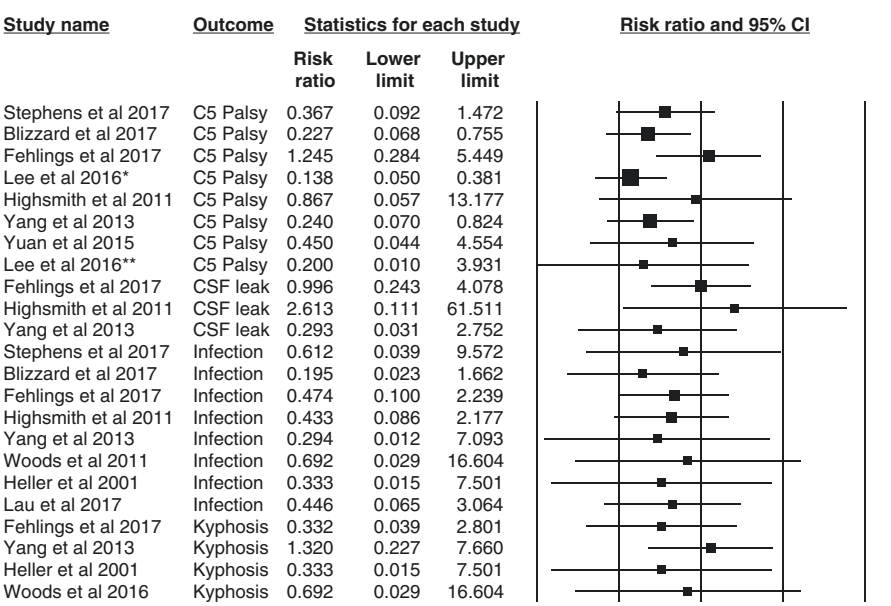


Fig. 11.2 (**a**) Summary of standardized mean difference comparing the improvements of neurological and functional outcomes as measured by JOA/mJOA and NDI achieved through laminoplasty and laminectomy and fusion as reported by individual studies. (**b**) Compiled summary of standardized mean differences of secondary outcomes achieved by laminoplasty and laminectomy and fusion as reported by individual studies

Table 11.3 Summary of studies reporting complications of laminectomy vs. laminectomy and fusion, laminoplasty vs. laminectomy, laminoplasty vs. selective/skip laminectomy, and laminoplasty vs. laminectomy and fusion

	Dural tear/CSF leak	C5 palsy	Infection	Kyphosis	Dural tear/CSF leak	C5 palsy	Infection	Kyphosis
	Laminectomy				Laminectomy and fusion			
Lee et al. [51][a]	NR	0/15 (0%)	NR	NR	NR	2/21 (9.52%)	NR	NR
Yehya [61]	1/30 (3.33%)	NR	2/30 (6.67%)	NR	2/32 (6.25%)	NR	3/32 (9.38%)	NR
	Laminoplasty				*Laminectomy*			
Della Pepa et al. [62]	0/33 (0.0%)	NR	0/33 (0%)	0/33 (0%)	0/24 (0%)	NR	0/24 (0%)	3/24 (12.5%)
Lee et al. [51][a]	NR	0/21 (0%)	NR	NR	NR	0/15 (0%)	NR	NR
	Laminoplasty				*Selective laminectomy*			
Shiraishi et al. [36]	0/51 (0.0%)	3/51 (5.88%)	NR	NR	2/43 (4.7%)	0/43 (0%)	NR	NR
Yukawa et al. [37]	NR	0/21 (0%)	0/21 (0%)	NR	NR	0/20 (0%)	0/20 (0%)	NR
	Laminoplasty				*Laminectomy and fusion*			
Blizzard et al. [21]	NR	3/41 (7.31%)	1/41 (2.43%)	NR	NR	10/31 (32.25%)	4/31 (12.9%)	NR
Fehlings et al. [67]	3/100 (3.0%)	3/100 (3%)	2/100 (2%)	1/100 (1%)	5/166 (3.0%)	4/166 (2.41%)	7/166 (4.21%)	5/166 (3%)
Heller et al. [22]	NR	NR	0/13 (0%)	0/13 (0%)	NR	NR	1/13 (7.69%)	1/13 (7.69%)
Highsmith et al. [55]	1/30 (1.3%)	1/30 (3.33%)	2/30 (6.67%)	NR	0/26 (0.0%)	1/26 (3.85%)	4/26 (15.38%)	NR
Lau et al. [56]	NR	NR	2/101 (1.98%)	NR	NR	NR	2/45 (4.44%)	NR
Lee et al. [51][a]	NR	0/21 (0%)	NR	NR	NR	2/21 (9.52%)	NR	NR
Lee et al. [63][b]	NR	4/100 (4%)	NR	NR	NR	26/90 (28.89%)	NR	NR
Stephens et al. [58]	NR	3/85 (3.53%)	1/85 (1.18%)	NR	NR	5/52 (9.62%)	1/52 (1.92%)	NR
Woods et al. [59]	NR	NR	0/39 (0%)	0/39 (0%)	NR	NR	1/82 (1.22%)	1/82 (1.22%)
Yang et al. [23]	1/75 (1.33%)	3/75 (4%)	0/75 (0%)	3/75 (4%)	3/66 (4.55%)	11/66 (16.67%)	1/66 (1.52%)	2/66 (3.03%)
Yuan et al. [60]	NR	1/20 (5%)	NR	NR	NR	2/18 (11.11%)	NR	NR

[a]Lee et al. [51]
[b]Lee et al. [63]



*Lee CH, Jahng TA, Hyun SJ, Kim KJ, Kim HJ. Expansive laminoplasty versus laminectomy alone versus laminectomy and fusion for cervical ossification of the posterior longitudinal ligament. Journal of Spinal Disorders and Techniques. 2016;29(1):E9-E15
**Lee SH, Suk KS, Kang KC, Cho SW, Juh HS, Lee JH, et al. Outcomes and Related Factors of C5 Palsy Following Cervical Laminectomy With Instrumented Fusion Compared With Laminoplasty. Spine. 2016;41(10):E574-9.

Fig. 11.3 Summary of risk ratios comparing rates of complications between laminoplasty and laminectomy and fusion

What Is the Efficacy of LA or sLA Compared to LF Based on Clinically Important Changes in Neurological and Functional Status?

Comparison of LA versus LF was found in two retrospective comparative studies and no studies were found comparing sLA to LF (Table 11.2). Only one identified study compared the neurological recovery between the two procedures. Du et al. [50] reported significant JOA improvement in both the LA (n = 30) and LF (n = 32) treatment groups, with a statistically significant difference in recovery in favor of LF. In terms of functional recovery, one of the studies compared NDI recovery in patients with cervical myelopathy secondary to OPLL treated with either LA (n = 15) or LF (n = 21) [51]. In this study, Lee et al. [51] noted that patients in both treatment groups demonstrated substantial improvement in the NDI score, and the degree of recovery was not significantly different between the groups.

In terms of the secondary outcomes, a single study by Lee et al. [51] found no significant difference in the postoperative improvement in the VAS-neck score between LA and LF. The cervical curvature was assessed by both studies using the Ishihara Index [50, 51]. Their conclusions, however, were inconsistent with Du et al. [50] reporting significantly more loss of cervical lordosis after LA, while Lee

et al. [51] reported an equivocal decrease over time with both procedures. Interestingly in the latter study, a lower mean preoperative Ishihara Index was noted in the LF group, demonstrating the authors' predilection for fusion in patients with less cervical lordosis [51].

None of the studies reported on postoperative ROM changes.

What Is the Efficacy of LP Compared to LA or sLA Based on Clinically Important Changes in Neurological and Functional Status?

LP Versus LA

Three retrospective studies compared clinical outcomes between patients treated with LP and LA (Table 11.2). Du et al. [50] reported significant improvements in postoperative JOA score with both LP (n = 36) and LA (n = 30), but revealed significantly higher recovery rates in patients treated with LP. In terms of NDI improvement, one article by Lee et al. [51] did not find a statistically significant difference between LP (n = 21) and LA (n = 15).

For the secondary outcomes, two studies evaluated the change in VAS-neck score. The study by Lee et al. [51] showed equivocal postoperative improvements in both procedures. A relatively larger study by Nurboja et al. [53] (n = 48 for LP, n = 33 for LA) reported no difference in VAS-Neck scores with either surgical technique. Interestingly, authors of the latter study found that the pain relief in the LA group only became significant when surgery was performed on ≥4 vertebral levels.

The changes in Ishihara Index were also compared between the two procedures and reported by all three studies. In the retrospective study by Du et al. [50], a loss of cervical lordosis was described in both groups with more pronounced changes noted after LA, but their results were not reproduced by the other studies. Lee et al. [51], on the other hand, found the loss of lordosis to be of similar magnitude amongst techniques, and Nurboja et al. [53] in their evaluation of LP (n = 75) and LA (n = 34) reported minimal change in sagittal alignment over time in either group.

None of the studies in this review compared the postoperative changes in ROM.

LP Versus sLA

A total of three articles were identified in the literature search addressing the outcomes of LP compared to sLA (Table 11.2). In a single prospective randomized control trial, Yukawa et al. [37] concluded that the long-term JOA score improvements or other functional outcomes were not significantly different between DCM patients treated with LP (n = 21) and sLA (n = 20). Chang et al. [52], in a retrospective review of patients treated with LP (n = 35) and sLA (n = 32), showed improvement in both NDI and VAS-Neck with no difference between the two treatment groups.

Shiraishi et al. [36] reported the postoperative changes in Ishihara index on their cohorts undergoing sLA (n = 43) in comparison to LP (n = 51), and noted that while the curvature index was maintained after sLA, a significant decrease was seen in the LP group.

Finally, the pre- and postoperative ROM was assessed by two of the studies with inconsistent findings. While Yukawa et al. [37] reported slightly more preserved ROM after sLA, the article by Chang et al. [52] reported significantly less postoperative ROM.

What Is the Efficacy of LF Compared with LP Based on Clinically Important Changes in Neurological and Functional Status?

For eight studies that reported the preoperative and postoperative JOA/mJOA scores, the calculated SMD and the 95% CI are demonstrated in Fig. 11.2a. The majority (five studies) reported no or "small" effect without statistical significance. Only in one study was a significantly "large" effect detected in favor of LP (SMD 1.231). In this retrospective analysis by Stephens et al. [58], the comparison was made between LP (n = 85) and LF (n = 52). Although significant results were noted, the authors reported baseline differences between groups and possible selection bias in treatment. Two studies reported "medium" effect with conflicting findings. One single retrospective study by Miyamoto et al. [57] favored LF (n = 30) over LP (n = 30) in JOA improvement, while a large multicentered, prospective, observational study by Fehlings et al. [54] (n = 100 for LP, n = 166 for LF) showed more improvement in the LP group [54]. The assessment of functional improvement using preoperative and postoperative NDI was reported by five studies. Most of the support for LP derives from two studies with one "large" (SMD 1.165) and one "medium" (SMD 0.655) effect by Stephens et al. [58] and Yang et al. [23], respectively. The study by Stephens et al. [58] suffers from the possibility of bias as mentioned above, but the retrospective study by Yang et al. [23] showed significant NDI improvement in LP (n = 75) compared to the LF (n = 66) group. Two other studies were in favor of LP with "small" and non-significant effect [21, 54], while one study showed no difference between procedures [51].

The results of the assessment of secondary outcomes were summarized in Fig. 11.2b. A total of six studies reported postoperative improvement of VAS-neck pain. Of the studies that were found to favor LF, the retrospective study by Highsmith et al. [55] (n = 30 for LP, n = 26 for LF) showed the largest effect (SMD 1.217), with the LP group experiencing an increase in VAS-neck pain while the LF group reported a significant improvement. To a lesser extent, the retrospective study by Stephens et al. [58] also supported LF with statistical significance (SMD 0.732). Three other studies showed "small" effects in favor of LF. On the other hand, the study by Yang et al. [23] was found to have a "large" (SMD −1.050) effect favoring LP.

In terms of the Ishihara Index, two of the three studies favored LF in maintaining the curvature index with a "small" effect, while one study showed a SMD of 0.083 in favor of LP. None of the studies showed a strong effect. Finally, all three

studies comparing ROM revealed a "large" effect favoring LP in preserving more neck motion.

What Is the Safety Profile of LA or sLA Compared to LF?

The comparison of complication rates between LA and LF were found in two studies (Table 11.3). The rate of C5 palsy was reported by a single retrospective review by Lee et al. [51]. The authors found no incidence of the event (0/75) in the LA group and 9.52% (2/21) in the LF group [51]. In a prospective randomized comparative study, postoperative infection was documented in 6.67% (2/30) and 9.38% (3/32) after LA and LF, respectively [61]. In the same study, the authors reported the observed incidence of dural tear/CSF leak after LP at 3.33% (1/30) while it was 6.25% (2/32) for LF. None of the studies reported or compared the rates of postoperative kyphosis, and no studies comparing sLA to LF were found.

What Is the Safety Profile of LP Compared to LA or sLA?

Two studies compared complication rates between LP and LA (Table 11.3). Della Pepa et al. [62], in their retrospective review, found no infection (0/33 for LP, 0/24 for LA) or dural tear/CSF leak (0/33, 0/24) in both groups. However, the LA group demonstrated a 12.5% (3/24) rate of postoperative kyphosis in comparison to none (0/33) reported in the LP group [62]. Regarding the rate of C5 palsy, Lee et al. [51], reported 0% in both LP (0/21) and LA (0/15) groups in their retrospective study.

In terms of LP and sLA, the data on complications were acquired from two studies. In the RCT by Yukawa et al. [37], the rate of infection was found to be 0% in both groups (0/21 for LP, 0/20 for sLA). In the retrospective study by Shiraishi et al. [36], no incidence of CSF leak was reported in the LP (0/51) group compared to 4.65% (2/43) in the sLA group. Both studies reported on postoperative C5 palsy, with rates of 5.88% (3/51) versus 0% (0/43) [36], and 0% (0/21) versus 0% (0/20) [37], respectively, compared between LP and sLA.

What Is the Safety Profile of LF Compared to LP?

A total of 11 articles presented a comparison of complication rates between LP and LF (Table 11.3). The calculated RR and 95% CI are presented in Fig. 11.3. Of the studies that reported on rates of C5 palsy, the majority (seven of the eight articles) showed reduced risk of this complication with LP. However, only three studies [21, 23, 63] reached statistical significance with RR of 0.227, 0.240, and 0.138. Only one article showed a slight favoring of LF (RR 1.245), which failed to reach statistical significance [54].

Three studies reported rates of dural tear/CSF leak, with one study showing no difference in the rate between the two procedures [54], while the other two studies were inconsistent with one favoring LF (RR 2.613) [55] and the other favoring LP (RR 0.293) [23]. However, none of the studies reached statistical significance.

There were eight articles reporting on postoperative rates of infection. Analysis of RR revealed that all studies trended toward reduced risk of infection with LP, however, none of the studies reached statistical significance.

The rate of postoperative kyphosis was also described in four studies. Although none showed statistically significant differences, two studies reported a lower risk of postoperative kyphosis in LP (RR 0.332 and 0.692) [22, 54], while one study was in favor of LF (RR 1.320) [23].

Level of Evidence

The strengths of evidence are presented in Table 11.4.

Discussion

With the rapid advancement in the field of DCM, evidence-based clinical management guidelines have been developed to assist clinicians and surgeons in formulating treatment decisions [64–69]. While the clinical importance and efficacy of surgical decompression is not called into question, controversy still exists concerning the best surgical approach in the treatment of DCM. This chapter focuses on the common types of posterior cervical procedures and provides a synopsis of current evidence.

The clinical efficacy of posterior cervical decompressive procedures has a long track record of proven success in the treatment of DCM by providing clinically important improvements in neurological and functional outcomes [21, 23, 36, 37, 50–52, 54, 55, 57, 58, 60, 70]. Due to the unique characteristics of each technique, the selection of one over the other is still based mostly on surgeon preference and remains a heated debate in the spine community. However, it is generally accepted that due to the risk of instability and delayed deformity development, pre-existing cervical kyphosis is a contraindication for LA and LP [5, 8–11, 29–33, 39].

To best present the evidence, a systematic review of the literature was conducted focusing on the contemporary literature (after year 2000) and on studies with comparative data between the procedures. Due to the heterogeneity intrinsic to the available literature, the inconsistent methods of reporting outcomes and complications, as well as the lack of well-designed high-quality studies, it was not possible to recommend one of the surgical techniques as being superior. However, from the review of the current evidence, several important conclusions can be drawn to assist the surgeons and patients in making evidence-based decisions concerning surgical approach.

Table 11.4 Strength of evidence summary

	Strength of evidence	Comments and conclusions	Baseline	Upgrade	Downgrade
Question 1: What is the efficacy of laminectomy or selective/skip laminectomy compared to laminectomy and fusion regarding clinically important change in neurological and functional status?					
Laminectomy vs. laminectomy and fusion					
JOA/mJOA score	Low	There is low evidence to support laminectomy and fusion procedures regarding JOA improvement. Based on a single study, there is reportedly more statistically significant improvement in JOA score in the laminectomy and fusion group. However, due to the limited study and small sample size, estimates are at risk of imprecision	Low	Large effect (1)	Imprecise (1)
NDI score	Insufficient	There is insufficient evidence to favor either approach regarding improving functional (NDI) recovery. A single retrospective study reported improvement of NDI with both procedures with no significant difference. Given the small number of participants and limited study, estimates are at risk of imprecision	Low	None	Imprecise (1)
VAS neck	Insufficient	There is insufficient evidence to suggest either approach as superior in terms of reducing postoperative VAS neck score. A single retrospective study reported no significant difference in improvement between the treatments. However, estimates are imprecise due to limited study with small number of participants	Low	None	Imprecise (1)
Ishihara index	Insufficient	There is insufficient evidence to suggest either procedure would lead to more loss of cervical lordosis. One study reported equivocal loss of cervical lordosis with both procedures. Whereas the other reported more loss of cervical curvature with laminectomy, the calculated effect is "small"	Low	None	Inconsistent (1) Imprecise (1)
ROM	Insufficient	No studies reported on ROM	NA	NA	NA
Skip laminectomy vs. laminectomy and fusion:					
NA	NA	No study was found comparing skip laminectomy to laminectomy and fusion	NA	NA	NA
Question 2: What is the efficacy of laminoplasty compared to standard laminectomy or skip laminectomy regarding clinically important change in neurological and functional status?					
Laminoplasty vs. standard laminectomy					

JOA/mJOA score	Insufficient	There is insufficient evidence in favoring either procedure regarding overall JOA improvement. A single retrospective study reported showing significant difference in JOA improvement in favor of laminoplasty. However, the calculated effect was found to be "medium". Evidence is downgraded due to limited study and small sample size	Low	None	Imprecise (1)
NDI score	Insufficient	There is insufficient evidence to suggest one procedure as more efficacious over the other in regard to NDI improvement. A single retrospective study reported no difference in the overall NDI improvement between the two procedures. Evidence downgraded secondary to limited study and small number of participants	Low	None	Imprecise (1)
VAS neck	Insufficient	There is insufficient evidence in supporting either procedure with in regard to postoperative VAS neck improvement. Of the two retrospective studies identified, one reported that VAS neck did not change postoperatively with either procedure. The other study however, reported improvement in VAS neck but failed to detect any significant difference between the magnitude of improvement	Low	None	Inconsistent (1)
Ishihara index	Insufficient	There is insufficient evident to suggest one procedure in being more protective toward reducing loss of cervical lordosis than the other. Of the three retrospective studies, two slightly favored laminectomy and one favored laminoplasty in reduced loss of cervical lordosis. All three studies did not reach statistical significance	Low	None	Inconsistent (1)
ROM	Insufficient	No studies reported on ROM	NA	NA	NA
Laminoplasty vs. skip laminectomy					
JOA/mJOA score	Insufficient	There is insufficient evidence in supporting either procedure in terms of postoperative JOA improvement. A single randomized control trial showed no difference between the two treatment groups. However due to the poor technique of randomization and blinding of evaluators, the overall quality of evidence downgraded. Additionally, the lack of reporting of standard deviation limited our analysis	Low	None	Risk of bias (1) Impression (1)

(continued)

Table 11.4 (continued)

	Strength of evidence	Comments and conclusions	Baseline	Upgrade	Downgrade
NDI score	Insufficient	The overall strength of evidence is insufficient in favoring either procedure regarding NDI improvement. Given one prospective cohort study, no significant difference in NDI improvement between the two procedures. Evidence downgraded for imprecision of estimate due to limited study and small sample size	Low	None	Imprecise (1)
VAS neck	Insufficient	There is insufficient evidence favoring either procedure in providing more improvement in postoperative VAS score. One prospective cohort study detected no significant difference between the treatment groups. Due to limited study and small number of participants, estimate is at risk of imprecision	Low	None	Imprecise (1)
Ishihara index	Insufficient	There is insufficient evidence to suggest that one procedure is more protective of postoperative loss of cervical lordosis. One study reported more reduction in Ishihara index with laminoplasty, but limited study and the lack of reporting of standard deviation limited our analysis	Low	None	Imprecise (1)
ROM	Insufficient	There is insufficient evidence to conclude whether one procedure would be more protective of preserving postoperative ROM. One prospective cohort study reported significantly more loss of ROM with skip laminectomy, while another randomized control trial concluded more preserved ROM with the procedure. Overall evidence downgraded due to inconsistency, and limitation in the methodology of the randomized control trial	Low	None	Risk of bias (1) Inconsistency (1)
Question 3: What is the efficacy of laminectomy plus fusion procedure compared with laminoplasty regarding clinically important change in neurological and functional status?					
JOA/mJOA score	Insufficient	There is overall insufficient to favor either procedure regarding JOA/mJOA improvement in treating DCM. Amongst the eight studies, three favored laminectomy and fusion. One study was found to have “moderate” effect, whereas the other two studies had “small” effects that are not statistically significant. Two studies supported laminoplasty with “large” and “moderate” effect. Three studies showed minimal to no effect between the two procedures. The overall evidence downgraded for inconsistency in the results and risk of bias as reported by the authors with the study showing the largest effect	Low	None	Risk of bias (1) Inconsistency (1)

NDI score	Insufficient	There is overall low evidence in favor of laminoplasty in terms of postoperative NDI improvement. Of the five studies, three studies showed evidence supporting more improvement of NDI in patients treated with laminoplasty procedure with one "large", one "moderate" and one "small" effect. The remaining two studies, one was a prospective cohort study showing trend favoring laminoplasty without reaching statistical significance, and the other was a small retrospective study (n = 21 in each group) showing no significant difference between the techniques. The evidence was down grade due to inconsistency and risk of bias as reported by the author of the study with the largest effect	Low	Large effect (1)	Risk of bias (1) Inconsistency (1)
VAS neck	Insufficient	There is overall insufficient evidence to favor either procedure in terms of improvement of postoperative VAS neck score. Of the six studies, four of which are in favor of laminectomy and fusion with one "large", two "moderate" and one "small" effect. Although one study showed "large" effect in favor of laminoplasty. The presence of major inconsistency and downgraded the overall strength of evidence	Low	None	Inconsistency (1)
Ishihara Index	Insufficient	There is overall insufficient evidence to suggest either procedure as more protective of postoperative loss of cervical lordosis. Of the three retrospective studies, two showed "small" effect favoring laminectomy and fusion in reducing the loss of cervical lordosis and one study showing minimal effect favoring laminoplasty	Low	None	Inconsistency (1)
ROM	Moderate	The is overall moderate evidence favoring laminoplasty as the more ROM preserving procedure. All three retrospective studies showed "large" effects favoring more ROM in laminoplasty patients postoperatively	Low	Large effect (1)	None
Question 4: What is the safety profile of laminectomy alone compared to laminectomy and fusion?					
Dural tear/ CSF leak	Insufficient	There is insufficient evidence to conclude the safety profile in favor of either procedure regarding dural tear/CSF leak. One randomized control trial reported 3.3% in laminectomy and 6.3% in laminectomy and fusion. The evidence is downgraded due to is imprecise estimate secondary to low number of events	Low	None	Imprecision (1)

(continued)

Table 11.4 (continued)

	Strength of evidence	Comments and conclusions	Baseline	Upgrade	Downgrade
C5 palsy	Insufficient	There is insufficient evidence to conclude the safety profile in favor of either procedure in terms of rate of C5 palsy. One retrospective study reported 0% with laminectomy and 9.5% with laminectomy and fusion. The estimate however is imprecise due to small number of events	Low	None	Imprecision (1)
Infection	Insufficient	There is insufficient evidence in favoring either procedure regarding rate of postoperative infection. One single study reported 6.67% in laminectomy group and 9.38% in laminectomy and fusion group. Due to small number of events, estimate is limited by imprecision	Low	None	Imprecision (1)
Kyphosis	Insufficient	No studies reported on rate of postoperative kyphosis	NA	NA	NA
Question 5: What is the safety profile of laminoplasty compared to standard laminectomy or skip laminectomy?					
Laminoplasty vs. standard laminectomy					
Dural tear/ CSF leak	Insufficient	There is insufficient evidence to favor either procedure in terms of dural tear/CSF leak. The single study found in this review showed no dural tear/CSF leak in either treatment group. However, based on the methodology reported by authors, confounding cannot be ruled out	Low	None	Risk of bias (1) Imprecision (1)
C5 palsy	Insufficient	The overall strength of evidence is insufficient to draw conclusions on the rate of C5 palsy in either procedures. Since the single study reported 0% rate of event in both treatment group	Low	None	Imprecision (1)
Infection	Insufficient	There is insufficient evidence to conclude on the rate of infection comparing both procedures. Since the single study reported 0% in either group. Based on the methodology reported by authors, confounding cannot be ruled out	Low	None	Risk of bias (1) Imprecision (1)
Kyphosis	Insufficient	There is insufficient evidence to draw conclusion on the comparative rate of postoperative kyphosis between the two procedures. The single study reported 0% vs 12.5% kyphosis in the laminoplasty and laminectomy group respectively. However, the study methodology used by authors and limited number events hindered the drawing of firm conclusion	Low	None	Risk of bias (1) Imprecision (1)

Laminoplasty vs. skip laminectomy					
Dural tear/ CSF leak	Insufficient	There is insufficient evidence to favor either procedure in the rate of dural tear/ CSF leak. The one prospective cohort study reported 0% in the laminoplasty group and 4.7% in the skip laminectomy group. The evidence is downgrade due to imprecision secondary to limited number of events	Low	None	Imprecision (1)
C5 palsy	Insufficient	There is insufficient evidence to favor either procedure in terms of the rate for postoperative C5 palsy. Two studies reported rate of C5 palsy. One study reported 5.88% with the laminoplasty procedure and 0% with skip laminectomy. The other reported no event in either treatment group. Given the limited study and small number of events, estimates are at risk of imprecision	Low	None	Imprecision (1) Inconsistency (1)
Infection	Insufficient	There is insufficient evidence to favor either procedure in terms of rate of postoperative infection. Since the single randomized control trial reported no infection in either group	Low	None	Imprecision (1)
Kyphosis	Insufficient	No studies reported on rate of postoperative kyphosis	NA	NA	NA
Question 6: What is the safety profile of laminectomy plus fusion compared to laminoplasty?					
Dural tear/ CSF leak	Insufficient	The overall strength of evidence is insufficient to suggest either procedure as the safer procedure for reduced rate of dural tear CSF leak. Of the three studies, one study showed no difference in risk, one study favored laminectomy and fusion where as the other favored laminoplasty. Evidence downgraded for inconsistency and imprecision due to small number of events	Low	None	Imprecision (1) Inconsistency (1)

(continued)

Table 11.4 (continued)

	Strength of evidence	Comments and conclusions	Baseline	Upgrade	Downgrade
C5 palsy	Low	The overall strength of evidence is low in favor of laminoplasty in regard to lower rate of postoperative C5 palsy. Of the eight studies, three studies showed significant lower rate of C5 palsy with one study reaching "very large" effect (RR 0.138). Three other studies showed trends towards favoring the laminoplasty procedure without reaching statistical significance. Inconsistency exist where one study showed largely equivocal risk and another favoring laminectomy and fusion. Although both did not reach statistical significance. Evidence also downgraded due to small number of events and large confidence interval	Low	Very large effect (2)	Imprecision (1) Inconsistency (1)
Infection	Insufficient	The overall strength of evidence is insufficient to favor either procedure for rate of infection. Although all of the eight studies trended toward lower risk in the laminoplasty group, none of the studies reached statistical significance. Due to large confidence intervals, evidence downgraded for imprecision	Low	None	Imprecision (1)
Kyphosis	Insufficient	The overall strength of evidence is insufficient to favor either procedure for rate of postoperative kyphosis. Of the four studies, three reportedly favored laminoplasty while one study favored laminectomy and fusion. Given the inconsistency and low number of events the overall evidence was downgraded	Low	None	Imprecision (1) Inconsistency (1)

Regarding clinical outcomes, the systematic literature search resulted in only two retrospective studies addressing the efficacy of LA versus LF, and three retrospective studies evaluating LA versus LP. Similarly, the number of articles identified regarding the safety profile of the procedures was low (two studies comparing LA and LF and two studies for LP and LA). The paucity of literature on these comparisons likely reflects the dramatic decline in the utilization of LA in the contemporary era due to the increased awareness of the high-risk for postoperative kyphosis, instability, as well as the added possibility of neurological deterioration with their development [8–11, 50]. The extracted data from the limited number of studies provides "insufficient" evidence to recommend LA as a primary procedure for DCM (Table 11.4). In fact, there is "low" evidence in favor of LF regarding postoperative neurological improvement, and a trend toward potentially added improvement in functional outcomes with LF and LP [50].

From the included studies, it is recognizable that a trend exists suggesting loss of cervical lordosis post LA [50, 62]. Interestingly, it was noted that many of the authors, being aware of the issue of postoperative kyphosis, either limited their study by excluding patients with severe preoperative cervical deformity or tailored the treatment to offer fusion in the less-lordotic cases [50, 51]. Therefore, although the evidence presented was graded as "insufficient" in confirming an increased risk of kyphosis in LA, these studies indirectly provided insight that increased awareness surrounding this issue has led to changes in the practices of the spine community.

Given its relatively recent introduction, the evidence on the comparative effectiveness and safety of sLA compared to other posterior cervical procedures was limited to three studies found by literature search. Due to the overall lack of evidence and imprecision with reporting, no conclusive recommendation can be generated on the utility of sLA for DCM (Table 11.4), but studies appear to suggest that the clinical outcome and safety profile of sLA is comparable to that of LP [36, 37, 52]. The sLA procedure was designed to address issues with post decompression instability and kyphosis while preserving ROM [36, 38], and the limited reports on the potential of this procedure to maintain cervical curvature are promising [36–38], but this analysis fails to confirm these due to the limited and inconsistent evidence.

With the advancement of knowledge and the evolution of instrumentation technology, the field of spine surgery has seen rapid development over recent years. As LA has been gradually phased out in favor of LP and LF, a shift in the research focus nowadays is geared towards quality control and improvement. As a reflection of this change, 12 studies addressing the clinical outcomes and 11 studies comparing the complications of LP and LF were found by literature search. However, given the resources, there is still "insufficient" overall evidence to favor either procedure regarding neurological improvement, functional outcome or safety profile (Table 11.4). Given the inconsistencies seen in the literature and the difficulty in proving the superiority of one procedure over the other, it appears that LP and LF have overall clinical equipoise in treating DCM. While it is generally agreed upon that LP is associated with more postoperative neck pain [34, 35], insufficient evidence was found in this review in terms of VAS-neck pain score changes. However, it appears that the overall trend tends to favor more improvement with LF (Fig. 11.2). Unsurprisingly, a large difference was found with "moderate" evidence confirming greater loss of ROM with LF [21–23]. Of interest, it appears that "low" evidence exists supporting a lower rate

of C5 palsy in LP, which is an observation that has been previously reported [71, 72]. However, given the state of the literature, it is difficult to provide absolute evidence favoring either procedure, and further research is necessary.

Conclusion

In conclusion, this chapter summarizes the current evidence concerning the common posterior spinal surgical approaches for the treatment of DCM. The evidence presented here is not a strict guideline but should serve as a suggestion to assist clinicians, surgeons, and patients when deciding a treatment plan. Ultimately, the approach of choice should be based on clinical judgement and tailored toward each individual patient depending on their clinical presentation, imaging findings, and the surgeon's own experience. Overall this systematic review strengthens the evidence that LP and LF have overall clinical equipoise in terms of clinical outcome, while finding insufficient evidence to recommend LA or sLA as primary treatment options for DCM.

Patient Preference

See Table 11.5.

Table 11.5 Patient preference chart

	Advantage	Disadvantage
Laminectomy	Insufficient evidence to suggest any advantage of the procedure	Risk of postoperative kyphosis and instability
Skip laminectomy	Insufficient evidence to suggest any advantage of the procedure	Insufficient evidence to recommend this procedure over its counterparts
Laminoplasty	Clinical equipoise in providing neurological and function improvement compared to laminectomy and fusion	Evidence showing a trend toward increased postoperative neck pain
	Safety profile overall similar to laminectomy and fusion in rate of dural tear/CSF leak, infection, and postoperative kyphosis	
	Low level of evidence in support of reduced rate of C5 palsy compared to laminectomy and fusion	
Laminectomy and fusion	Low evidence in providing increased neurological improvement compared to laminectomy	Decreased postoperative neck ROM
	Clinical equipoise in providing neurological and functional improvement compared to laminoplasty	
	Safety profile ovSerall similar to laminoplasty in rate of dural tear/CSF leak, infection and postoperative kyphosis	
	Trend toward reducing loss of cervical lordosis with laminectomy and fusion	

Box

1. What is known:
   (a) Cervical laminectomy has a risk of postoperative instability and kyphosis.
   (b) Cervical laminoplasty is associated with postoperative neck pain.
   (c) Cervical laminectomy and fusion are associated with decreased postoperative ROM.
2. What is new:
   (a) There is a trend showing reduced cervical lordosis with laminectomy and fusion procedures, although not reaching statistical significance.
   (b) Cervical laminoplasty and laminectomy and fusion have shown similar effects regarding overall clinical outcomes and safety profile, with the exception of low level-evidence suggesting decreased rates of C5 palsy in the laminoplasty group.
3. Consequences for clinical practice:
   (a) We do not recommend cervical laminectomy as the primary treatment for degenerative cervical myelopathy.
   (b) We cannot make recommendations for cervical skip laminectomy due to insufficient evidence showing its superiority over other common posterior cervical procedures.
   (c) We do not recommend the use of cervical laminoplasty when there is present or suspected instability.
   (d) We do not recommend the use of cervical laminoplasty in the presence of cervical kyphosis.
   (e) We recommend both cervical laminoplasty and laminectomy and fusion in degenerative cervical myelopathy but recommend laminectomy and fusion when instability and/or cervical deformity are present.

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Early Versus Delayed Surgery for Cervical Disc Herniation

12

Lukas Bobinski and Yohan Robinson

Introduction

Age-related intervertebral disc changes lead to decrease of the disc height, which triggers a cascade of degenerative deterioration of the motion segment. During the early stages, the annulus fibrosus of the disc becomes susceptible to fissuring and tearing. This leads to so-called "soft herniation" with disc extrusion and sequestration. The pathophysiology of radiculopathy involves both mechanical compression and chemical irritation of the nerve root. Soft disc herniation has a high chance of spontaneous resorption, and hence improvement of clinical symptoms.

However, further degenerative changes result in reactive formation of osteophytes and hypertrophy of the yellow ligament. These can protrude into the foramina and compress the nerve roots. The additional development of kyphosis of the cervical spine in later stages of segmental degeneration further compromises the integrity of nerve roots [1]. This radicular entrapment due to spondylosis, referred to also as "hard herniation", is characterized by slowly progressing deterioration. However, even at this stage, the subsequent release of inflammatory cytokines and other agents is partially responsible for the generation of radicular pain [2].

Spontaneous resolution of this inflammatory process explains why even patients with advanced spondylosis can experience spontaneous resolution of the symptoms as well as long asymptomatic periods. Spondylosis, with cervical foraminal stenosis, is responsible for almost two thirds of cervical radiculopathy cases. The remaining one third of cases are due to cervical disc herniation.

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Cervical radiculopathy has a peak annual incidence of 2.1 cases per 1000, occurring in the fourth and fifth decades of life [3].

Cases of radiculopathy due to cervical degenerative disease initially present with intense pain and moderate levels of disability. Nevertheless, substantial improvements tend to occur within the first 4–6 months after onset [4].

According to the current literature, the general natural history of cervical radiculopathy is typically favorable and self-limited, with up to 90% of patients presenting improvement with conservative treatment [3, 5].

However, in some patients, a conservative regime is insufficient. This results in persistent severe neuropathic pain and a high level of disability. These patients are referred for surgical treatment.

There is no current consensus about which patients would fail to benefit from non-operative treatment and are in need of surgery. Anterior cervical discectomy and fusion (ACDF) still remains the gold standard for surgical treatment [6] with good or excellent results that are primarily dependent on the nerve root decompression [7, 8].

According to current practice, surgery is recommended after six to 12 weeks of persistent radiculopathy despite optimal conservative treatment [9, 10]. However, the optimal timing for surgical treatment is still not clearly defined.

Surgical intervention implies removal of the disc herniation either by anterior access with subsequent fusion or disc replacement or by posterior foraminotomy. There is little evidence of the superiority of one method over the other (discussed elsewhere in this book), and it is unclear whether the timing of surgery has more of an effect on the outcome after surgery than the type of implant.

There are several theories supporting early intervention:

1. Long standing radicular compression could result in a poorer clinical outcome by inducing development of chronic pain [11]
2. Prolonged radiculopathy and cervicalgia postpones the return to work if surgical intervention is delayed [6, 12].

According to population-based studies, up to 25% of patients with cervical radiculopathy will have persistent symptoms and might require surgical intervention.

[3]. Therefore, decisions about selection for surgery and its timing might have an impact on long-term clinical results. The goal of this review is a critical analysis of the current literature regarding optimal timing of surgery as a treatment for cervical radiculopathy with ACDF.

The objective of this trial is to investigate if there is enough evidence in the current literature to identify the optimal timing for surgical treatment.

Methods

Study Selection

Only studies presenting results based on randomized controlled trials published after December 31st, 1999 were considered for inclusion. Randomized controlled trials on surgical and non-surgical treatment of acute cervical radiculopathy were

included. Studies with more than 10% pediatric patients (<18 years of age) or more than 10% elderly patients (≥65 years of age) were excluded, as well as studies that did not contain information on the surgical technique or did not include timing data.

Participants were patients with acute radiculopathy due to cervical disc herniation. Myelopathy and bilateral radiculopathy were not exclusion criteria but were entered as covariates. Surgical interventions included were anterior cervical discectomy without fusion (ACD), anterior cervical discectomy and fusion (ACDF) and cervical disc replacement (CDR).

Early surgical treatment was defined as surgical treatment within 6 months from the onset of symptoms. Delayed surgical treatment was defined as surgical treatment after 6 months from the onset of symptoms.

Types of Outcome Measures

The following outcome measures were included in the systematic review:

- Neck Disability Index (NDI)
- Arm pain (VAS arm)
- Neck pain (VAS neck).

Using the reported minimally clinically important difference (MCID) of possible endpoints of interest, the following numbers of participants must be included to reach 80% power [13]:

Endpoint	MCID	SD	N in each group to reach 80% power
NDI (0–50)	7.5	7.9	19
VAS arm (0–10)	2.5	3.4	30
VAS neck (0–10)	2.5	2.3	15

NDI Neck Disability Index, *VAS* visual analog scale, *MCID* minimally clinically important difference, *SD* standard deviation

Search Methods for Identification of Studies

The protocol to this review was registered in PROSPERO (CRD42017079420). We applied the PRESS criteria for the electronic literature search to elaborate the search strategy [14].

The following search terms were used on databases from January 1st, 2000 to December 31st, 2017:

NLM PubMed MEDLINE

((((cervical disc) AND (radiculopathy OR herniation OR prolapse OR radiating OR conservative) AND ("01/01/2000"[Date—Publication]: "3000"[Date—Publication]))) AND Clinical Trial[ptyp])

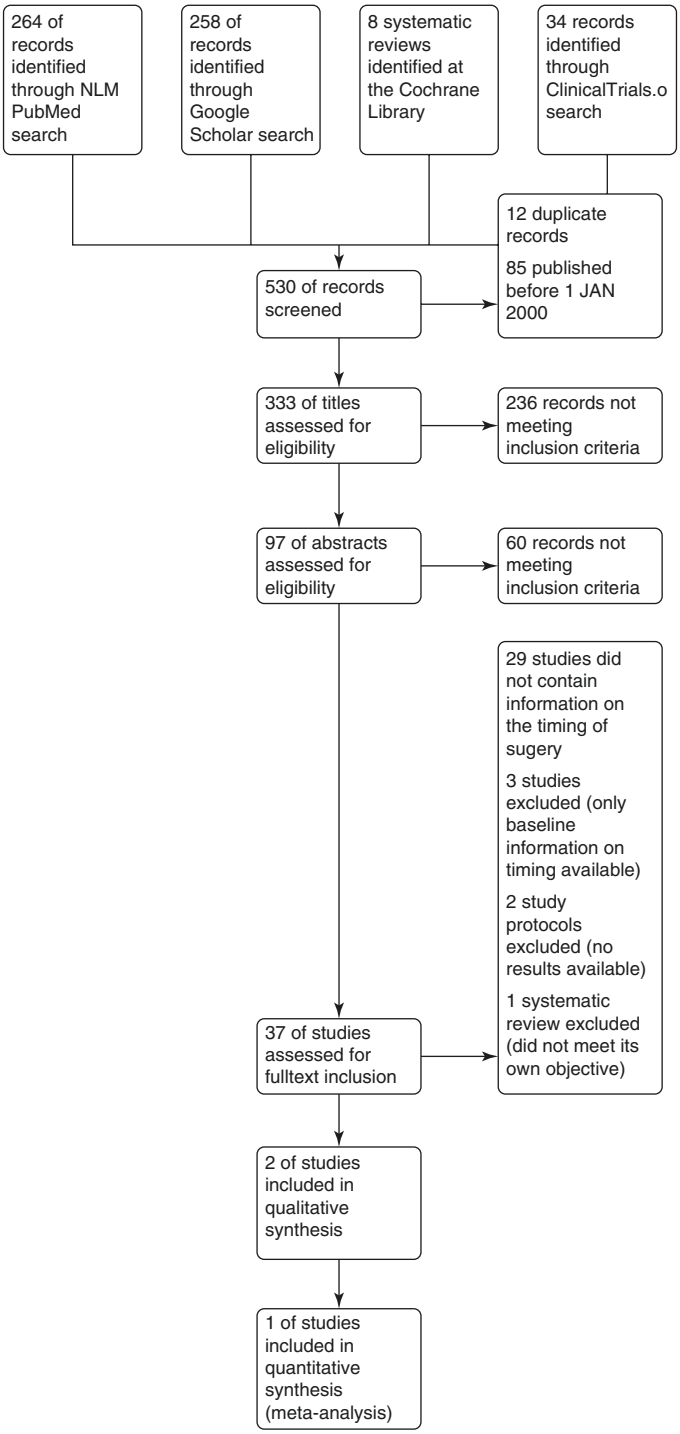

Fig. 12.1 PRISMA inclusion flow diagram

Google Scholar:
allintitle: (radiculopathy OR herniation OR prolapse OR radiating OR conservative) AND “cervical disc”
Cochrane Library:
cervical AND disc
ClinicalTrials.gov:
“Cervical Disc” AND (radiculopathy OR herniation OR prolapse OR radiating OR conservative).

Data Collection and Analysis

Data were collected by both co-authors and the analysis followed the Cochrane guidelines.

The literature search in the electronic databases resulted in a list of eligible studies which were included in the systematic review. A PRISMA flow diagram, including reasons for exclusions at each stage, illustrates the study inclusion process (Fig. 12.1).

For each study, we considered characteristics for which data were extracted (study size, PICOS, follow-up period).

Assessment of Risk of Bias in Included Studies

The risk of bias in each included study was assessed according to GRADE recommendations [15].

Measures of Treatment Effect

For all outcomes considered for each study, we used: (a) a simple summary of data for each intervention group and (b) effect estimates and confidence intervals, with a forest plot.

Results

Study Selection

The numeric search results are summarized as a flow chart in Fig. 12.1. Two studies were included for qualitative synthesis and one study for meta-analysis. The number of excluded studies and the related reasons for exclusion are summarized in Fig. 12.1.

Risk of Bias in Included Studies

The details regarding bias are given in Table 12.1 and Fig. 12.2. Both studies present with a high risk of selection bias. In the study by Burneikiene et al., this is due to the post hoc analysis of previous RCTs [9, 16]. In the study by Engquist et al., it is due to an unclear description of their patient selection process [17].

Both studies showed a high risk of performance bias because they were unblinded. The risk of detection bias was evaluated as very low because in both studies there was a patient-reported outcome measurement. Both studies presented complete outcome data, but they reported their results post hoc.

Table 12.1 Characteristics of included studies

Bureneikiene et al. [9]	
Methods	Post-hoc analysis of prospective trial [16]
Participants	58 patients (52% male), age 49 (range 27–73) years, with one- or two-level ACDF for cervical degenerative radiculopathy
Interventions	1. Early (within 6 months) vs 2. Delayed (after 6 months) surgical intervention
Outcomes	Neck and arm pain was evaluated using Visual Analog Scale (VAS) Health-Related Quality-of-Life using Short-Form 36 Health Survey (SF-36) physical component summary (PCS) and mental component summary (MCS) Disability was determined using Neck disability index (NDI)
Notes	The patients who had previous surgeries, were diagnosed with cervical myelopathy or had more than 2-level ACDF surgeries were excluded from this analysis (n = 64)

Bias	Authors' judgement	Support for judgement
Risk of bias table		
Random sequence generation (selection bias)	High risk	Post-hoc analysis
Allocation concealment (selection bias)	Low risk	Post-hoc analysis
Blinding of participants and personnel (performance bias)	High risk	unblinded for timing
Blinding of outcome assessment (detection bias)	Low risk	Patient-reported outcome measures
Incomplete outcome data (attrition bias)	Low risk	Complete outcome data
Selective reporting (reporting bias)	High risk	Post-hoc analysis
Other bias	Unclear risk	

Engquist et al. [17]	
Methods	Subgroup analysis of RCT
Participants	60 patients (52% male, age 49 ± 7 years) with cervical radiculopathy
Interventions	1. Surgical treatment (ACDF) followed by physiotherapy (n = 30) or 2. Nonsurgical treatment by physiotherapy alone (n = 30)
Outcomes	Pain (VAS), Disability (neck disability index, NDI), Patient expectations of treatment, Anxiety due to neck/arm pain, distress (Distress And Risk Assessment Method, DRAM), Self efficacy (self efficacy scale, SES) Health-related quality of life (EQ-5D)

Table 12.1 (continued)

Notes	Subgroup analysis of early (2–12 months) vs delayed (≥12 months) surgical treatment without number of participants in subgroups

Bias	Authors' judgement	Support for judgement
Risk of bias table		
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Low risk	SNOSE (sealed envelope)
Blinding of participants and personnel (performance bias)	High risk	Unblinded study
Blinding of outcome assessment (detection bias)	Low risk	Patient reported outcome measures
Incomplete outcome data (attrition bias)	Low risk	Complete outcome data
Selective reporting (reporting bias)	High risk	Post-hoc reporting
Other bias	Unclear risk	

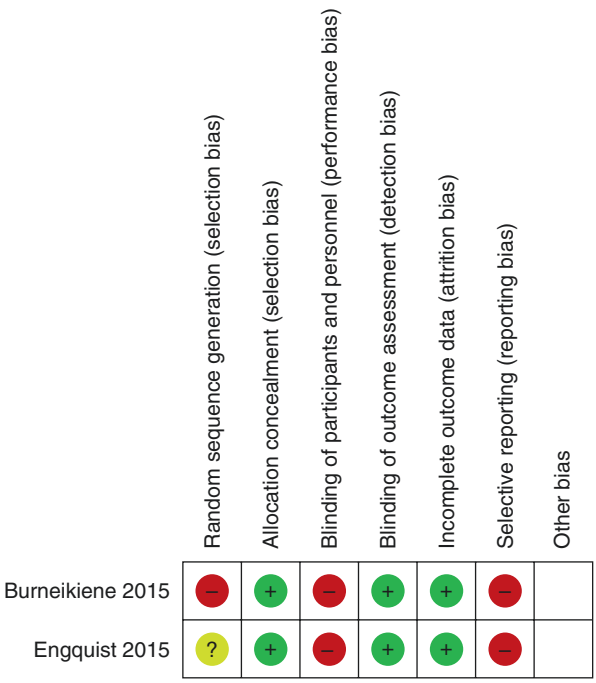

Fig. 12.2 Risk of bias summary: review authors' judgements about each risk of bias item for each included study

Effects of Interventions

Neck Pain in Cervical Radiculopathy

The details regarding effect of intervention on neck pain are summarized in Fig. 12.3.

One trial included randomized data from 58 patients and evaluated neck pain in cervical radiculopathy related to surgical timing [9]. The pain intensity was assessed

Study or Subgroup	< 6 months Mean	SD	Total	≥ 6 months Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI	Year
Burneikiene 2015	2.7	3.4	29	3.6	3.8	29	100.0%	–0.90 [–2.76, 0.96]	2015
Total (95% CI)			**29**			**29**	**100.0%**	**–0.90 [–2.76, 0.96]**	

Heterogeneity: Not applicable
Test for overall effect: Z = 0.95 (P = 0.34)

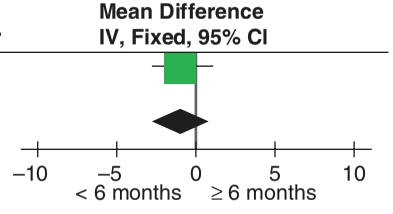

Fig. 12.3 Forest plot on neck pain (Visual Analogous Scale, range 0–100) related to timing of surgery

by means of a visual analog scale (VAS, range 0–10). Pain was reported at the time of inclusion and at 6 months and 1 year after symptom debut, and the mean value was used for statistical analysis.

There is low-quality evidence (unable to be generalized, post hoc data) from one trial (N = 58) that at 6 months, patients treated in a timely manner had no difference in neck pain from those treated surgically after 6 months from symptom debut (MD −0.9, 95% CI −27.56 to 0.56).

Arm Pain in Cervical Radiculopathy

The details regarding effect of intervention on arm pain are summarized in Fig. 12.4.

One trial included randomized data from 58 patients and evaluated radicular pain in cervical radiculopathy related to surgical timing [9]. The pain intensity was assessed by means of a visual analog scale (VAS, range 0–10). Pain was reported at the time of inclusion and at 6 months and 1 year after symptom debut, and the mean value was used for statistical analysis.

There is low-quality evidence (unable to be generalized, post hoc data) from one trial (N = 58), that at 6 months, patients treated in a timely manner had significantly less arm pain than those treated surgically after 6 months from symptom debut (MD −1.4, 95% CI −27.36 to −0.64).

Neck Function in Cervical Radiculopathy

The details regarding effect of intervention on neck function are summarized in Fig. 12.5.

One trial included randomized data from 58 patients and evaluated neck function in cervical radiculopathy related to surgical timing [9]. The neck function was assessed by means of the Neck Disability Index (NDI, range 0–100). Pain was reported at the time of inclusion and at 6 months and 1 year after symptom debut, and the mean value was used for statistical analysis.

There is low-quality evidence (unable to be generalized, post hoc data) from one trial (N = 58), that at 6 months, patients treated in a timely manner had no difference in neck disability from those treated surgically after 6 months from symptom debut (MD −4.80, 95% CI −24.36 to 14.76).

A summary of the major findings is shown in Table 12.2.

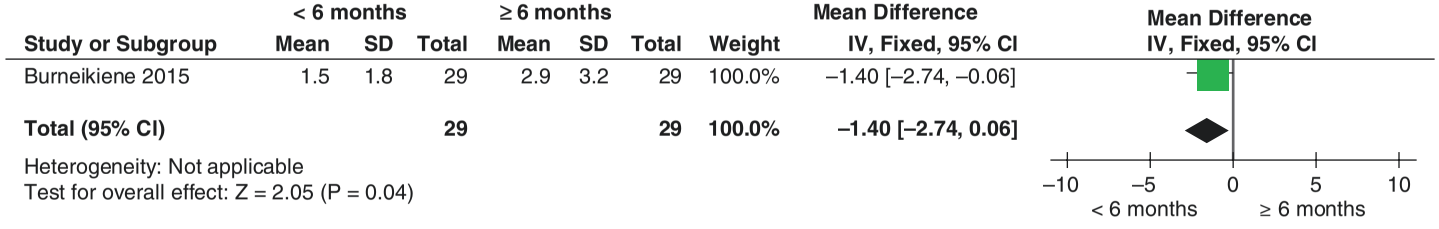

Fig. 12.4 Forest plot on arm pain (Visual Analogous Scale, range 0–100) related to timing of surgery

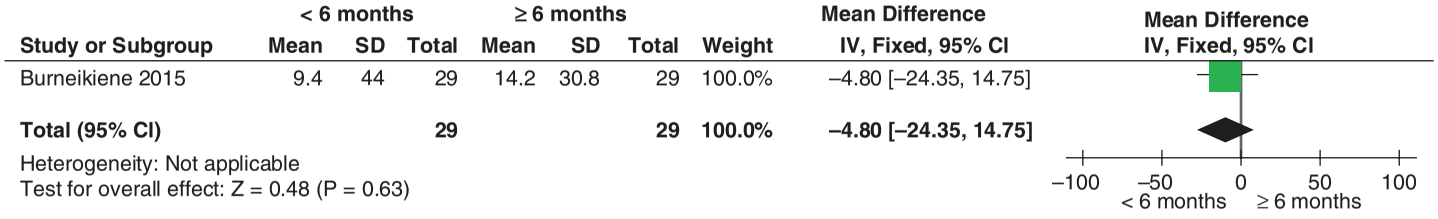

Fig. 12.5 Forest plot on the neck function (Neck Disability Index, range 0–100) related to timing of surgery

Table 12.2 Summary of findings

Outcomes	Illustrative comparative risks[a] (95% CI)		Relative effect	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	surgery >6 months	surgery <6 months				
Early compared with delayed surgical treatment for cervical disc herniation						
Patient or population: 58 patients with 1-or 2-level surgery for cervical disc herniation *Settings:* Post-hoc analysis of randomised controlled trial with 12–37 months follow-up *Intervention:* early surgical intervention within 6 month *Comparison:* delayed surgical intervention after 6 months						
VAS neck range 0–10, 12–37 months follow-up	The mean VAS neck ranged across control groups from 1 to 8 cm	The mean VAS neck in the intervention groups was0.9 cm lower	0.68 ($p = 0.3$)	58 (1)	⊕⊕⊖⊖ *low*	Post-hoc
VAS arm range 0–10, 12–37 months follow-up	The mean VAS arm ranged across control groups from 0 to 10 cm	The mean VAS arm in the intervention groups was1.4 cm lower	0.46 ($p = 0.04$)	58 (1)	⊕⊕⊖⊖ *low*	Post-hoc
NDI range 0–50, 12–37 months follow-up	The mean NDI ranged across control groups from 0 to 30 points	The mean NDI in the intervention groups was4.8 points lower	0.54 ($p = 0.06$)	58 (1)	⊕⊕⊖⊖ *low*	Post-hoc

CI Confidence interval; *RR* risk ratio; *VAS* visual analogous scale, *NDI* neck disability index
GRADE Working Group grades of evidence
High quality: further research is very unlikely to change our confidence in the estimate of effect
Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Very low quality: we are very uncertain about the estimate
[a]The basis for the *assumed risk* (e.g. the median control group risk across studies) is provided in footnotes. The *corresponding risk* is based on the assumed risk in the comparison group and the *relative effect* of the intervention (and its significance)

Discussion

This study summarizes the sparse evidence on the effects of the timing of surgical treatment for cervical radiculopathy. Early intervention within 6 months has a beneficial effect on arm pain compared to non-surgical management. No significant effect on function and neck pain was found. Since only one study fulfilled the inclusion criteria and this study was a post hoc analysis of a randomized controlled trial, the quality of evidence leaves room for improvement.

There is always a risk of unintentional selection bias when performing a qualitative synthesis with meta-analysis. However, in order to reduce selection bias, the authors followed a well-defined inclusion process with clear inclusion criteria. Only two studies matched these inclusion criteria.

Agreements and Disagreements with Other Studies or Reviews

Cervical radiculopathy can cause difficulties regarding the surgical decision, due to variations in its natural course. The correlation between the symptoms and the MRI findings is controversial because of high rates of false-positive findings among asymptomatic patients [18, 19]. Moreover, it has been shown that cervical disc herniation, like lumbar disc herniation, can undergo spontaneous regression [20, 21]. The herniation triggers an acute phase of the radiculopathy in which neurapraxia leads to local ischemia followed by an inflammatory response. Therefore, initial non-operative management is widely accepted, as it has a high rate of success with substantial improvement of pain and disability. Improvement usually occurs within the first four to 6 months [22, 23]. Therefore, surgical treatment is considered only in cases of persistent radicular pain and/or neurological disability. ACDF provides a very high chance of improvement of the radicular pain. However, although surgery has been shown to be superior to conservative treatment at 4 months of follow-up, at 16 months there was no statistically significant difference between surgery and conservative treatment [24].

The systematic review by Gebremariam et al., compared effects of different surgical techniques as a treatment of cervical disk herniation [25]. The authors included 11 RCTs in their evaluation with only one comparing surgery with conservative treatment. The review did not provide any information on the optimal timing of surgery.

Burneikiene et al. present a post hoc analysis of data collected during a prospective,

randomized, double-blind clinical trial [9, 16]. They demonstrate that surgery performed within 6 months after onset of the radiculopathy resulted in statistically significant improvement in arm pain (measured using the VAS scale) and lower NDI, in comparison to the results for patients undergoing surgery after the six-months cut-off.

Similar results are obtained in the prospective, randomized trial by Engquist et al. [17]. The authors conclude that duration of neck and arm pain (less than

12 months) is significantly associated with a better outcome in the group treated with ACDF. In comparison, the same factors had no effect on the outcome in the group treated with physiotherapy.

Our critical review reflected the dilemma of designing and conducting high-quality clinical research and its impact on clinical practice. Only 0.4% of the available publications met the rigorous criteria for inclusion in our final investigation of the quality of the clinical evidence. We finally presented the results of two publications which both reached an evidence level of Level II, allowing only simplified conclusions. Further methodological analysis investigating these two trials revealed that even these prospective, randomized studies are afflicted by selection, performance and reporting bias with regard to the endpoints of interest. Although the results suggest that surgery performed earlier than 6 months after onset leads to better outcomes, the level of evidence is insufficient. Randomized, controlled trials comparing acute cervical radiculopathy treated surgically within 3 months, 6 months and 12 months, with return-to-work data, EQ5D, NDI and pain scales, as well as full hospital and societal cost data as endpoints, could elucidate the value and cost-effectiveness of early surgical intervention. This design would require a multicentric approach and should preferably be funded by an independent and unbiased funder.

Alternatively, if a national patient registry included data on the onset of pain, date of surgery and patient-reported outcome measures, a randomized registry trial could provide some of the required answers.

Our analysis revealed that large, prospective randomized trials, avoiding or adjusting for bias, are difficult or even impossible to execute. This reflects the situation in clinical practice, where there is a general surgical agreement among spine surgeons despite the fact that it is supported by only weak evidence from the literature.

For instance, the current expert opinion is that at least six to 12 weeks of non-surgical treatment with anti-inflammatory medication and physiotherapy can be proposed as initial treatment in the presence of severe pain without functionally important motor deficit [6]. Similar results were presented by a survey among practicing Dutch neurosurgeons [10]. Almost half (47.9%) of the surgeons waited until at least eight to 12 weeks of persistent radiculopathy had been present before recommending surgery. Therefore, due to the difficulties of providing solid evidence at Level I, there should be an alternative, in order to maintain good clinical practice and a high quality of surgical healthcare. In our opinion, a multicenter, prospectively collected data register could be a valuable source summarizing the results of daily surgical practice. Thus, studies based on these data should receive more acceptance, financial support and credit, even with lower evidence status. As they gained popularity, these types of clinical studies would certainly stimulate surgeons to be more active in reporting their results and comparing them with those of colleagues from different centers.

Conclusions

There is weak evidence that surgical treatment, if performed within 6 months after pain debut, leads to better clinical outcomes with regard to radiculopathy. Therefore, if we decide to treat a patient surgically, it would be better to do so within 6 months. If our surgical wait lists do not allow early planned surgical intervention, we should consider surgical treatment only if red flags force us to do so.

Even these studies were not completely free from bias. Since there is an overwhelming amount of contradictory results from low-evidence studies, it is currently impossible either to determine the reproducibility of these results or to compare these findings to other studies of similar quality. There is a need for further high-quality research and for alternative clinical investigations that would support spine surgeons in their daily clinical struggle. Future studies should focus on the utility of surgical treatment as well as on return-to-work data, as both are strong drivers of healthcare policy.

Box

1. What is known?
   Early surgical treatment may improve time to recovery and lower societal costs.
2. What is new?
   Surgical treatment, if performed within 6 months after pain debut, leads to better clinical outcomes with regard to radiculopathy
3. What are the consequences for clinical practice?
   If we decide to treat a patient surgically, it would be better to do so within 6 months. If our surgical wait lists do not allow early planned surgical intervention, we should consider surgical treatment only if red flags force us to do so.

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The Oblique Corpectomy, Forgotten but an Effective Procedure? A Systematic Review

13

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Introduction

Cervical spondylotic myelopathy (CSM) is the most common cause of spinal cord dysfunction in elderly [1]. When CSM results in neurological deficits, surgical decompression is often the treatment of choice, aiming to prevent further decline by widening of the cervical spinal canal.

In 1993 George et al. [2] reported oblique corpectomy (OC) for the first time as an alternative technique for the treatment of CSM opposed to the anterior and posterior approaches e.g. anterior corpectomy with bone grafting with or without plating, laminectomy with or without fusion and laminoplasty [3–7] The technique of OC is often performed as a multilevel oblique corpectomy (MOC). According to Chibbaro et al. [8] the predominant indications for OC are anterior compression associated with either straightening or kyphosis of the cervical spine, in the absence of instability [8]. In 1994 Ohara et al. [9] also reported the use of MOC for treating ossification of the posterior longitudinal ligament (OPLL) of the cervical spine [9].

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The OC procedure uses a lateral route to access the cervical vertebrae, with close control of the vertebral artery (VA), to provide a wide window for decompression. The posterolateral part of the corpus is obliquely drilled out, while the anterior portion is maintained. As a result, the stability of the spine is preserved allowing for multilevel decompression and obviating the need for arthrodesis. This also reduces the costs and possible complications that are accompanied by instrumentation. The technique is considered technically demanding since close control of the VA is warranted and despite several advantages, the usage of OC is not as widespread as that of the anterior or posterior approaches.

A narrative review was performed by Tykocki et al. [10] on the application of OC in case-reports, biomechanical cadaveric and clinical studies [10]. They showed that OC was an effective and safe approach for various pathologies of the cervical spine, especially for tumors of the ventral part of the cervical spine [10]. Overall clinical improvement was found to be at least 70% or more, which is comparable to studies with the central corpectomy [10, 11]. They acknowledged that the approach carries a high risk (15.7%) of Horner syndrome (HS), but a modification of the technique was proposed to reduce the incidence of permanent HS. However, limitations of the review are that the search strategy cannot be reproduced, no information is included on the risk of bias in individual studies and different studies describing the same patients were included.

To our knowledge, no systematic review has been performed focusing solely on the clinical outcome and related costs of OC performed in the recent years. Therefore, the aim of this systematic review is to present up-to-date clinical data on the surgical procedure of OC in patients with symptomatic CSM regarding clinical outcome and related costs.

Method

Study Selection

A comprehensive systematic search that adhered to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) [12] was performed on the application of OC in various pathologies of the cervical spine. The search strategy was made in consultation with a professional librarian for the databases: Pubmed, Embase, Scopus, Web of Science and Google Scolar. For this review, only articles written in English were included and a search filter was applied to exclude articles published before 2000th. In addition, reference lists of identified reviews were also searched to find possible eligible articles.

The following key terms were applied in the PubMed search (94 hits, May 7th 2018): (“Spinal Cord”[Mesh] OR “Cervical Vertebrae”[Mesh] OR cervical[tiab]) AND (“Decompression, Surgical”[Mesh] OR surgical decompress* [tiab] OR corpectom*[tiab] OR corporectom*[tiab] OR ventral decompress*[tiab] OR vertebrect*[tiab] OR vertebrotom*[tiab]) AND (oblique[tiab] OR anterolateral[tiab] OR anterolateral[tiab]).

Inclusion and Exclusion Criteria

Clinical studies, cohort studies and case-reports on the application of OC for myeloradiculopathy were included in this review. Pure biomechanical/cadaver studies were excluded, because of the clinical outcome of interest. We were interested in the following clinical outcome profiles: neurological, functional, cervical range of motion, sagittal alignment, complication rate and related costs. Only studies describing one-level or multilevel OC for the treatment of cervical levels C3 t/m C7 were included. Studies performing OC on levels C1 or C2 were excluded, because the relatively different anatomy of these vertebrae possible associated with a difference in clinical outcome. A detailed description of inclusion and exclusion criteria can be found in the Supplemental Digital Content.

Data Selection and Extraction

The results from the electronic search were screened by two independent reviewers (NS and AB) on title, abstract and full-text. If any disagreement existed, the opinion of a third independent reviewer was consulted (JK). Full-text articles were retrieved for further eligibility assessment. If a full-text version was not accessible, contact was sought with the first author.

A data extraction form was designed by the same reviewers who performed the screening and data was collected from the included studies on study design, year of publishing, patient socio-demographics, diagnosis, intervention details, follow-up, clinical outcome measurements, radiographic results, complications and costs.

Risk of Bias Assessment

Quality assessment of non-randomized cohort studies was conducted according to the MINORS-tool (Methodological Index for Non-randomized Studies) [13]. Eight different items for non-comparative studies and 12 for comparative studies were scored 0 (not reported), 1 (reported but inadequate) or 2 (reported and adequate). We considered low risk of bias when studies fulfilled all MINORS criteria or had a score above 12 for non-comparative or a score of 20 or more for comparative studies.

For case-series, the modified Delphi technique developed by Moga et al. [14] was used to assess the methodological quality [14]. Eighteen different items were scored with yes/no and a score of >70% being yes was of acceptable quality. In addition, the overall body of evidence was assessed according to the guidelines of the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) [15].

Data Synthesis and Analysis

For continuous outcome measures, we reported a change in the mean or median scores. Because of the differences in outcome measurements and the lack of control

groups, we did not combine studies into a meta-analysis. However, we presented studies side by side in summary tables and figures to make a qualitative assessment of treatment effectiveness and complications.

Results

Study Selection

The search strategy yielded 375 potentially relevant citations. Of these, 196 duplicates were identified. The remaining records were screened on title and abstract. Thirty-six full-text records were selected for assessment of eligibility and of these an additional 23 articles were excluded. A flow-chart of the selection procedure is depicted in Fig. 13.1.

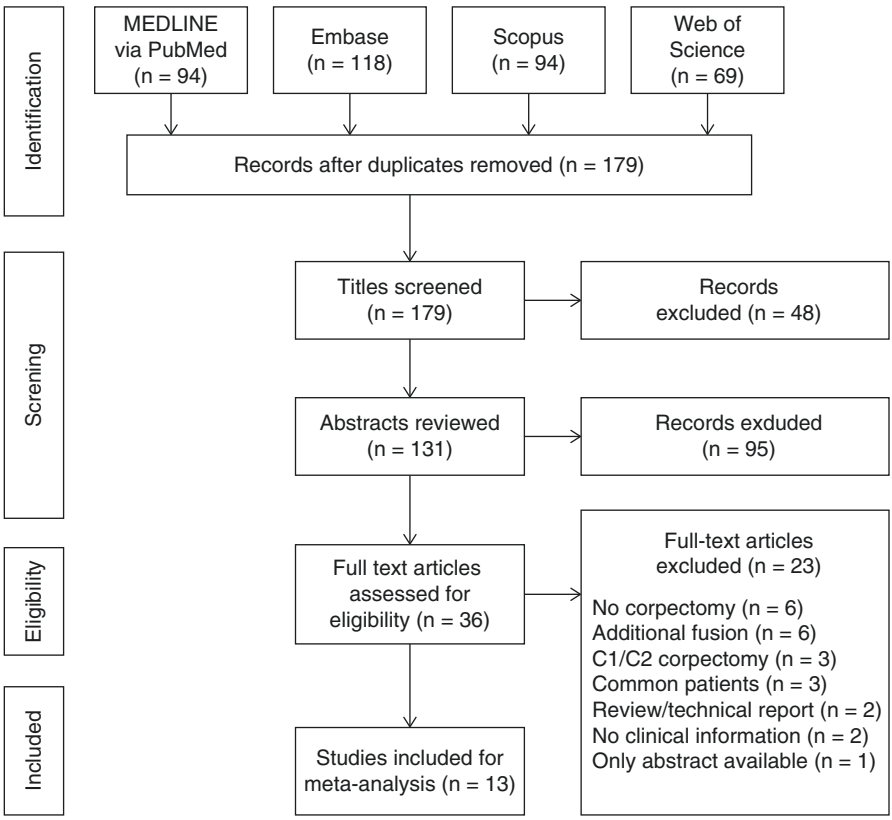

Fig. 13.1 Flow-chart of study selection process for articles describing oblique corpectomy for treatment of cervical spondylotic myelopathy

Study Characteristics

Seven prospective, 3 retrospective cohort studies, 2 case-series and one case report were identified. The mean age of our patient population (n = 740) was 54 years and the majority (72.2%) were male. Follow-up times differed across studies, varying from 6 to 96 months with a mean of 34.2 months. Most operated level was C5 and most studies performed a multilevel OC (details are provided in Fig. 13.2). Details regarding the literature studies on patient socio-demographics are illustrated in Table 13.1.

Risk of Bias Within Studies

Risk of bias was determined according to the GRADE guidlines [15]. The majority of the studies (n = 9) was assigned to level III evidence and 4 studies were classified as level IV.

Concerning the risk of bias in the non-RCT studies, no information regarding "unbiased assessment of study endpoints" was available, except for the study of Sakar et al. [16] In addition, prospective calculation of "the study size" was not

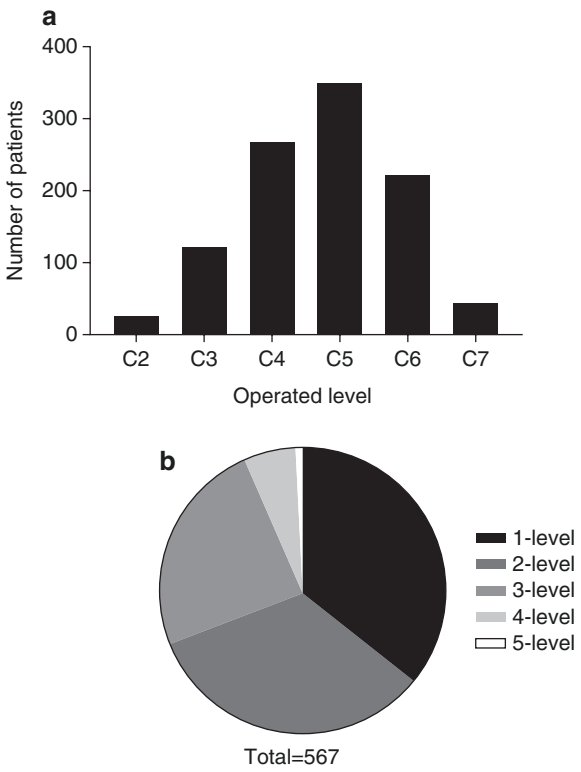

Fig. 13.2 (**a**) Division of operated levels. (**b**) One level or multilevel operation

Table 13.1 Socio-demographic information

Study	Year	N	Design	Diagnosis	Clinical and radiological outcome	Mean follow-up in months[a] (range[b])	Stability	Mean age (range[b])	Male/female	Mean duration of clinical history[a] (range[b])	Mean operation time (range[b])	Level of evidence[c]
Koc et al. [17]	2004	26	Prospective	12 CSM, 12 CSR	JOA, cervical spinal alignment	16.8 (12–24)	92.3%	51.3 (30–72)	18/8	NR	NR	III
Goel et al. [24]	2005	4	Prospective	4 OPLL	Nurick grade	33 (6 months–5 years)	Yes	55.3 (46–72)	4/0	25.75 (8 months–4 years)	NR	IV
Rocchi et al. [25]	2005	48	Prospective	39 CSM, 9 CSR	JOA, Nurick grade	24	Yes	57.4 (36–74)	35/13	19.4 (9–48)	NR	III
Barrey et al.	2006	1	Case-report	Chordoma	Complications described	18	Yes	29	F	NR	NR	IV
Chacko et al. [23]	2007	3	Case-series retrospective	3 OALL + OPLL	JOA, Nurick grade	18 (6 months–3 years)	Yes	54.7 (53–56)	3/0	7.3 (2–12)	NR	IV
Kiris et al. [19]	2008	40	Prospective	40 CSM, (8 CSM + CSR)	JOA, spinal neck pain score, spinal canal diameter, cervical spinal alignment	59 (24–98)	Yes	55 (43–78)	27/13	32.6 (3–174)	NR	III
Momma et al. [26]	2008	91	Prospective	66 CSM, 25 CSM + OPLL	NCSS ROM, cervical spinal alignment	50.4 (3–84)	Yes	65.3 (r30–90)	56/35	NR	NR	III
Chibbaro et al. [21]	2009	268	Retrospective	268 CSM	JOA, NDI, VAS neck, spinal canal diameter	96	98%	58 (29–83)	161/107	9.6 (4–33)	129 (92–183)	III
Moses et al. [22]	2010	24	Prospective	19 CSM, 5 CSM + OPLL	Nurick grade, spinal canal diameter	6	NR	54 (34–83)	23/1	NR	NR	III

Lee et al. [20]	2011	22	Prospective	22 OPLL	JOA	14.4 (11–18)	NR	58 (39–80)	13/9	NR	253.5 (165–410)	III
Chacko et al. [23]	2013	153	Retrospective	153 CSM (patients OPLL excluded)	JOA, Nurick grade, cervical spinal alignment	34.6 (SD ±25.4)	Yes	51.1 (23–82)	141/12	18.28 (SD ±26.7)	NR	III
Sakar et al. [16]	2014	56	Retrospective	42 CSM, 14 CSM + OPLL	JOA, Nurick grade	Median 16 (10–98)	Yes	49.6 (SD ±8.73)	52/4	15.4 (SD ±17.4)	NR	III
Kunert et al. [27]	2016	4	Case-series retrospective	4 CSM (due to SEA)	Frankel grade	66 (3 days–110)	Yes 3/4	63 (44–90)	2/2	19.3 days (7 days–1 month)	NR	IV

NR Not reported, *CSM* cervical spondylotic myelopathy, *CSR* cervical spondylotic radiculopathy, *OPLL* ossified posterior longitudinal ligament, *OALL* ossified anterior longitudinal ligament, *SEA* spinal epidural abscess, *JOA* Japanese Orthopaedic Association score, *NDI* neck disability index, *VAS* visual analogue scale, *NCSS* neurological cervical spinal scale, *ROM* range of motion

[a]Mean is given, unless otherwise specified (*d = days, w = weeks, m = months, y = years)

[b]Range is given, unless otherwise specified as SD = standard deviation (*d = days, w = weeks, m = months, y = years)

[c]Level of evidence according to the GRADE criteria [15]

Table 13.2 Risk of bias in non-RCT studies according to the MINORS criteria

	Non-comparative studies								Comparative studies			
Clearly stated aim	Cleary stated aim	Inclusion of consecutive patients	Prospective data collection	Endpoints appropriate to study aim	Unbiased assessment of study endpoint	Follow-up period appropriate to study endpoint	<5% lost to follow up	Prospective calculation of study size	Adequate control group	Contemporary groups	Baseline equivalence of groups	Adequate statistical analyses
Koc [2004]	?	+	+	+	–	+	+	?	NA	NA	NA	NA
Rocchi [2005]	?	+	+	+	–	+	+	?	NA	NA	NA	NA
Kiris [2008]	?	+	+	+	–	+	+	?	NA	NA	NA	NA
Momma [2008]	+	+	?	+	–	+	+	?	NA	NA	NA	NA
Chibbaro [2009]	+	+	+	+	–	+	+	?	NA	NA	NA	NA
Chacko [2013]	+	+	?	+	–	+	?	?	NA	NA	NA	NA
Sakar [2014]	+	?	?	+	+	+	+	?	NA	NA	NA	NA
Moses [2010]	+	+	+	+	–	+	+	?	+	?	–	–
Lee [2011]	+	+	+	+	–	+	+	?	+	+	+	?

NA= Not applicable

Table showing ratings using the MINORS tool to assess the risk of biases in a group of studies. This tool provides a grading scale: 0 for not reported (-), 1 for reported but inadequate (?) and 2 for reported and adequate (+).

clearly described in all studies. In total 6/9 studies were considered high risk of bias. (details are provided in Table 13.2 and the complete risk of bias calculation can be found in the Supplemental Digital Content).

In all 3-case series, the "aim of the study" was not clearly described, and relevant outcomes were not measured with appropriate method or statistical test. In addition, none of the studies provided "estimates of the random variability" in data analysis. All 3-case series were considered to be of high risk of bias. The complete risk of bias calculation can be found in the Supplemental Digital Content.

Clinical Outcomes

Japanese Orthopedic Association Score (JOA)

A mean pre- and postoperative JOA score was reported in 8 studies and improvement was seen in all studies. An additional standard deviation (SD) was given in 4 (Koc et al. [17]; Chacko et al. [18]; Kiris et al. [19]; Sakar et al. [16]) and a range score in 2 studies (Lee et al. [20]; Chacko et al. [18]). The greatest improvement was seen in the study of Chibbaro et al. [21] after a follow up of 96 months, however no

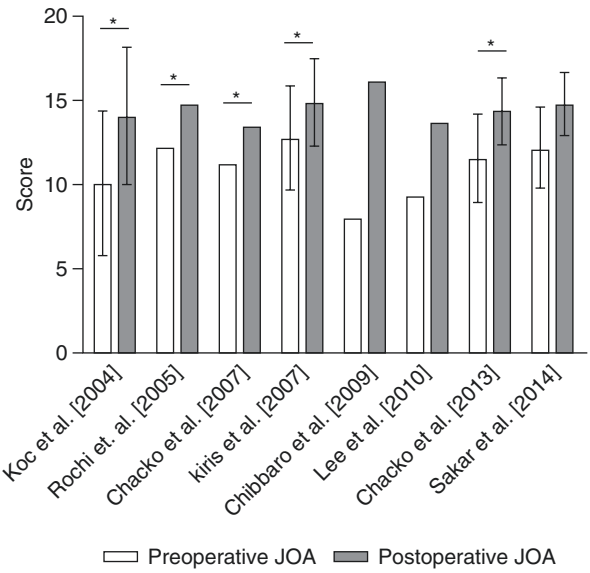

Fig. 13.3 Change in mean Japanese Orthopedic Association score

information on level of significance was reported. Among all studies, level of significance was given in 5/8 studies and was statistically significant in 5 (see Fig. 13.3).

Nurick Grades

A mean preoperative Nurick grade was given in 6 studies and a mean postoperative Nurick in 5 (the prospective study of Moses et al. [22] did not report a postoperative Nurick score but reported a clinical improvement of 83% at 6 months follow-up). In all 5 studies the Nurick grade was improved postoperative. An additional standard deviation (SD) was given in 2 (Chacko et al. [23]; Sakar et al. [16]) and a range in 3 studies (Goel et al. [24]; Chacko et al. [18]; Moses et al. [22]). The greatest improvement was seen in the study of Rocchi et al. [25] which was statistically significant ($p = 0.002$). The level of significance was also given in both studies of Chacko et al. [18, 23] (see Fig. 13.4).

Cervical Neck Pain Scores

Studies of Kiris et al. [19] and Chibbaro et al [21]. determined cervical neck pain pre- and postoperative. Kiris et al. [19] used a self-rated 10-point numeric scale to assess neck pain in which 0 represented no pain and 10 the most severe pain. Improvement was seen with a mean preoperative score of 3.7 ± 3.8 and mean postoperative score 2.2 ± 2.3 respectively. Chibbaro et al. [21] reported the Neck Disability Index (NDI) and the Visual Analogue Scale (VAS). Mean preoperative NDI was 55.2 which significantly improved after 6-weeks follow-up with a mean score of 31.2. The VAS improved from 65 to 14 after 6 weeks, staying relatively stable thereafter.

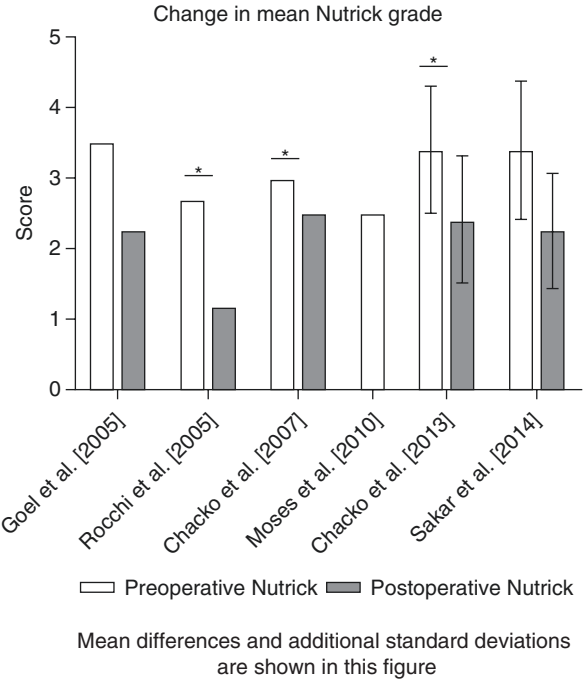

Fig. 13.4 Change in mean Nurick grade. Mean differences and additional standard deviations are shown in this figure. *Follow-up in months: Goel et al. [24] mean 32, Rocchi et al. [25]12, Chacko et al. [18] 12 + 6 weeks, Chacko et al. [23] mean 35.9, Sakar et al. [16] median 16

Neurological Cervical Spine Scale (NSCC) and Frankel Grade

The study of Momma et al. [26] used the Neurological Cervical Spine Scale (NCSS) to determine the clinical outcome after 6 months and 1-year follow-up. No baseline score was given, but the mean improvement in NCSS was 72% for n = 90 at 1-year follow-up.

The study of Kunert et al. [27] used the Frankel grade to determine clinical outcome in 4 patients treated with OC for spinal epidural abscesses. One patient died during follow-up due to cardiac arrest and the clinical outcome of the remaining 3 patients was Frankel grade D in 2 (fair to good motor function below injury level) and grade E in 1 patient (normal function).

Radiological Outcomes

Information on the spinal canal diameter was given in 3 studies (Kiris et al. [19], Chibarro et al. [21], Moses et al. [22]). All studies reported an increase in canal diameter postoperative, among which the largest increase was observed in the study of Kiris et al. [19] (see Fig. 13.5a).

Four studies reported detailed information on spinal alignment to determine the efficacy of the OC. In the study of Koc et al. [17], Kiris et al. [19], and Chacko et al. [23] the preoperative spinal curvature was described. In all 3 studies, most patients had a lordotic spine preoperative (Fig. 13.5b). Koc et al. [17] and Chacko et al. [23] also mentioned the postoperative spinal curvature, which was mostly lordotic. In the study of Chacko et al. [23] 4 patients went from a lordotic spine to a kyphotic spine and 2 from a straight spine to kyphosis.

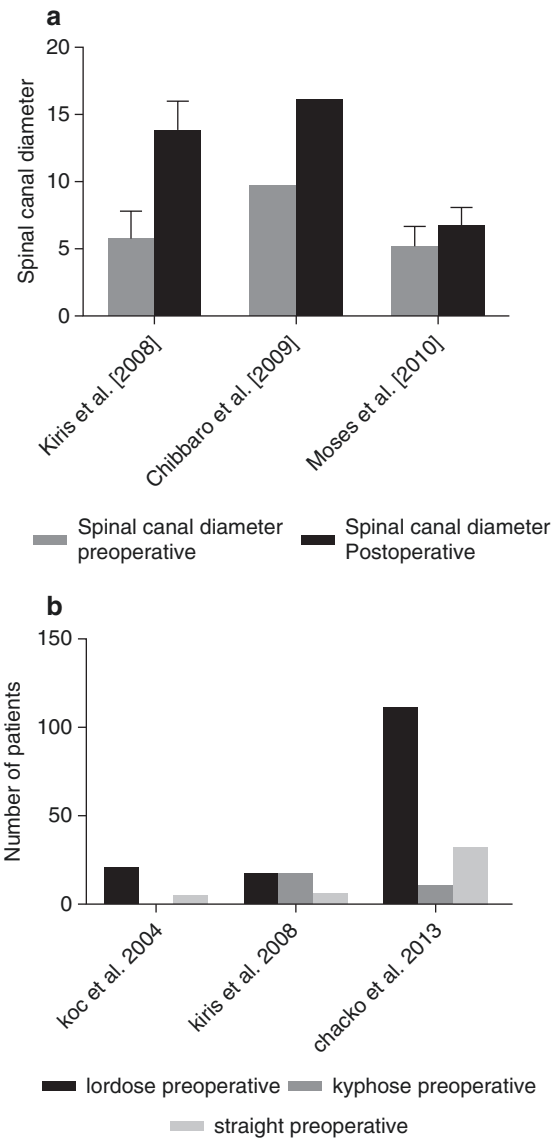

Fig. 13.5 (**a**) Change in spinal canal diameter. (**b**) Preoperative final curvature

In addition, 11/13 studies described the spinal stability to be maintained, with a cumulative rate for postoperative spinal stability of 99% (686 out of 694 patients).

Complications

The occurrence of HS was the most reported complication among all studies with a cumulative percentage of 13%. However, this HS resolved in most studies between 3 and 6 months and was permanent in 20/82 patients with HS (for more detailed information see Table 13.3).

Table 13.3 Postoperative complication rates

	Patients	HS (% perm)	Kyphos (% perm)	CSF leak (% perm)	CSF fistula (% perm)	Pers. Brachial (% perm)	Foramin stenosis(% perm)	C5 rad (% perm)	VA lesion (% perm)	Infection (% perm)	Axial pain (% perm)	Paresis trapez (% perm)	Dysphag (% perm)	Paresis deltoid (% perm)	Hematoma (% perm)	Dural tear (% perm)
Koc et al. [17]	26	8/26 (7.7%)	1/26 (3.8%)	NR	1/26 (3.8%)	1/26 (3.8%)	1/26 (3.8%)	NR	NR	NR	2/26 (7.7%)	NR	NR	NR	NR	NR
Rocchi et al. [25]	48	14/48 (2.1%)	NR	0/48	NR	NR	NR	NR	0/48	0/48	NR	NR	NR	NR	0/48	NR
Barrey et al. [2006]	1	0/1	NR	NR	NR	NR	NR	NR	NR	NR	NR	1/1	NR	NR	NR	NR
Chacko et al. [18]	3	1/1 (0%)	NR	NR	NR	NR	NR	1/1	NR	NR	NR	NR	0/3	NR	NR	NR
Kiris and Kilincer [19]	40	10/40 (10%)	NR	NR	0/40	NR	NR	3/40 (2.5%)	NR	NR	NR	NR	NR	3/40 (2.5%)	1/40	2/40
Chibbaro et al. [8]	268	14/268 (1.1%)	NR	0/268	NR	NR	NR	0/268	NR	0/268	NR	NR	0/268	NR	NR	NR
Lee et al. [20]	22	NR	NR	4/22	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	2/22	NR
Chacko et al. [23]	153	32/153 (5.9%)	5/153[a]	1/153	NR	NR	NR	5/153 (0.7%)	1/153	NR	NR	NR	NR	NR	NR	1/153
Momma et al. [26]	91	3/91 (1.1%)	NR	2/91	NR	NR	NR	NR	NR	NR	NR	NR	NR	2/91 (none)	1/91	NR

Between brackets (%perm) is the percentage of permanent complications depicted as percentage of the total patient group when this information was given, (none) indicates that this complication resolved in all of the patients

NR Not reported, *Patients* total number of patients, *HS* Horner syndrome, *Kyphos* kyphosis, *Pers. Brachial* persistent brachialgia, *For stenosis* foraminal stenosis, *C5 rad* C5 radiculopathy, *VA lesion* lesion of the vertebral artery, *Paresis trapez* paresis of the musculus trapezius, *Dysphag* dysphagia, *Paresis deltoid* paresis of the deltoid muscle

NR = indicates not reported

[a]Asymptomatic kyphosis (not associated with neurological deterioration or lack of clinical improvement)

Costs

Among all studies, no information was given on the costs of OC. However, two studies (Chibbaro et al. [21]; Lee et al. [20]) reported the mean operation time, which was 129 min (range 92–183) and 254 min (range 165–410) respectively. Regarding operated levels, the study of Chibbaro et al. [21] operated 1-level in 108 and multilevel in 160 patients. The study of Lee et al. [20] did not provide information on this.

Discussion

The aim of this systematic review was to evaluate the clinical outcome and effectiveness of OC. We found among all 13 included studies an overall clinical improvement postoperative, unfortunately we had to rely on observational studies of which the quality was low.

The pre- and postoperative JOA score was the most reported clinical outcome measurement (8/13 studies). In all studies the JOA score was improved postoperative, but we must keep in mind that the follow-up time differed across the studies. Interestingly, the study of Chibbaro et al. [21], the largest study (n = 268) with the greatest improvement after 96 months, did not report any statistical value. In addition, 5/8 studies did report a statistical value and all of them were statistically significant. This could indicate a potential publication bias. A systematic review and meta-analysis of Zhu et al. [28] demonstrates that a significant higher improvement in JOA score was seen after anterior approaches compared to posterior approaches for CSM. The postoperative improvement in JOA score after OC was comparable to the posterior approaches of the study of Zhu et al. [28] No study has been performed comparing OC directly to anterior and posterior approaches.

We found among all studies the sagittal alignment to be well preserved. Only one patient in the study of Koc et al. [17] and 5 in the study of Chacko et al. [18] developed kyphosis postoperative after a mean follow-up of 16.8 and 18 months respectively. In addition, spinal stability was excellent with a cumulative stability rate of 99% (686 out of 694 patients). Three studies reported information on the preoperative spinal curvature, which was lordotic in most of the patients. This is in contradiction with the study of Chibbaro et al. [8] which describe that predominant indications for OC are anterior compression associated with either straightening or kyphosis of the cervical spine [8, 17].

When evaluating safety of the procedure, similar complication profiles were reported with the most common complication being HS (13%). Such a high incidence of HS does not occur in studies on other decompression procedures for CSM, which report mostly instrument-related complications such as graft migration or dysphagia/hoarseness [28, 29]. The high incidence of HS after OC can be explained by the longitudinal dissection and lateral retraction of the longus colli muscle during the procedure, which lies medial to the sympathic chain. Therefore, a modification of the technique was proposed by Chacko et al. [23], which led to a lower incidence of

HS. Remarkably, no incidence of VA lesion was reported among all studies, while different studies on OC warn that the approach carries a high risk of VA injury. A possible explanation could be that because of the well-known risk of VA injury, only experienced surgeons perform OC leading to a lower incidence. Nevertheless, Chibbaro et al. [21] acknowledged that the technique requires a learning curve.

Unfortunately, no information on the costs was reported in any of the articles. Two studies did mention the operation time, which varied but was still comparable to the anterior and posterior approach [28]. None of our studies provided a cost-effectiveness analysis, possible because most of the studies were dated before the year of 2010 and the value of cost effectiveness analysis was mainly recognized after that time frame. We can postulate that OC is accompanied by lower costs compared to other surgical procedures, because there is no need for fusion and instrumentation.

There are some limitations to our study that warrant attention. First, the quality of all included studies was low, and no meta-analyses could be performed because the lack of control groups. In addition, only articles published in English were included, which could be a potential publication bias, and most of the studies focused on the evaluation of neurological and radiological improvement but neglected to evaluate the overall quality of life. Finally, follow-up times differed across studies which made comparison difficult.

Conclusion

To conclude, the OC is not a forgotten surgical technique, but other techniques seem to be more familiar to most surgeons and have a broader indication range. The multilevel OC is one of the surgical techniques which is appropriate to decompress the spinal cord in CSM patients, reflected as postoperative improvement in clinical JOA and Nurick scores (although not statistically confirmed in all studies). The OC technique demands more experienced skills from the surgeon and therefore a more prolonged learning curve should be faced if one wants to learn the technique to prevent serious complications such as VA lesions or permanent HS. Although literature does not elaborate on cost effectiveness of OC, no additional instrumentation is necessary and therefore direct costs may be lower in comparison with other instrumented techniques.

It could be suggested to initiate comparative prospective studies on OC in patients with CSM which, besides clinical radiological outcomes, focus on the Quality of life (QoL) and cost-effectiveness of the technique.

Box

1. What is known?

Multilevel oblique corpectomy allows for wide decompression of the cervical spinal canal in patients with CSM, without the need for vertebral stabilization.

2. What is new?

Surgeons seem to be more familiar with anterior or posterior approaches, because when one is facing the OC technique a prolonged learning curve is required to provide a safe and successful decompression of the cervical spinal cord.

3. What are the consequences for clinical practice?

The OC is not a forgotten surgical technique and has good results in terms of both clinical (JOA, Nurick) as radiological outcomes (spinal canal diameter and stability), but the technique is rather technically demanding and good clinical practice is required to prevent serious complications such as vertebral artery lesions or permanent Horner syndrome.

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Cervical Arthroplasty: The Evidence

14

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Introduction

The introduction of cervical spine total disc arthroplasty (CSTDA) in 2002 inaugurated a promise to lower the adjacent level degeneration in patients after cervical spine arthrodesis [1].

Some patients require other surgeries for new intervertebral disease adjacent to previously operated levels [2].

Although the nature of adjacent level disease (ALD), whether secondary to a natural process or due to previous arthrodesis, was under debate, several devices and products were developed to maintain spine movement close to normal levels and decrease ALD. A great research and industry effort has resulted in this much desirable device.

Initial preliminary reports have described good results, but several publications have pointed towards a lack of effect and complications with CSTDA [2].

Presently, more than 15 years after the initial descriptions, long term results can be assessed to obtain the results and rates of complication with the use of these devices [3–14]. The present chapter aims to analyze the effect of CA, as compared to classical techniques such as anterior cervical discectomy and fusion (ACDF) on the surgical treatment of symptomatic cervical disc degenerative disease, in studies with long term follow-up, in order to reveal the risks and benefits in the evidence-based scenario.

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Methods

In this chapter, a systematic review comparing CSTDA with fusion (ACDF) was done, in order to reveal the risks and benefits of CSTDA.

Systematic Review Protocol

Studies that evaluated CSTDA at one or two levels of the cervical spine were included. Eligibility criteria of the papers were based on the population, intervention, control and outcome characteristics of the published papers (PICO) as described below:

P- patients with myelopathy and/or radiculopathy refractory to conservative treatment who underwent surgery.

I-Intervention: Cervical spine total disc arthroplasty (CSTDA).

C-Control: Anterior cervical discectomy and fusion (ACDF).

O-Outcomes: Clinically and radiologically important outcomes:

Neck pain, arm pain, specific and generic quality of life scales (neck disability index (NDI) and SF-36 scale), reoperations: at the index and adjacent levels.

Compound outcomes unrelated to the patient's signs and symptoms, such as range of motion, were not evaluated.

Adverse effects were studied.

Method for the Collection of Evidence

Papers retrieved from MEDLINE (PubMed) and Cochrane Central Register databases of randomized trials published from 2002 to December 2016 were evaluated.

Two authors (AFJ and RVB) independently assessed the results of the electronic literature survey and any divergences were resolved by discussion between them.

The articles were first assessed according to their titles. Papers selected by titles had their abstracts evaluated, and abstracts selected were assessed in full.

Prisma flow diagram was used to illustrate the identification, screening, eligibility and finally in order to ensure long-term results, only randomized studies with at least 5 years of follow-up were included (Fig. 14.1).

The following text words or MeSH® terms were used in the electronic PubMed search:

> "cervical vertebrae"[All Fields] AND "intervertebral disc"[All Fields] AND (("arthroplasty"[MeSH Terms] OR "arthroplasty"[All Fields]) OR (("arthrodesis"[MeSH Terms] OR "arthrodesis"[All Fields]) AND ("random allocation"[MeSH Terms] OR ("random"[All Fields] AND "allocation"[All Fields]) OR "random allocation"[All Fields] OR "randomized"[All Fields]))) AND "humans"[MeSH Terms]—450.

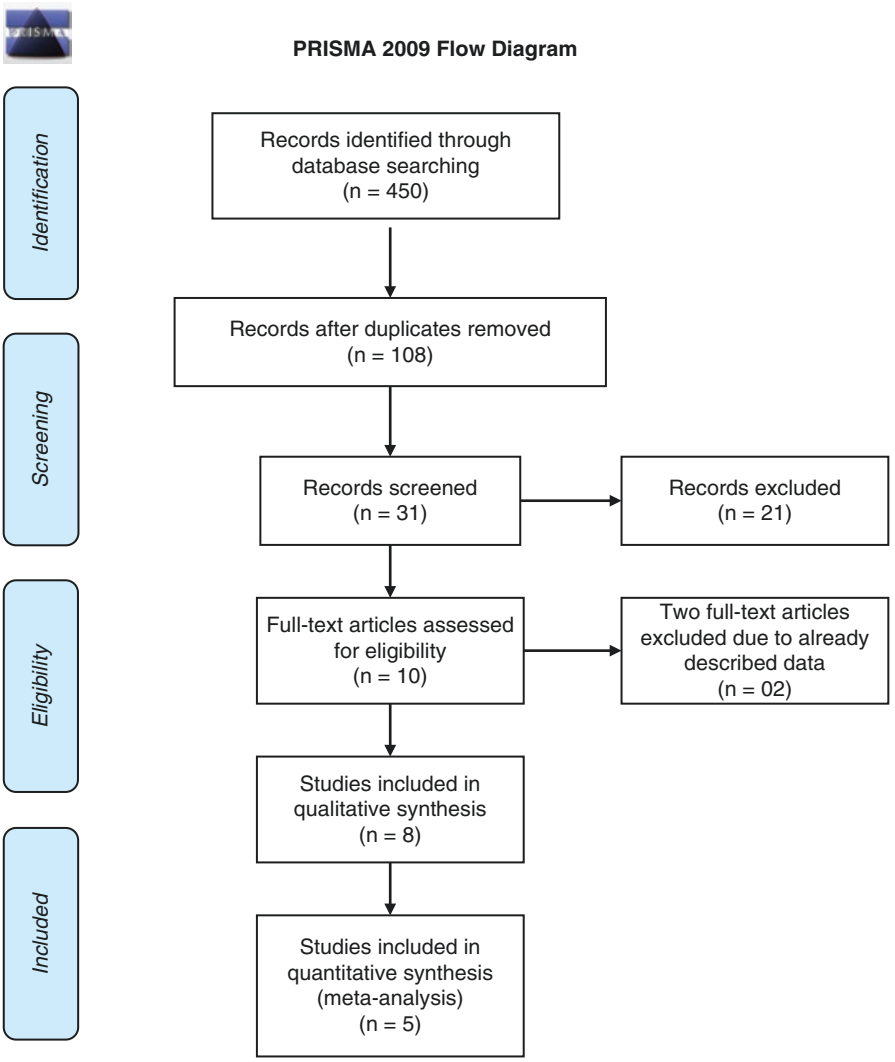

Fig. 14.1 PRISMA flow diagram of search results

The following terms were used in the search of the Cochrane Central Register:

> "cervical vertebrae" AND "intervertebral disc" AND (arthroplasty OR arthrodesis)—52.

Cross-references obtained from the primary articles were evaluated.

The WebPlotDigitizer® software was used to extract the graphic data of the original papers [15, 16].

Data Analysis

Data were analyzed using the Revman package. Values from some studies not immediately available were recalculated or obtained from graphs or figures. Visual Analogue Scale (VAS) data were adjusted on a scale from 0 to 100. Statistical heterogeneity was assessed using the chi-square test and I^2.

Fixed and random effects were used depending on the quantity of the inconsistencies detected. Moderate and high inconsistencies were analyzed using the random effect model [17].

Evaluation of Methodological Quality

The methodological quality of published papers was evaluated based on the Cochrane tool for risk of bias (ROB). The ROB was classified as low, moderate or high [17].

Methodological quality for each outcome was given by GRADE evaluation.

Results

The search characteristics and the papers included are described in the flow diagram (Fig. 14.1).

Four hundred and eight studies were selected from MEDLINE and 52 from Cochrane Central.

After removal of duplicates, 108 abstracts were examined, and 31 articles were evaluated in full. Ten articles were then included in the study, eight of them related to one level of arthroplasty [4–11] and two related to two levels [12, 13].

Studies That Reported the Outcomes at One Vertebral Level

Eight single level studies were described [4–11]. Three of them were excluded:

Loumeau [5], Hissey [6], and Delamarter et al. [10] had their papers excluded because their data were intermediate follow-up results described in more recent publications. Five studies at one level were evaluated.

Evaluated Outcomes

To accomplish results with only outcomes relevant for patients, clinical and radiologic outcomes were evaluated, without mention of composed non-clinical outcomes.

Neck Pain (VAS Neck)

Five studies compared neck pain between devices (Fig. 14.2).

A total of 607 patients were evaluated in the arthroplasty group and 469 in the fusion group in the last follow-up period (data extracted directly from tables and graphs). The analysis was carried out using the fixed effect model ($I^2 = 0$). The difference in mean VAS Neck was 4.6 (CI = 1.63–7.72) points, favoring the arthroplasty group. As the scale ranged from 0 and 100, this result was close to zero.

Arm Pain (VAS)

A total of 448 patients underwent arthroplasty and 341 underwent ACDF in the four studies analyzed (Fig. 14.3).

There was substantial statistical heterogeneity in results, $I^2 = 56\%$. There was no statistically significant difference among the devices results: −2.19 (−8.54 to 4.17).

Philips et al. [13] evaluated only the worst arm pain with at least 20% improvement. In this model of expressing results, not all patients were compared.

Neck Disability Index (NDI): This is a validated outcome for cervical spine diseases.

A random effect analysis of the difference(s) between groups revealed an effect of 4.03 [0.26–7.79] points in favor of arthroplasty (p = 0.05) (Fig. 14.4).

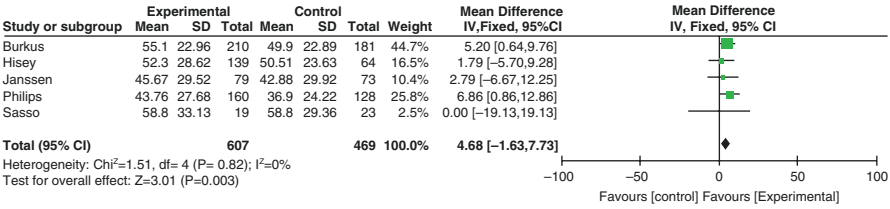

Fig. 14.2 Meta-Analysis- Neck Pain (VAS). Difference favors CSTDA group but on a scale ranging from 0 to 100, the result is close to zero and clinically irrelevant

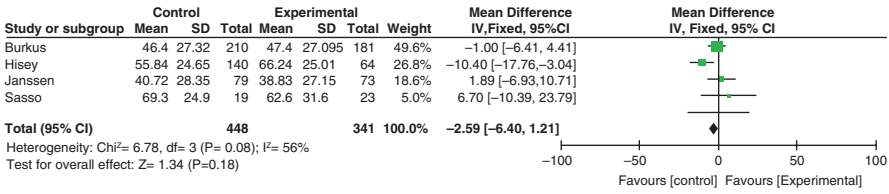

Fig. 14.3 Meta-Analysis—Arm pain (VAS). There is no difference between groups

Reoperation at Index Level (Fig. 14.5)

The description of the results by the authors in the abovementioned studies made it difficult to separate surgeries performed at the same level and at the adjacent level. It was assumed that reoperation at any level outside the index level should be considered reoperation at adjacent level.

The heterogeneity computed among effects in the four studies was low. ($tau^2 = 0$; H = 1.00 [1.00; 1.51]; $I^2 = 0.0\%$). However, one study accounted for 59.6% of the effect (Fig. 14.5). As per the random model, the odds ratio for reoperation at the same level between arthroplasty and arthrodesis was 0.5 [0.2909; 0.97], p = 0.01.

Reoperations at Adjacent Levels

Four studies evaluated the number of patients re-operated at adjacent levels (Fig. 14.6).

The heterogeneity among effects was small ($tau^2 = 0$, $I^2 = 0.0\%$). The odds ratio of being re-operated at the adjacent levels between arthroplasthy and arthrodesis was 0.30 [0.1824–0.4896], p < 0.0001.

Adverse Events (AE)

The description of adverse events was too varied and heterogeneous among the studies, thus preventing a pooled analysis.

Sasso and Hissey et al. did not report any adverse effects [4, 6].

Burkus et al. [9] evaluated adverse effects in both groups of patients. Ninety-eight percent (97.7%) of patients undergoing arthroplasty and 94.5% of patients in the ACDF group had at least one adverse effect reported.

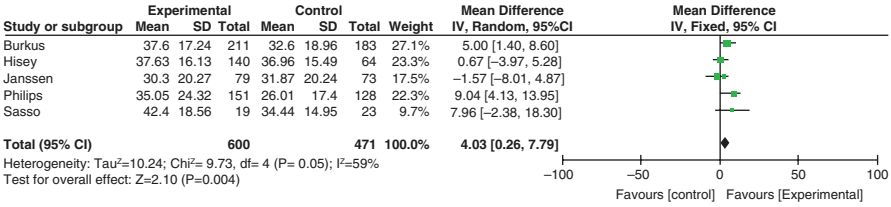

Fig. 14.4 Meta-analysis. Neck disability index. Difference favors CSTDA

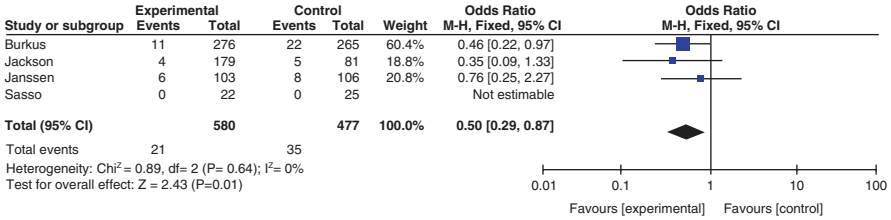

Fig. 14.5 Meta-Analysis- Reoperation rate at the same level. Results favor CSTDA

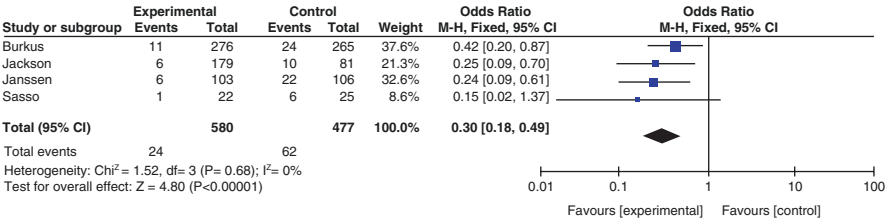

Fig. 14.6 Meta-Analysis- Reoperation at adjacent levels. Results favors CSTDA

Patients in the investigated group had fewer adverse effects than the control group (20.9% vs 38.9%, $p < 0.001$), whereas the control group had fewer urogenital effects than the investigational group (20.1% % vs. 12.2%, $p = 0.024$).

Philips et al. [8] described AE as VAS associated with dysphagia between the two groups, neurological success rate and number of patients worsened after the procedure. The number of worsened patients, and neurological success (maintained or improved) was not statistically different. The mean VAS associated with dysphagia was 8.8 ± 15. 7 for arthroplasty and 16.9 ± 24.2 for ACDF ($p = 0.001$).

Jansen et al. [7] reported 48 adverse effects in 30 (28%) of the 106 cases undergoing ACDF and 41 adverse events in 28 (27%) of the 103 cases of ProDisc-C® arthroplasty. There were no differences among groups in any category of reported effects ($p = 0.8778$).

Studies that Reported the Outcomes at Two Levels

Two studies related to the multicenter study of MOBI-C® prosthesis at two levels, registered by the same RCT number were found [12, 13] and are supposed to be part of the same study.

Outcomes

VAS arm and VAS neck: The difference in VAS arm pain and VAS neck pain between groups was not statistically significant.

NDI: The mean improvement in NDI in the arthroplasty group was 37 ± 20 versus the ACDF group 28 ± 18 ($p = 0.0003$). The difference between them was nine points in NDI.

SF-36 scale: The mean SF-12 PCS score differences between baseline and 60 months difference for both groups favored arthroplasty: 8.1 ± 11.58. There were no statistically significant differences in the MCS scores.

Secondary Surgeries

Same Level (Index) Reoperations

In Jackson's paper, as shown in Table 4 [12], nine CSTDA patients and 10 ACDF patients were re-operated at the same level as before (9/234 vs. 10/105; $p = 0.035$).

In Radcliff's paper [13], in the ACDF group, 7.6% (8 patients) were re-operated (8/105) while in the arthroplasty group 3.5% (8 patients) were re-operated (8/225) ($p = 0.10$).

Adjacent Level Reoperation

Adjacent level reoperations in the paper by Radcliff [13]: in the ACDF group 8.5% (9/105) of patients were re-operated at the adjacent level while 0.4% (1/225) CSTDA patients were re-operated ($p < 0.001$).

Jackson's [12] paper: We recalculated the number of reoperations at the adjacent level by number of patients operated (and not by the number of reoperations made), and excluding patient 33, who seems to have had an external cause for reoperation, (and not an adjacent level disease following ACDF), the difference favors arthroplasty ($8/234 \times 10/105$; $p = 0.020$).

Analysis of Methodological Quality: Risk of Bias (ROB)

Several studies had substantial differences between samples before interventions. In randomized trials, the samples were significantly different before comparison.

In one study there were mistakes in ascribing patients to each branch of the study [4].

Some studies included non-randomized patients from training cases. In some cases, patients were evaluated in the clinical setting. There were discrepancies between data from earlier and more recent studies [7, 8, 10, 11].

In some papers data were available only based on averages and did not provide absolute numbers [6]. In other studies [8] it was difficult or impossible to properly extract data from the text, with regard to the amount of disease from adjacent levels in each group.

There was substantial amount of sponsor influence in published papers [4, 6–9].

The amount of bias in all the papers was relatively high.

Level of Evidence Table 14.1 describes the quality of evidence for all evaluated outcomes. The overall level of evidence in all evaluated studies was low: Our confidence in the effect estimated is limited. The actual effect may be substantially different from the estimated effect.

Table 14.1 GRADE evidence profile: comparison between ACDF and CA

	Quality assessment						
Outcome	Number studies/ Design	Limitations	Inconsistency	Indirectness	Imprecision	Publication bias	Quality
VAS neck	5/ RCT	Serious limitations	No serious inconsistency	No serious indirectness	Moderate to high imprecision[a]	Undetected	Low
VAS arm	4/ RT	Serious limitations	Moderate inconsistency	No serious indirectness	Moderate to high imprecision-effect size is small	Undetected	Low
NDI	5/ RT	Serious limitations	Moderate inconsistency	No serious indirectness	Moderate imprecision-effect size is small[b]	Undetected	Low
Reoperation at index level	4/ RT	Serious limitations	No serious inconsistency	No serious indirectness	No significant imprecision	Undetected	Low
Reoperation at adjacent levels	4/ RT	Serious limitations	No serious inconsistency	No serious indirectness	No significant imprecision	Undetected	Low

[a]The effect size is very small, close to zero and doesn't suggest meaningful benefit or harm

[b]The 95% CI lower limit includes no meaningful benefit about the effect of the intervention and crosses the effect size of 0.5 in either direction

Discussion

The accumulated experience in spinal deformity correction with balance restoration in the last 60 years is immense. Experienced surgeons can restore kyphotic spines, which occur with increasing frequency in older ages, with ACDF. It is not known whether it is possible with CSTA. With some prosthetic devices, postoperative kyphosis is a concern. The undesirable effect associated with ACDF is the lack of mobility in operated segments.

Some studies have shown that the mobility in the decompressed and fused segments may still improve after ACDF. But CSTDA promises immediate preservation of spine mobility.

To date, the natural history of intervertebral disc mobility is known to be evolution to disc narrowing and ankylosis, and it is not known if mobility preservation is possible, and whether it will benefit patients.

Correcting adjacent levels of disc degeneration would be a desirable effect of CSTDA.

Any superiority in any clinical outcome from one of the devices would be of interest to the patients.

Clinically, at one vertebral level, the summary effect on the difference in neck pain was 4.68 points. As the scale established by the studies ranged from 0 to 100, the obtained difference was close to zero and not clinically significant.

For the arm pain, there was no significant difference between groups. For the NDI scale, the difference was 3.71, also without any clinically significant difference.

Reports of adverse events are extensive and not limited to those caused by the implants. Most of the adverse events were medical problems not related to the devices [17].

Number of reoperations at the same level was significantly lower in the arthroplasty group. However, two of the studies were responsible for 69% of the adverse effects. Additionally, the main causes for reoperation were pseudoarthrosis or non-union in the ACDF group in many patients and imbued certain subjectivity in the indication. Shriver et al. [18] published a systematic review and meta-analysis with all prospective studies reporting pseudoarthrosis rates for ACDF with plate fixation. Overall pseudoarthrosis rate was 2.6% (95% CI: 1.3–3.9). The non-union or pseudoarthrosis rates in the CSTDA-ACDF comparative studies were well over these rates.

The analysis of reoperation at two levels also was described differently by the articles.

There are several limitations regarding the quality of published papers. Some, although describing themselves as randomized, did not report the mode of randomization.

There were substantial differences between patient samples for practically all studies, such as patient age, number of alcoholic patients, imbalances in the pain scales, and in opioid consumption, among others. These types of imbalances may interfere with the results and suggest a type of inadequacy of randomization for treatment or control of the candidates for the procedures.

There was a significantly greater loss of data in the ACDF group for all studies and the follow-up losses were high for the long-term results, reducing the quality of the randomized trials, downgrading the quality of published evidence in this topic.

There was also high statistical heterogeneity for various outcomes.

Donk et al. [19] evaluate cervical sagittal alignment after three different anterior discectomy procedures for single-level cervical degenerative disease. They randomized patients for anterior cervical discectomy without fusion (ACD—45 patients), anterior cervical discectomy with fusion by stand-alone cage (ACDF—47 patients) and cervical arthroplasty (ACDA—50 patients). Upright cervical spine radiographs were used to evaluate cervical alignment (angles between C2 and C7 were used as well as the angle of the involved levels).

After a mean follow-up of 25.4 ± 18.4 months, although there were differences in the involved angles comparing ACD versus ACDA and ACD versus ACDF (in the ACD group a more negative angle was found postoperatively), the angle between C2 and C7 did not change between the groups. Regardless the technique used for single-level cervical disease, the global alignment of the cervical spine was similar.

Results Published in Existing Systematic Reviews

Some systematic reviews have been published in the last decade. There is a great difference in design between them. For example, Ma et al. [20] produced results pooling studies with follow-up time ranging between 1 and 6 years of follow-up. The authors evaluated several outcomes: Overall success, mean surgical duration, mean blood loss, mean hospitalization, patient satisfaction, neck Disability index, VAS pain score, reoperation rate, and complications. The only outcomes that had revealed differences between procedures were the operative time and overall success. The overall success outcome is a composite outcome and not a clinical outcome and its clinical significance may not be the same across several different countries. The VAS arm and VAS neck scales appear to have been grouped for analysis. The methodological quality of evaluated studies seems not to be described. Luo et al. [21] evaluated adjacent rate degeneration between fusion and Cervical spine arthroplasty. Follow-up of studies ranged between 24 and 60 months. Authors provided results based on papers with 24 months follow-up time. Only one study evaluated, among all, showed difference in the rate of adjacent degeneration between the devices and this same work was responsible for 27.8% of all summary weight, shifting the summary effect to the significance level. Boselie et al. [22] provided results for 1 or 2 years follow-time. At that time they concluded that differences in effect size were statistically significant but invariably small and not clinically relevant for all primary outcomes.

In this chapter, our analysis was based only on primary studies with long term follow-up, in which we could evaluate strong clinical outcomes.

Presumable Benefits and Risks of Each Treatment

Although the described data suggests some superiority for arthroplasty with regard to reoperation rates, the analysis of the quality evidence does not support the use of one technique over the other. Although there is some uncertainty related to any superiority of one device over the other, as the number of complications and side effects are low, both techniques remain as options for patients. As an option, both will be similar if the costs involved are similar.

Conclusions

Until now, the knowledge based on long-term randomized trials suggests that both devices have similar safety and the outcomes are very similar in both devices. The quality of evidence does not permit any conclusion related to the reoperation rates due to adjacent level degeneration. Both techniques must be considered as viable options in the surgeon's armamentarium.

Conflict of Interest There is no conflict of interest to be declared related to this work.

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Cauda Equina Syndrome Due to Ruptured Lumbar Intervertebral Disc: Optimal Timing for Surgery

15

Carmen L. A. Vleggeert-Lankamp, Nina S. Korse, and Henk W. Elzevier

Introduction

Cauda equina syndrome (CES) is a rare neurological condition which is caused by compression of several of the nerve roots of the cauda equina. In 1929, Dandy was the first in English literature to publish about CES-like complaints, describing two patients with CES which were surgically decompressed, stating that it was disc material causing CES in those cases, and not, as was suggested before, spinal tumor [1]. Mixter and Barr raised much more attention with their publication 5 years later in which they demonstrated the positive effects of surgical decompression in 19 patients with CES due to lumbar herniated disc and thus advocated timely surgical intervention in all such cases [2].

Although CES can be instigated by any pathological process compressing the cauda equina, e.g. epidural hematoma, tumor, trauma or infection [3], a herniated lumbar disc is the most common cause of caudal compression in literature (45%) [4]. The incidence of CES in lumbar herniated disc patients is reported to be about 0.12% of herniated discs [5], and 2–6% in operated lumbar disc herniations [6]. Due to the strong indication for (emergency) decompression, CES incidence is believed to be much lower in the total group of sciatica patients.

Clinically, CES is suspected by a combination of complaints, which are not necessarily all manifest at the time of presentation, and which may vary greatly per patient. The most widespread definition of CES is the one proposed by Fraser et al. after reviewing hundreds of CES articles, stating that at least one or more of the

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following items must be present for diagnosis: (1) bladder and/or bowel dysfunction, (2) reduced sensation in the saddle area, (3) sexual dysfunction, with possible neurologic deficit in the lower limb (motor/sensory loss, reflex changes) [4].

Historically, CES is considered to be a strong indication for prompt surgical intervention [2]. Thus, in supporting this conception with scientific evidence, CES research has traditionally concentrated on the effects of time between presentation and surgical decompression (time to decompression). Probably one of the most influential publications in this respect is the meta-analysis of Ahn et al. [7], concluding a significant worse outcome (in sensory, motor, urinary and rectal function) if time to decompression exceeded 48 h [7]. It was however criticized because of methodological flaws and its stringent conclusion about the 48 h time frame. This conclusion was believed to be too strong since figures suggested that early surgery was more beneficial than late surgery, even within the 48 h group. Critics mentioned that the conclusion of the safety of the 48 h time frame could lead to devaluation of the benefits of even earlier surgery [8]. Up to date, several additional studies have been performed focusing on the timing of surgery in case of cauda equine syndrome due to a lumbar herniated disc. The main research question in this review is to evaluate whether a smaller time window between onset of symptoms and surgery leads to better micturition outcome.

Methods

Literature Search Strategy

The initial literature search strategy was performed in PubMed, EMBASE, Web of Science, and COCHRANE focusing on publications between Jan 2001 till July 2018. This time period was chosen in follow up of the publication of Ahn [7]. All English-language publications on the influence of timing of surgery on micturition outcome in patients with a cauda equina syndrome were retrieved. Search strategy was based on the search strategy as shown in Fig. 15.1.

Selection criteria were stated as followed:

- the article was published in English;
- the study included patients diagnosed with cauda equina syndrome due to hernia nuclei pulposi (HNP), diagnosed by MRI or CT-scan;
- the study reported function of micturition at follow-up (e.g. post operative), with a follow-up period of at least 2 weeks;
- the study was a case study (with a minimum of ten patients), cohort study or randomized controlled trial. Systematic reviews or meta-analysis were not included;
- the study evaluated micturition outcome with respect to timing of surgery (time to surgery after onset of cauda equina compression complaints) in different time intervals, comprising at least the <48 h and >48 h intervals;
- the article was published fully in a peer reviewed journal.

Search string:

PubMed

(OR "lumbar herniated disk"[tw] OR "lumbar herniated disc"[tw] OR ("Intervertebral Disc Displacement"[mesh] AND ("Lumbar Vertebrae"[mesh] OR "lumbar"[tw])) OR "lumbar diskectomy"[tw] OR "lumbar discectomy"[tw] OR ("Diskectomy"[mesh] AND ("Lumbar Vertebrae"[mesh] OR "lumbar"[tw])) OR "Lumbar Vertebrae/surgery"[mesh] OR "prolapsed intervertebral disk"[tw] OR "prolapsed intervertebral disc"[tw] OR "discogenic compression"[tw] OR "lumbar disk"[tw] OR "lumbar disc"[tw] OR "lumbar disks"[tw] OR "lumbar discs"[tw] OR "Lumbar Vertebrae"[mesh]) AND ("cauda syndrome"[tw] OR "cauda equina"[mesh] OR "cauda equina"[tw] OR "cauda equine"[tw] OR "Polyradiculopathy"[Mesh]) AND ("timing"[tw] OR "Operative Time"[mesh] OR "Surgical Time"[tw] OR "Operative Time"[tw] OR "Time Factors"[mesh] OR "Time"[mesh]) AND ("2000/01/01"[PDAT] : "3000/12/31"[PDAT]))

Embase

(("lumbar disk herniation".mp OR "lumbar disc herniation".mp OR "lumbar herniated disk".mp OR "lumbar herniated disc".mp OR "lumbar disk hernia"/ OR "lumbar diskectomy".mp OR "lumbar discectomy".mp OR ("Diskectomy".mp AND (exp "Lumbar Vertebra"/ OR "lumbar".mp)) OR "lumbar disk surgery".mp OR "lumbar disc surgery".mp OR "Lumbar Vertebra"/su OR "lumbar disk prolapse".mp OR "lumbar disc prolapse".mp OR "prolapsed intervertebral disk".mp OR "prolapsed intervertebral disc".mp OR "discogenic compression".mp OR "lumbar disk".mp OR "lumbar disc".mp OR "lumbar disks".mp OR "lumbar discs".mp OR exp "Lumbar Vertebra"/) AND ("cauda equina syndrome"/ OR "cauda equina syndrome".mp OR "cauda equine syndrome".mp OR "cauda equina compression".mp OR"cauda equine compression".mp OR "cauda syndrome".mp OR "cauda equina"/ OR "cauda equina".mp OR "cauda equine".mp) AND ("timing".mp OR "Surgical Time".mp OR "Operative Time".mp OR"Time Factor"/ OR "Time"/) AND (200* OR 201*).yr) NOT (conference review or conference abstract).pt

Web of Science

TS=(("lumbar disk herniation" OR "lumbar disc herniation" OR "lumbar herniated disk" OR "lumbar herniated disc" OR "lumbar disk hernia" OR "lumbar diskectomy" OR "lumbar discectomy" OR ("Diskectomy" AND ("Lumbar Vertebra" OR "lumbar")) OR "lumbar disk surgery" OR "lumbar disc surgery" OR "Lumbar Vertebra"su OR "lumbar disk prolapse" OR "lumbar disc prolapse" OR "prolapsed intervertebral disk" OR "prolapsed intervertebral disc " OR "discogenic compression" OR "lumbar disk" OR "lumbar disc" OR "lumbar disks" OR "lumbar discs" OR "Lumbar Vertebra") AND ("cauda equina syndrome" OR "cauda equina syndrome" OR "cauda equine syndrome" OR "cauda equina compression" OR "cauda equine compression" OR "cauda syndrome" OR "cauda equina" OR "cauda equina" OR "cauda equine") AND ("timing" OR "Surgical Time" OR "Operative Time" OR "Time Factor " OR "Time")) AND py=(2000 OR 2001 OR 2002 OR 2003 OR 2004 OR 2005 OR 2006 OR 2007 OR 2008 OR 2009 OR 2010 OR 2011 OR 2012 OR 2013 OR 2014 OR 2015 OR 2016 OR 2017 OR 2018 OR 2019)

NOT ti=(veterinary OR rabbit OR rabbits OR animal OR animals OR mouse OR mice OR rodent OR rodents OR rat OR rats OR pig OR pigs OR porcine OR horse* OR equine OR cow OR cows OR bovine OR goat OR goats OR sheep OR ovine OR canine OR dog OR dogs OR feline OR cat OR cats))

Fig. 15.1 Search strategy in pubmed, embase and web of science

Cochrane

((("lumbar disk herniation" OR "lumbar disc herniation" OR "lumbar herniated disk" OR "lumbar herniated disc" OR"lumbar disk hernia" OR "lumbar diskectomy" OR "lumbar discectomy" OR ("Diskectomy" AND ("Lumbar Vertebra" OR "lumbar")) OR "lumbar disk surgery" OR "lumbar disc surgery" OR "Lumbar Vertebra"su OR "lumbar disk prolapse" OR "lumbar disc prolapse" OR "prolapsed intervertebral disk" OR "prolapsed intervertebral disc " OR"discogenic compression" OR "lumbar disk" OR "lumbar disc" OR "lumbar disks" OR "lumbar discs" OR "Lumbar Vertebra") AND ("cauda equina syndrome" OR "cauda equina syndrome" OR "cauda equine syndrome" OR "cauda equina compression" OR "cauda equine compression" OR "cauda syndrome" OR "cauda equina" OR "cauda equina" OR "cauda equine") AND ("timing" OR "Surgical Time" OR "Operative Time" OR "Time Factor"OR "Time")):ti,ab,kw
(("lumbar disk herniation" OR "lumbar disc herniation" OR "lumbar herniated disk" OR "lumbar herniated disc" OR "lumbar disk hernia" OR "lumbar diskectomy" OR "lumbar discectomy" OR ("Diskectomy" AND ("Lumbar Vertebra" OR "lumbar")) OR "lumbar disk surgery" OR "lumbar disc surgery" OR "Lumbar Vertebra"su OR "lumbar disk prolapse" OR "lumbar disc prolapse" OR "prolapsed intervertebral disk" OR "prolapsed intervertebral disc " OR "discogenic compression" OR "lumbar disk" OR "lumbar disc" OR "lumbar disks" OR "lumbar discs" OR "Lumbar Vertebra") AND ("cauda equina syndrome" OR "cauda equina syndrome" OR "cauda equine syndrome" OR "cauda equina compression" OR "cauda equine compression" OR "cauda syndrome" OR "cauda equina" OR "cauda equina" OR "cauda equine")):ti,ab,kw
AND py=(2000 OR 2001 OR 2002 OR 2003 OR 2004 OR 2005 OR 2006 OR 2007 OR 2008 OR 2009 OR 2010 OR 2011 OR 2012 OR 2013 OR 2014 OR 2015 OR 2016 OR 2017 OR 2018 OR 2019)

Fig. 15.1 (continued)

Quality Assessment

The methodological quality of all studies was assessed using an adjusted version of the checklist for cohort studies of the Dutch Cochrane Center [9]. The items reviewed in the assessment were: clear definition of cauda syndrome and clinical information about patients (saddle anesthesia, radicular complaints, micturition problems); clear description of timing of surgery; method for assessing outcome (urodynamic/grading/descriptive); selection bias, and loss to follow-up. Three points were maximally given for clear description of patient group, timing of surgery and outcome. One point was assigned if there was no selection bias, and one point was awarded if there was no or less than 20% loss to follow-up. A maximum of five points could thus be awarded.

Data Extraction

Data from the studies were extracted on number of patients, mean age at presentation, gender, time interval between start of symptoms and surgery, follow up time after surgery, number of patients operated in each time interval, and outcome of micturition. If patients with complete (indicated as CESR) and incomplete (indicated as CESI) cauda equina syndrome (with regard to micturition) were discerned, outcome parameters were presented separately for each group.

Level of Evidence

The quality of evidence for all outcome parameters was evaluated using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach according to Atkins [8] and adapted from Furlan [10].

Results

Characteristics of Included Studies and Risk of Bias

Through our search, 176 articles were identified, of which 127 original articles were left after removing duplicates (Fig. 15.2). Titles and abstracts were screened, resulting in 22 eligible articles. These articles were read full-text and, in total, ten studies met all criteria to evaluate micturition outcome with respect to timing of surgery in cauda equina syndrome [11–20]. Reasons for exclusion: eight of these studies appeared to be reviews, two studies were letters to the editors, one study only reported results on <24 h delay surgery [21] and one article was in Serbian [22]. No studies were excluded due to absence of micturition symptoms.

In the ten included studies, 559 patients were described (Table 15.1). All were retrospective studies with relatively small sample sizes (range 18–91), with the exception of one study that included 200 patients [15]. The mean age of patients included was ca 40 years without a clear predominance of gender. The time intervals that were distinguished in the articles comprised in general a time interval of <24 h after onset of micturition complaints, a time interval between 24 and 48 h and a time interval of more than 48 h after onset of complaints. With respect to follow

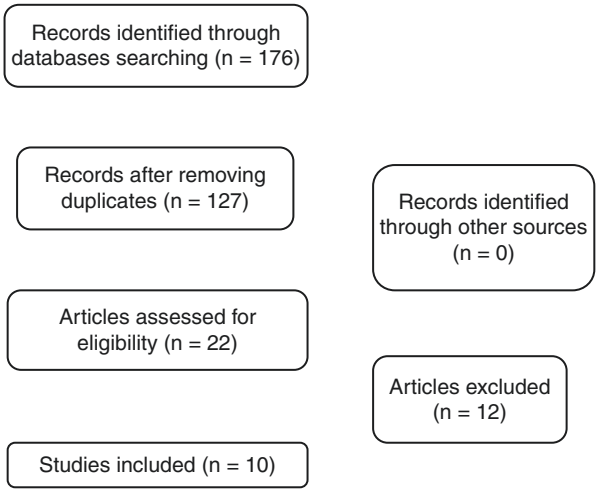

Fig. 15.2 Search strategy in the Cochrane Library

Table 15.1 Risk of bias

Study (year of publication)	N (559)	Mean age in years (range)	Men in %	Timing to surgery intervals (h)	Follow-up in months
Buchner (2002) [11]	22	42 (22–67)	55	<24 h, >24 h	Mean 45
McCarthy (2007) [12]	42	41 (24–67)	55	3 timing intervals, incl <24, <48, >48	Mean 60
Qureshi (2007) [13]	33	43 (30–79)	58	7 timing intervals, incl <12, <48	3 and 12
Olivero (2009) [14]	31	39 (24–79)	61	3 timing intervals, incl <24, <48, >48	Mean 60
Srikandarajah (2015) [15]	200	40	46	3 timing intervals, incl <24, <48, <72	Mean 3
Foruria (2016) [16]	18	42 (25–71)	44	<48 h, > 48 h	Mean 12
Beculic (2016) [17]	25	49 (29–68)	88	5 timing intervals, incl 1 <48 h and 4 timing intervals >48 h	6
Bydon (2016) [18]	45	42	62	6 timing intervals, incl <12, <24, <48	Mean 27
Kaiser (2018) [19]	52	41 (20–86)	42	3 timing intervals, incl <24, <48, >48	Mean 32
Heyes (2018) [20]	91	40 (25–82)	46	<24, <48, >48	At least 24

up, all articles described a follow up of at least several months if micturition complaints persisted. In case symptoms disappeared after surgery, as for instance described by Olivero [14], shorter follow up times were described. Mean follow up time varied from three to 60 months.

Seven studies were assessed to have a low risk of bias, scoring 4 or 5 out of 5 points [10, 12, 13, 15, 17, 18, 23] (Table 15.2). The other three studies showed intermediate risk of bias, mainly due to an inability to rule out selection bias. In none of these articles selection bias was obvious, however, it was merely the absence of a clear indication of its absence [12, 13, 16, 18].

Clinical Presentation of CES

Micturition dysfunction was regarded as an important element of CES by all authors and all articles assessed bladder function at presentation and at follow up. Micturition outcome was descriptive in all eight studies; none of the studies evaluated micturition by urodynamic tests. Two articles discerned grades of urinary dysfunction, by making a distinction between ‘urinary leakage’ and ‘catheter’ [11], and between partial and complete urinary retention [15], but in both articles, the outcome in the two groups was comparable. Four articles discerned complete cauda equine syndrome (CESR) from incomplete cauda equine syndrome (CESI) [13–15, 18], but only two of these determined outcome for these two entities separately [13, 18].

Table 15.2 Risk of bias assessment

Study (year of publication)	Score on risk of bias scale	Clearly defined patient group, timing and outcome	Absence of selection bias	Absence of attrition bias
Buchner (2002) [11]	****	**	*	*
McCarthy (2007) [12]	****	***	–	*
Qureshi (2007) [13]	***	**	–	*
Olivero (2009) [14]	*****	***	*	*
Srikandarajah (2015) [15]	*****	***	*	*
Foruria (2016) [16]	***	**	–	*
Beculic (2016) [17]	*****	***	*	*
Bydon (2016) [18]	***	***	–	–
Kaiser (2018) [19]	*****	***	*	*
Heyes (2018) [20]	****	**	*	*

Postoperative Micturition Dysfunction in Relation to Timing of Surgery

In most articles the majority of patients was operated more than 48 hours after onset of symptoms (Table 15.3). Urinary dysfunction persisted in on average 40% of patients, irrespective of the timing of surgical intervention. Four articles did not specifically give results on micturition for the time interval groups separately, but merely presented the conclusion that there was no statistical significant difference in outcome comparing those who underwent decompression within 24, 24–48, and after 48 h of developing symptoms [11–13, 19]. Furthermore, both Qureshi [13] and Bydon [18] distinguished 7 respectively 6 different time intervals in 33 resp. 45 patients, which results in an inability to find statistically relevant differences between time intervals.

Two articles discerned patients with a complete (CESR) and an incomplete cauda equina syndrome (CESI) with respect to micturition [15, 20]. Srikandarajah [15] defined CESR as ‘painless urinary retention and overflow incontinence ± complete perianal sensory loss’. CESI was defined as ‘altered urinary sensation and partial perianal sensory loss’. Micturition outcome was only defined as ‘no dysfunction’ if there was ‘complete normal control of function of the bladder’. Patients with CESI (139 patients) that were operated on within 48 h had a dysfunction at follow up in 16% of cases, in contrast to those that were operated more than 48 h after onset of symptoms demonstrating urinary dysfunction of 56% at the end of follow up. An evaluation was also done for the 24 h time interval: 11% of CESI patients that were operated on within 24 h (36 patients) had micturition dysfunction at final follow up, compared to 47% of CESI patients that were operated more than 24 h after onset of complaints (102 patients). The OR for normal bladder function at final follow up when operated on within 24 h opposed to after 48 h was 5.04 (CI 1.68–15.14). This was in contrast to the results for the CESR group in which no correlation of timing of surgery and micturition outcome could be demonstrated.

Table 15.3 Outcome

Study (year of publication)	<24	24 < 48	>48	Outcome at final follow up and correlation timing-micturition outcome
Buchner (2002) [11]	11	11		23% 'incomplete or poor bladder recovery', no correlation
McCarthy (2007) [12]	5	21	16	31% urinary retention or incontinence, no correlation
Qureshi (2007) [13]	7	5	21	44% 'leaking urine', no correlation
Olivero (2009) [14]	6	8	19	>90% 'not requiring catheterization', no correlation
Srikandarajah (2015) [15] Complete (61)	29	16	16	No correlation
Incomplete (139)	36	28	75	<24 h: 11% dysf, >24 h: 47% dysf
				<48 h: 16% dysf, >48 h: 56% dysf
Foruria (2016) [16]		6	6	25% 'urinary incontinence' (3 pts. in >48 h group), no correlation
Beculic (2016) [17]		9	16	89% 'normal bladder function' in <48 h group, 6% 'normal bladder function' in >48 h group, no stat performed
Bydon (2016) [18]	16	11	18	51% bladder dysfunction, six groups, no correlation
Kaiser (2018) [19]	11	5	36	39% urinary dysfunction, no correlation
Heyes (2018) [20]				
Complete (69)	7	15	47	25% 'painless urinary retention', no correlation
Incomplete (22)	1	4	17	45% 'painless urinary retention', no correlation

In the article of Heyes [20], CESI was defined as 'dysuria, frequency, urgency and altered urinary sensation in the absence of infection' and CESR was defined as 'painless urinary retention/neurogenic bladder'. Micturition outcome was distinguished in 'incomplete urinary function', 'painless urinary retention', and normal function. In this article, no correlation was identified between timing of surgery and outcome in the CESI group. However, the number of patients in this article is much smaller, and only 22 patients are allocated to the CESI group, of which 17 patients were operated after 48 h. In the CESR group, half of the patients was operated after 48 h (9 within 24 h), resulting in 13% of patients still suffering from painless urinary retention at long term follow up. In the group of 9 CESR patients, 57% still suffered from painless urinary retention at follow up.

Foruria [16] and Beculic [17] reported data in very small patient groups, which did not lead to statistically relevant data, but the micturition outcome data of patients that were operated within 48 h were better than those in the patients that were operated after 48 h.

Level of Evidence

All articles are observational studies and therefore the quality of evidence is low to very low (Table 15.4). The risk of bias was low to intermediate, but the studies had

Table 15.4 Reliability of outcome

Study (year of publication)	Relevance of conclusions on time intervals
Buchner (2002) [11]	No data specified on micturition per time interval
McCarthy (2007) [12]	No data specified on micturition per time interval
Qureshi (2007) [13]	33 patients over 7 time intervals, problem: Small numbers
Olivero (2009) [14]	Micturition outcome does not include bladder dysfunction, problem: Outcome definition
Srikandarajah (2015) [15] Complete (61)	Numbers are sufficient, outcome is well described, distinction in CESR and CESI, no problems
Incomplete (139)	
Foruria (2016) [16]	12 patients, problem: Small numbers
Beculic (2016) [17]	Numbers are small, outcome well described, no time interval less than 24 hours, problem: No statistics performed, no conclusions on early surgery
Bydon (2016) [18]	45 patients over six time intervals, problem: Small numbers
Kaiser (2018) [19]	No data specified on micturition per time interval
Heyes (2018) [20]	Numbers in the <24 h and 24–48 h group are small, problem: Small numbers
Complete (69)	
Incomplete (22)	

inconsistent findings, statistics were imprecise (small numbers), publication bias was unlikely, and the estimate of effect is insufficiently precise. Therefore, the evidence for the statement that micturition outcome after surgery for cauda equina syndrome due to herniated disc is dependent of the timing of surgery is very low.

Patient Preferences

Without doubt, there is a strong indication for decompressive surgery if a lumbar herniated disc is compressing the cauda equina to such an extent that micturition problems arise. Therefore the pros and cons of surgery are not a source of debate. The timing of surgery is debatable though data available in literature are not conclusive. Patient preference however is in the vast majority of cases to carry out surgical intervention with minimal delay in order to start recovery and to possibly regain normal micturition within due time.

Discussion

The current study covers the recent literature describing 559 patients (ten articles) in follow up of the study of Ahn [7] that was published in 2000, describing 322 patients (42 articles). Ahn's conclusion was that' there was a significant advantage to treating patients within 48 h versus more than 48 h after the onset of cauda equina syndrome'. The systematic literature that we performed covering the literature from 2000 up till 2018 cannot convincingly confirm nor reject this conclusion.

There are several reasons why literature does not offer a clear answer to the main research question. To begin with, the number of patients operated within 24 h or between 24 and 48 h was in the majority of studies low to very low. This is the same problem as was encountered by Ahn, according to a critical comment on this review by Kohles [8]. Ahn described data of 322 patients from 42 articles (mean of eight patients per article) and in only 11 of these articles data on patients that were operated in the time intervals '<24 h' and 'between 24 and 48 h' were described. Besides that, Kohles criticizes the epidemiological value of the conclusions of Ahn, which lead to the understatement of the value of early surgical intervention (<48 h).

Secondly, micturition function can be defined differently across studies. It is obvious that the definition of a 'good' outcome is largely dependent on the criteria for the success of regaining micturition. Olivero, for instance, concludes that outcome is 'good' (micturition is regained) if catheterization is not required at long follow up [14]. In the concerning article, a group of 31 patients is described of which 28 required catheterization upon inclusion, and in which only one patient needed catheterization at long term follow up. This result can be observed as a very positive result, namely regaining continence in the vast majority of patients, but it is very well possible that urinary leakage is still present in patients, and that patients experience this as discomfort and loss of quality of life. Concluding, in giving an overview of results, the degree of regaining micturition has to be taken into account.

Thirdly, the diagnosis of cauda equina syndrome before surgery is not always easy to make. An objective tool to evaluate function of micturition would be an urodynamic measurement, although even with such a tool, a premorbid dysfunction of the bladder cannot be excluded. In the postoperative setting, this could be a useful tool, but in the preoperative setting, urodynamic measurement would lead to a delay in surgery and is therefore not feasible. Another objective evaluation tool is the degree of postvoiding residue or urine retention. However, incomplete voiding can also be caused by severe pain, by use of opioids, and by horizontal positioning of the patient. These factors usually play a role in the patient suffering from a lumbar herniated disc coincidingly suffering from sciatica. It is therefore difficult to establish whether a CES is complete before surgery. The included articles all describe a retrospective setting, in which it is even more difficult to establish the completeness of cauda equine syndrome. Incomplete CES is however much easier to determine.

Fourthly, the retrospective design of the included studies poses a problem in demonstrating a correlation between timing of surgery and outcome, since it might be cumbersome to determine the exact timing of onset of complaints. In some cases, acute pain with direct inability to void, combined with sensory loss in the perineum and buttocks clearly indicates onset of CES. However, in the majority of cases, symptoms develop more gradually and the onset of micturition problems may be debatable.

An additional problem is the fact that the cause of surgical delay might be correlated to prognostic factors, therefore introducing bias. It is reasonable to suggest that in case of a complete CES, delay of both patient and surgeon is minimal. This leads to the situation that patients with the most serious urinary incontinence (and thus: most unfavorable prognosis) are operated in the smallest time frame, which thus might display a correlation (and not necessarily a causal relationship) of a small time frame with an unfavourable prognosis. Summarized, this might

underestimate the beneficial effects of early decompression. This theory is consistent with the results of Heyes [20], who reports postoperative urinary retention in 57% of patients that were operated within 24 h, versus 20% and 13% in the 24–28 h and > 48 h groups, respectively. In addition, Srikandarajah reports better results on micturition in the group of CESI patients that were operated within 24 h, but fails to demonstrated this for the CESR group [15].

The only study that convincingly demonstrated a correlation between timing and outcome of micturition is the study of Srikandarajah, describing 200 patients and discerning CESR from CESI [15]. The result is remarkable: CESI patients that are operated within 24 h have an OR of 504 of regaining normal bladder function compared to the patients operated after 48 h. Even compared to the patients operated within 24–48 h, the results are better in the <24 h time interval group (OR 1.93). The group of CESI patients is sufficiently large and the number of patients in each time interval group is satisfactory. These results could not be confirmed by others: in 8 of 10 studies, CESI was not studied separately and in the other study evaluating CESI and CESR separately [18], only four patients in the CESI group were operated within 48 h.

Conclusion

The most obvious conclusion is that surgery for CES due to a herniated disc is performed as timely as possible, even for incomplete CES. Chau [24] similarly concludes from their qualitative systematic review that 'there is no strong basis to support 48 h as a blanket safe time point to delay surgery'. Chau advises, like we do, that 'the earlier the surgical intervention, the more beneficial the effects for compressed nerves'. This is however not unequivocally confirmed in literature for several, above mentioned, reasons.

Box

What is known?

Cauda equine syndrome due to lumbar herniated disc is deemed to be surgically treated promptly and gives better results if performed within 48 h after onset of complaints.

What is new?

In incomplete cauda equina syndrome with micturition dysfunction, it is relevant to perform surgery urgently. Moreover, it seems advisable to perform surgery within 24 h. There is no convincing evidence that in complete cauda equina syndrome the 48 h time frame should be shortened.

What are consequences for clinical practice?

Not only in CESR, but also in CESI, timely surgical intervention is promoted, and surgery within 24 h is preferred over longer time intervals.

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The Use of Minimal Invasive Techniques for Lumbar Herniated Disc in Comparison to More Classical Approaches

16

Mark P. Arts and Wilco C. H. Jacobs

Introduction

Sciatica due to lumbar disc herniation refractory to conservative treatment is effectively treated by surgery. The primary goal of surgery is retrieval of herniated disc fragments and decompression of the nerve root. After the historical publication of Mixter and Barr [1], who performed extensive laminectomy with transdural excision of the herniated disc, lumbar disc surgery became one of the most frequently performed surgical procedures worldwide. With the introduction of the microscope in the late 1960s, Yasargil and Caspar launched the unilateral microdiscectomy [2]. Presently, unilateral transflaval microdiscectomy by using the microscope or headlight with loupe magnification, is regarded as the golden standard. However, a shift towards minimally invasive approaches to the spine has started. The rationale behind minimally invasive spine surgery is less tissue damage, shorter hospitalisation, and faster recovery while achieving a good clinical outcome comparable with that of open conventional surgery. Minimally invasive spine surgery has adopted several techniques from other fields and has been influenced by endoscopy, biochemical advances, lasers, and image guidance systems. Intradiscal chymopapaine has been used more than 30 years but has been abandoned since it is less effective than surgical nerve root decompression [3]. Hijikata and Kambin are credited for their first report of percutaneous nucleotomy by inserting a 7 mm diameter tube under local anaesthesia with partial resection of disc material [4]. Choi and Ascher reviewed the first results of percutaneous laser disc decompression aiming at decreasing

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intradiscal pressure and subsequent nerve root relief [5]. The concept of posterolateral endoscopic discectomy changed from central nucleotomy to transforaminal nerve root decompression, which was launched by Hoogland [6] A few years later, Foley and Smith introduced the transmuscular approach of microendoscopic tubular discectomy with advanced optics and instruments applicated in laparoscopic surgery [7], which was later modified with the operative microscope.

Nowadays, many thousands of patients have been operated by minimally invasive techniques in public and private hospitals, mainly stimulated by commercial interests. However, the literature regarding minimally invasive spine surgery is criticized as being overly optimistic and scientific proof supporting the superiority of minimally invasive techniques is often lacking. Therefore, every new minimally invasive technique should be compared with the golden standard open technique (unilateral transflaval microdiscectomy) by means of randomized controlled trials prior to implementation the new procedure on a large scale.

In this chapter we will outline the literature on randomized controlled trials focussing on various minimally or less invasive surgical techniques in the treatment of patients with symptomatic lumbar disc herniation. By this means we may answer the question whether minimally invasive techniques are at least as effective as conventional open microdiscectomy.

Methods

From 2000 up to 2017, all randomized and quasi-randomized controlled trials in any language were identified. All surgical interventions and techniques in the treatment of lumbar intervertebral disc prolapse were included. We used the PRESS criteria for literature search and GRADE criteria for assessing the level of evidence. Based on these criteria, we have included a total of 20 randomised controlled trials evaluating the outcome of 2249 patients.

We have defined four different minimal invasive treatment strategies and compared these with conventional open discectomy: (1) microscopic discectomy (by using microscope or loupe-headlight) vs. open discectomy, (2) microtubular discectomy (by using endoscope or microscope) vs. open discectomy, (3) percutaneous discectomy vs. open discectomy, and (4) percutaneous ablation vs. open discectomy.

Results

Microscopic Discectomy Vs. Open Discectomy

Three studies on 473 patients were included [8–10] (Table 16.1). Both microscope and loupe-headlight combination were regarded as microscopic techniques. There was no difference in clinical outcome between microscopic discectomy and open discectomy. Conventional open discectomy has a reduced surgical time compared to

Table 16.1 Characteristics of the included studies comparing microscopic assisted techniques versus open discectomy

Author (year)	n	% Female	Average age (range)	Participants	Outcomes	Follow-up	Group	OP time	Blood loss (gr or ml)	LOS (days)	Incision	Pain (VAS in mm) (sd, range) at 2 years	Recovery/ clinical outcome at 2 years	Qualitative conclusions
Katayama (2006) [8]	119	36	37 (14–65)	Primary surgery for HNP	OP time, blood loss, LOS Pain medication JOA VAS back pain VAS sciatica Complications reoperations	2.67 years (1–4)	Open (macro) discectomy (OD)	40 (12)	39 (11)	8.3 (0.8)	–	VAS lumbar at 2.7 years: 16 (7) VAS sciatica at 2.7 years: 13 (5)	JOA at 2.7 years: 27 (1)	Small differences in OP time, blood loss, hospitalization. No difference in analgesics. Long term: Small difference in VAS lumbar pain. No differences in VAS sciatica or JOA
							Microscopic discectomy (MD)	45 (8)	25 (9)	8.5 (2.3)		VAS lumbar at 2.7 years: 12 (04) VAS sciatica at 2.7 years: 12 (04)	JOA at 2.7 years: 27 (1)	
Teli (2010) [9]	240	34	39.3 (27–61)	Symptomatic, single level HNP, 18–65 years, concordant neurological signs, failed conservative treatment (6 weeks, pain medication, epidural steroids), no additional spinal disorders	OP time, incision Back pain (VAS) Leg pain (VAS) Oswestry disability SF36 Cost	10 days 6, 12, 24 months	Open discectomy (OD)	36 (10)	–	–	Skin: 23	VAS leg pain: 20 (10) VAS back pain: 10 (10)	Oswestry: 14 (5)	Comparable outcome, MED more costly and more complications
							Microscopic discectomy (MD)	43 (8)			Skin: 22	VAS leg pain: 20 (10) VAS back pain: 20 (10)	Oswestry: 13 (5)	
							Microendoscopic discectomy (MED)	56 (12)			Skin: 10	VAS leg pain: 20 (10) VAS back pain: 20 (10)	Oswestry: 15 (5)	
Tureyen (2003) [10]	114	43	41.6 (18–61)	Lumbar disc herniation, leg pain, MRI verified	OP time, LOS, incision Radicular pain (VAS) Muscle strength (MRC) Sensation Reflex	10 days 1 month 1 year	Laminectomy and macrodiscectomy (OD)	25 (20–90, 7.07)	–	1 (1–2)	6 (5–7)	Radicular pain (VAS): 14 (0–30)	RTW at 4 weeks: 54%	Differences in incison and operative time and earlier return to work, and analgesics use. No further differences
							Microscopic discectomy (MD)	54 (25–95, 5.25)		1 (1–2)	4 (3–5)	Radicular pain (VAS): 12 (0–30)	RTW at 4 weeks: 88%	

LOS Length of stay, *RTW* Return to work, *JOA* Japanese Orthopaedic Association score
None of the studies reported crossover rates

microscopic surgery, but only in cases where a microscope is being used. Microscopic discectomy has less blood loss and a smaller incision length, as compared to open discectomy.

Microtubular Discectomy (by Using Endoscope or Microscope) Vs. Open Discectomy

Ten studies have been included on 1168 patients [9, 11–21] (Table 16.2). There was no difference in clinical outcome between microtubular discectomy and open discectomy, with regards to leg pain and quality of life. There was conflicting evidence on back pain and functional performance as measured with the Oswestry Disability Score (ODI). Surgical time is longer in the microtubular discectomy group, while incision length was shorter. Also long-term follow-up showed no difference.

Percutaneous Discectomy Vs. Open Discectomy

Five studies on 493 patients were included [22–26] (Table 16.3). There was no difference in clinical outcome between percutaneous discectomy and open discectomy, although percutaneous surgery may result in shorter hospitalisation. There was conflicting evidence for leg pain, where one study found a significant difference favoring PTED [24], while two others found no difference [25, 26]. However, long-term data is lacking.

Percutaneous Ablation Vs. Open Discectomy

Three studies on 473 patients [27–29] (Table 16.4) were included focusing on laser disc decompression including one study on hydrosurgery [29]. There was no difference in leg and back pain between percutaneous ablation and open discectomy. Nearly 50–70% of the patients treated with percutaneous ablation techniques had a successful outcome and, consequently, open surgery was prevented.

Level of Evidence

Overall, the level of evidence was “low” or “very low” for almost all comparisons (Table 16.5). The main reasons for downgrading the level of evidence was risk of bias in included studies and possible reporting bias, where not all studies report the required outcomes. Only for leg and back pain there was “high” level of evidence for an absence of difference between open and ablation techniques. Further, there is moderate level of evidence for shorter length of stay for percutaneous transforaminal and/or endoscopic discectomy compared to open microdiscectomy. For microscopic assisted techniques there was “low” or “very low” level of evidence for lower operative trauma (blood loss,

Table 16.2 Characteristics of the included studies comparing microtubular versus open versus discectomy

Author (year)	n	% Female	Average age (range/ SD)	Participants	Outcomes	Follow-up	Group	Crossover (n, %) to other group	OP time (min)	Blood loss (gr or ml)	LOS (days)	Incision	Pain (VAS in mm) (sd, range) at 2 years	Recovery/ Clinical outcome at 2 years	Qualitative conclusions
Arts (2009) [11–13]	328	47	41.5 (18–70, 10.8)	HNP + persistent radicular pain (>8 weeks). Unsuccessful conservative treatment. The Netherlands	OP time, blood loss, LOS Roland-Morris (RMDQ) Back pain (VAS) Leg pain (VAS) SF36 Sciatica frequency and bothersome (SFBI) Recovery (self-reported) Muscle injury Cost effectiveness	2, 4, 6, 8, 12, 26, 38 weeks 1, 2 years	Conventional microdiscectomy (MD)	2	36 (16)	% <50 ml: 85	3.3 (1.1)	–	VAS leg pain 14.0 (se 1.8) VAS back pain 19.4 (se 1.9)	RMDQ: 3.7 (se 0.5) SF 36: Physical 82.4 (se 1.8)	TD bit more leg and back pain, other outcomes not different. Not less muscle injury
							Transmuscular tubular discectomy (TD)	2	47 (22)	% < 50 ml: 92	3.3 (1.2)		VAS leg pain 15.3 (se 1.7) VAS back pain 23.5 (se 1.9)	RMDQ: 4.5 (se 0.5) SF36: 78.9 (se 1.7)	

(continued)

Table 16.2 (continued)

Author (year)	n	% Female	Average age (range/ SD)	Participants	Outcomes	Follow-up	Group	Crossover (n, %) to other group	OP time (min)	Blood loss (gr or ml)	LOS (days)	Incision	Pain (VAS in mm) (sd, range) at 2 years	Recovery/ Clinical outcome at 2 years	Qualitative conclusions
Belykh (2016) [14]	131	37	40 (median, 80% 31 to 56)	Failed conservative treatment (3 months), frequent LBP and sciatica, MRI or CT confirmed LDH L3-S1	Surgical time Blood loss Incision length Pain (VAS) Oswestry	Before discharge 3, 6, 12 months	Microdiscectomy (MD)	–	105 (70,125) (median, IQR)	50 (30, 50) (median, IQR)	10 (9, 11; 5–19) (median, IQR; range)	30 (30, 30) (median, IQR)	VAS only reported in graph	ODI only reported in graph	No differences between groups in improvement of ODI. Pain only different at discharge between MD and ED
							Endoscopically assisted MD (tubular) (EAD-T)	–	90 (70, 115)	50 (30, 50)	10 (9, 11; 7–19)	30 (25, 30)	–	–	
							Tubular endoscopic diskectomy (TED)	4 to EAD, ITT	103 (90, 115)	40 (30, 50)	10 (8.5, 10; 6–11)	25 (20, 25)	–	–	
Brock (2008) [15]	125	49	51 (20–79)	First time lumbar microdiscectomy, failed conservative treatment (12 weeks). Germany	Leg pain (VAS) Back pain (VAS) Oswestry LOS Analgesics use	Before discharge 1, 6 days	Subperiosteal microdiscectomy (MD)	?	–	–	–	–	VAS leg pain discharge: 14 VAS back pain discharge: 17	Oswestry at discharge: 20	Analgesics consumption less with transmuscular approach. Pain and Oswestry similar
							Transmuscular discectomy (tubular) (TD)	?	–	–	–	–	VAS leg pain discharge: 9 VAS back pain discharge: 12	Oswestry at discharge: 25.7	

Garg (2011) [16]	112	29	37 (range 26–57)	Single-level disc herniation	Surgical time Anaesthesia time LOS Blood loss Weight of disc material removed ODI Satisfaction	Postoperative 6 weeks 6, 12 months	Open (laminotomy) discectomy (OD)	?	56 (33)	306 (120)	12 (3)	–	–	ODI at 12 months: 2.14	Surgical and anaesthesia times were significantly longer in MED. Blood loss and hospital stay were significantly reduced in MED. Greater improvement in ODI at 1 week for MED
							Tubular microendoscopic discectomy (TMED)	?	84 (36)	41 (12)	3 (1)	–	–	ODI at 12 months: 1.75	
Huang (2005) [17]	22	32	39.4 (10.9)	Failed conservative treatment (3 months), OR acute attack of intractable back and leg pain, no improvement 1–2 weeks bedrest. No motor deficit or sphincter disturbance	OP time, blood loss, LOS Interleukines and CRP Pain (VAS) MacNab	18.9 months (10–25)	Open discectomy (OD)	0	72.1 (17.8)	190 (115)	5.92 (2.39)	6.3 (0.98)	VAS at 18.9 months 14 (01,10–30)	MacNab at 18.9 months: 90%	Surgical trauma is less with MED than OD. Clinical outcomes are comparable
							Microendoscopic discectomy (MED)	1	109 (35.9)	87.5 (69.4)	3.57 (0.98)	1.86 (0.13)	VAS 15 (02, 10–20)	MacNab at 18.9 months: 91.6%	

(continued)

Table 16.2 (continued)

Author (year)	n	% Female	Average age (range/ SD)	Participants	Outcomes	Follow-up	Group	Crossover (n, %) to other group	OP time (min)	Blood loss (gr or ml)	LOS (days)	Incision	Pain (VAS in mm) (sd, range) at 2 years	Recovery/ Clinical outcome at 2 years	Qualitative conclusions
Hussein (2016) [18]	80	40	31 (?)	Single level HNP, highly migrated HNP, radiculopathy (>80 NRS), LP >> LBP, MRI confirmed	Surgical time Blood loss Analgesic use LOS NRS back pain NRS leg pain ODI Return to work Revision rate Complication rate Satifaction	2 weeks 1, 6 months 1, 2 years	Conventional discectomy (OD)	?	92.5 (20.5)	126 (25.8)	45 h (20)	?	NRS leg: 1.2 (0.7) NRS back 3.62 (0.8)	ODI: 34.9 (9.0)	MED-T significantly better than OD on most parameters, significance not reported
							Microendoscopic discectomy (tubular) (MED-T)	?	85.4 (15.7)	35.4 (10.2)	9.8 h (3.6)	?	NRS leg: 1.4 (0.9) NRS back 1.6 (0.8)	ODI: 49.7 (11.4)	
Righesso (2007) [19]	40	43	43.9 (11.5)	Posterolateral HNP and persistence of sciatica, failed conservative treatment (4–8 weeks) with rest, analgesia, NSAIDs and physical therapy. MRI verified. Brazil	OP time, blood loss, LOS Incision Pain (VAS) Oswestry Neurological status	12 hrs 1, 3, 6, 12, 24 months	Open discectomy with loupe (MD)	?	63.7 (15.5)	40 (11–450)	26 (16–72) h	2.6 (0.4)	VAS: 0 (0–60)	Oswestry: 10 (0–30)	MD longer LOS and incision, MED longer OP time. No clinical differences
							Microendoscopic discectomy (MED)	?	82.6 (21.9)	50 (10–700)	24 (11–72) h	2.1 (0.2)	VAS: 10 (0–30)	Oswestry: 10 (0–22)	

Ryang (2008) [20]	60	47	38.7 (21–69, 10.3)	Single level virgin HNP; typical monoradicular symptoms, sciatica > > lower back pain, failed conservative treatment (8 to 12 weeks). Germany	Pain: VAS (10 cm) Oswestry SF-36	16 months (6–26)	Open microscopic discectomy (MD)	0	92 (33–150, 28.6)	63.8 (0–300, 86.8)	4.4 (1–15, 2.8)	4 to 5	VAS Back pain at 16 months: 21 (0–98, 24)	Oswestry at 16 months: 12 (0–86, 18.8) SF 36: At 16 months physical 47.5 (9.4) and mental 51.9 (7.8)	No differences
							Minimal access microdiscectomy (trocar) (MAD-T)	0	82 (37–120, 25.1)	26.2 (0–100, 29.7)	4 (2–14, 2.3)	1.6	VAS Back pain at 16 months: 21 (0–75, 24)	Oswestry at 16 months: 12 (0–46, 14) SF36: Physical 47.6 (10.7) and mental 44 (13.2)	
Shin (2008) [21]	30	60	45.4 (14.6)	Single-level unilateral HNP, failed conservative treatment (>6 weeks), CT or MRI verified. Korea	Back pain (VAS) Leg pain (VAS) Blood enzymes (CPK, LDH)	1, 3 and 5 days	Microscopic discectomy (MD)	?	47 (5)	34 (11)	–	–	VAS Back at 5 days: 36 (11) VAS leg at 5 days: 24 (21)	–	MED faster relief of back pain within the first five days post-operatively, but no differences in leg pain
							Microendoscopic discectomy (tubular) (MED-T)	?	49 (5)	35 (9)			VAS Back at 5 days: 19 (11) VAS leg at 5 days: 25 (16)		

(continued)

Table 16.2 (continued)

Author (year)	n	% Female	Average age (range/ SD)	Participants	Outcomes	Follow-up	Group	Crossover (n, %) to other group	OP time (min)	Blood loss (gr or ml)	LOS (days)	Incision	Pain (VAS in mm) (sd, range) at 2 years	Recovery/ Clinical outcome at 2 years	Qualitative conclusions
Teli (2010) [9]				See (Table 16.1)			Open discectomy (OD)	?	36 (10)	–	–	Skin: 23	VAS leg pain: 20 (10) VAS back pain: 10 (10)	Oswestry: 14 (5)	Comparable outcome, MED more costly and more complications
							Microscopic discectomy (MD)	?	43 (8)			Skin: 22	VAS leg pain: 20 (10) VAS back pain: 20 (10)	Oswestry: 13 (5)	
							Microendoscopic discectomy (tubular) (MED-T)	?	56 (12)			Skin: 10	VAS leg pain: 20 (10) VAS back pain: 20 (10)	Oswestry: 15 (5)	

LOS length of stay, *RTW* Return to work

Table 16.3 Characteristics of the included studies comparing percutaneous transforaminal and/or endoscopic discectomy versus open microdiscectomy versus

Author (year)	n	% Female	Average age (range/ SD)	Participants	Outcomes	Follow-up	Group	Crossover (n, %) to other group	OP time (min, (SD))	Blood loss (gr or ml)	LOS (days, (SD))	Incision	Pain (VAS in mm) (sd, range) at 2 years	Recovery/ clinical outcome at 2 years	Qualitative conclusions
Chen (2008) [22]	153	42	40 (NR, 11.3)	MRI or CT confirmed LDH (predominantly L4-S1) with radicular pain and signs of radiculopathy; for whom surgery was warranted	ODI SF36-bodily pain SF36-Fysical function EQ5D VAS Back pain VAS leg pain	1 week, 1, 3, 6 months 1 year	Microendoscopic discectomy (MED)	0	91.7 (42.5)	?	11.2 (3.8)	?	?	ODI 1 year: 3.2 (5.7)	No differences in clinical outcome and complications
							Percutaneous Transforaminal endoscopic discectomy (PTED)	0	97.2 (45.8)	?	8.1 (4.2)	?	?	ODI 1 year: 3.9 (7.6)	
Franke (2009) [23]	100	40	44 (21–72, 11.7)	Disc dislocations grades 3–5 (Kramer), no lateral HNP (predominantly L4-S1), no protrusions	OP time, LOS RTW ODI Back pain (VAS) Leg pain (VAS) Neurological deficits	8 weeks 6, 12 months	Microscopic discectomy (MD)	0	56.3 (19.2)	?	4.9	?	?	?	Shorter OP time and quicker recovery at experienced center for MAPN. No clinical or complication rate differences
							Percutaneous Nucleotomy (MAPN)	0	41.8 (15.5)	?	3.8	?	?	?	

(continued)

Table 16.3 (continued)

Author (year)	n	% Female	Average age (range/ SD)	Participants	Outcomes	Follow-up	Group	Crossover (n, %) to other group	OP time (min, (SD))	Blood loss (gr or ml)	LOS (days, (SD))	Incision	Pain (VAS in mm) (sd, range) at 2 years	Recovery/ clinical outcome at 2 years	Qualitative conclusions
Gibson (2017) [24]	140	50	41 (25–69, 9)	Single level (L4-S1) prolapse with exiting and/or traversing nerve root compression	ODI VAS back pain VAS leg pain SF-36	3, 12, 24 months	Microdiscectomy (MD)	0	65 (36)	?	1.4 (1.3)	?	VAS Back 3.0 (2.8) VAS affected leg 3.5 (3.1)	ODI 22 (20) SF PCS 47.4 (10.6) SF MCS 45.2 (14.8)	TED less sciatica at 2 years. TED more rapid recovery, but greater revision rate
							Transforaminal endoscopic discectomy (TED)	3 (not to MD)	61 (16)	?	0.7 (0.7)	?	VAS Back 2.5 (2.5) VAS affected leg 1.9 (2.6)	ODI 18 (17) SF PCS 47.7 (10.6) SF MCS 49.4 (14.1)	
Lee (2015) [25]	40	33	42.7 (NR, 11.5)	Unilateral leg pain with disc herniation as determined by magnetic resonance imagining (MRI)	ODI VAS Back pain VAS leg pain	1, 3, 6, 12 months	Microdiscectomy (MD)	?	82.6 (23.7)	117 (56.2)	?	?	1 year: VAS Back 1.63 (1.54) VAS leg 1.50 (1.91)	1 year: ODI 11.8 (10.8)	No differences in clinical and radiological outcome found
							Automated open lumbar discectomy (AOLD)	?	85.5 (24.8)	107 (32.8)	?	?	1 year: VAS Back 1.62 (1.94) VAS leg 2.52 (2.14)	1 year: ODI 12.95 (11.3)	
Nie (2016) [26]	60	37	37 (13–67, NR)	Central, paracentral, or prolapsed L5–S1 disc herniation	ODI VAS leg and waist pain	>24 months (24–37 months, mean 28 months)	Percutaneous endoscopic Interlaminar discectomy (PEID)	0	65 (14.9)	?	4.8 (1.1)	?	Leg and waist pain 2.2 (1.37)	ODI 20.4 (7.7)	PETD has shorter OP time, less intraoperative radiation exposure, but comparable outcomes
							Percutaneous endoscopic Transforaminal discectomy (PETD)	0	86 (15.4)	?	4.6 (1.2)	?	Leg and waist pain 2.3 (1.02)	ODI 22.0 (9.1)	

Table 16.4 Characteristics of the included studies comparing ablation techniques open versus discectomy

Author (year)	n	% Female	Average age (range/ SD)	Participants	Outcomes	Follow-up	Group	Crossover (n, %) to other group	OP time	Blood loss (gr or ml)	LOS (days)	Incision	Pain (VAS in mm) (sd, range) at 2 years	Recovery/ Clinical outcome at 2 years	Qualitative conclusions
Brouwer (2015) [28]	115	37	44 (NR, 11)	MRI confirmed Lumbar disc herniation (predominantly) L3-S1	RMDQ VAS leg pain VAS back pain VAS general health PROLO scale RAND SF 36 Sciatica frequency and Bothersomeness index	1, 3, 4, 6, 8, 12, 26, 38, 52 weeks	Conventional surgery (OD/ MD)	–	?	?	?	?	1 year: Leg pain 12.6 (2.4) Back pain: 16.6 (2.6)	1 year: RMDQ: 4.4 (0.7) Prolo functioning: 3.0 (0.1) SF-36 PF 81.2 (2.7)	PLDD was non-inferior to OD/MD, with faster recovery and less re-operations in OD/MD
							Percutaneous laser disc decompression (PLDD)	N = 5 9%	?	?	?	?	1 year: Leg pain 18.1 (3.1) Back pain: 22.9 (3.3)	1 year: RMDQ: 5.4 (1.0) Prolo functioning:2.8 (0.1) SF-36 PF 77.8 (3.2)	

(continued)

Table 16.4 (continued)

Author (year)	n	% Female	Average age (range/ SD)	Participants	Outcomes	Follow-up	Group	Crossover (n, %) to other group	OP time	Blood loss (gr or ml)	LOS (days)	Incision	Pain (VAS in mm) (sd, range) at 2 years	Recovery/ Clinical outcome at 2 years	Qualitative conclusions
Abrishamkar (2015) [27]	200	20	40 (NR, 9)	Lumbar disc herniation (L2-S1) and low back pain	NRS lumbar pain NRS radicular pain	14 days 1, 2, 3 months 1-year	Open discectomy (OD)	?	?	?	?	?	1 year: Radicular pain: 2.14 (1.17) Lumbar pain 2.08 (1.55)	?	Only pain reported, no differences in repeated measures over one year follow up
							Plasma-laser nucleoplasty (PLN)	?	?	?	?	?	1 year: Radicular pain: 3.04 (2.57) Lumbar pain 2.9 (2.33)	?	
Cristante (2016) [29]	40	50	43 (NR, 9.4)	MRI-confirmed, one level disc protrusion or small herniation	ODI VAS lumbar pain VAS radiating leg pain	1, 3, 6, 12 months	Open microdiscectomy (OD)	?	?	?	?	?	1 year: Lumbar pain: 4.06 (3.54) Leg pain: 3.37 (3.8)	1 year: ODI: 11 (6.82)	No differences in clinical outcomes (pain and disability)
							Percutaneous microdiscectomy by hydrosurgery (PMD-H)	?	?	?	?	?	1 year: Lumbar pain: 3.03 (3.32) Leg pain: 2.67 (3.3)	1 year: ODI 12.7 (12.2)	

Table 16.5 Quality of evidence for reported outcomes

Comparison			Grade limitations					Summary of findings	
Outcome	Studies	Patients	Publication bias	Inconsistency	Indirectness	Imprecision	Risk of bias	Effect[a]	Quality
Open microdiscectomy versus percutaneous transforaminal and/or endoscopic discectomy five studies									
Surgery duration (min)	5	493	+	–	+	+	–	Conflicting evidence	Low
Blood loss	1	40	–	?	+	+	–	No difference	Very low
Length of stay (days)	4	453	+	+	+	+	–	Shorter for PTED	Moderate
Leg pain (mm VAS)	3	240	–	–	–	–	–	Conflicting evidence	Very low
Back pain (mm VAS)	2	180	–	+	+	–	–	No difference	Very low
Oswestry	4	393	+	+	+	–	–	No difference	Low
SF36	1	60	–	?	+	+	–	No difference	Very low
Open (OD) versus microscopic assisted (MD) techniques three studies									
Surgery duration (min)	3	473	+	+	+	–	–	MD longer than OD	Low
Blood loss	1	119	–	?	+	?	–	MD less than OD	Very low
Length of stay (days)	2	233	–	–	+	–	–	No difference	Very low
Incision	2	354	–	–	–	–	–	MD smaller incision than OD	Very low
Leg pain (mm VAS)	3	473	+	+	+	–	–	No difference	Low
Back pain (mm VAS)	2	359	–	–	+	–	–	Conflicting evidence	Very low
Oswestry	1	80	–	?	+	–	–	No difference	Very low
Open or microscopic (OD) versus microtubular discectomy (TD) ten studies									
Surgery duration (min)	9	1043	+	–	+	–	–	TD longer than OD	Very low
Blood loss	8	803	+	–	+	+	–	Conflicting evidence	Low
Length of stay (days)	7	773	–	–	+	+	–	Conflicting evidence	Low
Incision	5	493	–	+	–	+	–	TD shorter than OD	Very low
Leg pain (mm VAS)	5	803	–	+	+	–	–	No difference	Very low
Back pain (mm VAS)	6	863	–	–	–	–	–	Conflicting evidence	Very low
Oswestry	6	657	–	–	+	–	–	Conflicting evidence	Very low

(continued)

Table 16.5 (continued)

Comparison			Grade limitations					Summary of findings	
Outcome	Studies	Patients	Publication bias	Inconsistency	Indirectness	Imprecision	Risk of bias	Effect[a]	Quality
SF36	2	388	–	+	+	+	–	No difference	Low
Open versus ablation techniques three studies									
Leg pain (mm VAS)	3	355	+	+	+	+	+	No difference	High
Back pain (mm VAS)	3	355	+	+	+	+	+	No difference	High
Oswestry	1	40	–	?	+	–	–	No difference	Very low
SF36	1	115	–	?	+	+	+	No difference	Low

MD Mean difference, *OR* odds ratio

[a]< or > Effect is superior for one of both treatments; <> None of either treatments is superior; ? unclear relative effectiveness due to conflicting results

incision length) but with longer surgery duration than open techniques. For microtubular discectomy there was "very low" level of evidence for lower operative trauma (incision length) but with longer surgery duration than open techniques.

Patient Preferences

Patients may prefer certain minimal invasive techniques because of reduced tissue damage and assumed better clinical outcome regarding leg pain, low back pain, and speed of recovery. However, there is no proof of minimal invasive lumbar discectomy being superior to conventional open surgery in terms of clinical and functional outcome. Some patients demand smaller skin incisions for cosmetic reasons and therefore prefer percutaneous techniques and tubular techniques but so far there is no scientific evidence of percutaneous procedures being superior to conventional open discectomy. The only moderate evidence is shorter hospitalization when patients are being treated with percutaneous tranforaminal discectomy. In general should the patients make their choice in surgical techniques based on fair counseling by the consulting surgeon and not by often overly optimistic statements in the media.

Discussion

Lumbar discectomy is one of the most frequently performed spinal surgery with good outcome in the majority of patients. However, irrespective of the surgical techniques and approach, nearly 20% of the patients have persistent or recurrent complaints and may need revision surgery in the following years after the primary surgery. Every consecutive surgery will result in worse outcome and for this reason it is of utmost importance to primarily treat the patient with the best possible strategy, which may mean a case-by-case approach. A recently performed international query among 817 surgeons from 89 countries, has documented large variety of surgical techniques and lack of consensus [30]. More than 80% routinely perform unilateral transflaval microdiscectomy in the majority of their patients with symptomatic disc herniation. Therefore, unilateral transflaval microdiscectomy presently can be regarded as the golden standard.

Since the introduction of the microscope in the early 1990s of the last century, many less invasive or minimal invasive techniques have been introduced. The rational of minimal invasive techniques is less tissue damage, less postoperative low back pain and consequently faster recovery. However, based on the literature, clinical outcome of microscopic discectomy, microtubular discectomy and percutaneous discectomy, seem equally effective as compared to conventional open surgery. The only significant difference in favor of minimal techniques, is shorter hospitalization when patients have undergone percutaneous transforaminal discectomy.

Conclusion

In summary, unilateral transflaval microdiscectomy is the most frequent surgical procedure at present. Various alternative less invasive techniques have been introduced which are shown to be safe and at least as effective as the golden standard. The

optimal surgical strategy in every patient should be based on surgeons' experience and preference of both the patient and the surgeon, in which the patient should be counseled honestly.

Box

What is known?

- Lumbar discectomy is one of the most frequently performed surgeries with good outcome in the majority of patients. Most surgeons perform open surgery; i.e. unilateral transflaval microdiscectomy.

What is new?

- Various minimal invasive strategies like tubular discectomy, percutaneous transforaminal discectomy, and ablation techniques have been introduced, aiming at better outcome and faster recovery.

What are consequences for clinical practice?

- Clinical and functional outcome of minimal invasive techniques are similar to open discectomy and, therefore, treatment strategy should be based on preferences of both the patient and the surgeon.

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17 Comparative Analysis of Open Versus Minimally Invasive Techniques for Posterior or Transforaminal Lumbar Interbody Fusion

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Introduction

Lumbar spinal fusion is an effective treatment for various pathologies, including degenerative conditions. With an aging population, the demand for spinal fusion procedures continues to increase. The morbidities associated with the traditional open midline techniques for spinal fusion, such as significant blood loss and prolonged hospitalization, may warrant consideration of alternative minimally invasive surgical (MIS) approaches. First described by Foley in 2003 [1], MIS techniques have become more widely utilized with the potential benefits of less structural damage to paraspinal tissues and faster postoperative recovery. As with any new surgical method, the associated learning curve requires time, potentially increasing the length of the operation and complication rates. To date, many studies have reported the outcomes of MIS lumbar fusion as well as the comparative analysis of open versus MIS approaches.

Multiple lumbar interbody arthrodesis techniques were developed to improve fusion rates, maintain vertebral alignment, and relieve back and leg pain. Posterior lumbar interbody fusion (PLIF) was first described in 1944 by Briggs and Milligan [2], who placed bone fragments from the laminectomy in the disc space as an interbody graft. Then in 1982, Harms and Rolinger first described the open transforaminal lumbar interbody fusion (TLIF) technique [3], which relied on exposing only the ipsilateral foramen to place a graft within the anterior or middle portion of the disc space to restore lumbar lordosis.

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Traditional open PLIF and TLIF often require extensive retraction and muscle dissection, leading to increased iatrogenic tissue injury, greater blood loss, higher likelihood of intractable postoperative pain, extended hospitalization, and significant financial burden [4–7]. MIS techniques for lumbar interbody fusion were introduced with the goal of creating smaller surgical wounds, minimizing trauma to adjacent tissues, and promoting faster postoperative recovery. However, visibility of the surgical field is often limited—making it a technically demanding and challenging procedure, often associated with increased operative time [8]. Furthermore, multiple studies have reported high complication rates during the learning stage [9–11].

As with any new technique, potential benefits should be weighed against potential risks particularly in comparison to other approaches already in use. This chapter addresses the following question: Is there a role for minimally invasive techniques as an alternative approach to posterior or transforaminal lumber interbody fusion?

Methods

Search Strategy and Criteria

Three independent reviewers (LH, VC, WK) performed a meticulous review of the literature using PubMed using guidelines proposed by the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) as well as the Peer Review of Electronic Search Strategies (PRESS). Medical Subject Heading (MeSH) search terms utilized included a combination of the terms "posterior lumbar interbody fusion" or "PLIF" and "transforaminal lumbar interbody fusion" or "TLIF" with "MIS", "minimally invasive", or "minimally invasive spine surgery". Studies were limited to those published in the English language. The initial search yielded a total of 142 articles (Fig. 17.1), including literature from January 2000 until present. After a thorough title, abstract, full-text, and reference list review, 48 were identified as meeting our study inclusion criteria.

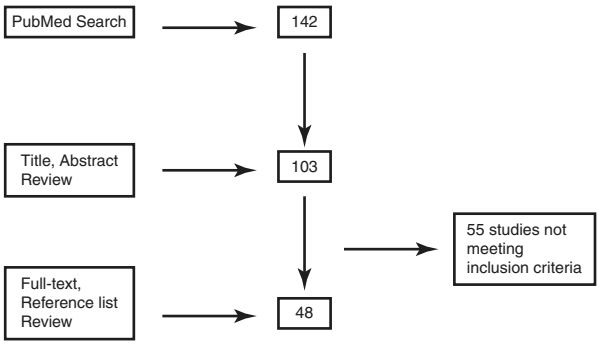

Fig. 17.1 Flow chart of the combined results of our initial and subsequent systematic literature reviews for identification of included studies

Data Extraction

Relevant information from each study was extracted independently then cross-checked by all three reviewers. Data components of interest included the study design, patient population demographics, interventions performed, study outcome measures, statistical methods, and study results. Outcomes included operative time, intraoperative estimated blood loss (EBL), length of hospital stay (LOS), visual analogue scale (VAS) scores for back and leg pain, visual analogue thermometer (VAT) scale, Oswestry disability index (ODI), EuroQoL (EQ-5D) quality of life assessment, Japanese Orthopedic Association (JOA) score, physical component summary (PCS) and mental component summary (MCS) of SF-12 and SF-36, as well as Roland Morris Questionnaire. The extracted data were then entered into a spreadsheet (Microsoft® Excel® 97–2004; Microsoft Corp, Redmond, WA, USA) by each reviewer with confirmation of accuracy performed by the other reviewers.

Assessment of Study Quality

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) system was incorporated into the literature review to determine the quality of each included study [12]. Data pertaining to the study design, study quality, consistency of results, directness of evidence, and study precision was extracted from each paper by three independent reviewers (LH, VC, WK). Based on this information, the overall quality of each study was rated as high, moderate, low, or very low according to the GRADE protocol [12]. Consensus regarding the final GRADE rating was established through discussion by the three reviewers when necessary.

Results

Literature Review

The results of our literature review are illustrated in Fig. 17.1. In total, the initial electronic search yielded 142 papers, which were narrowed down to 103 after reviewing the titles and abstracts. Then 48 were identified as meeting our study inclusion criteria after full-text and reference list reviews. Of the 48 included studies, only three were prospective randomized controlled trials (PRCTs) [13–15]. A prospective comparative cohort design was used in 16 of the studies, and the remaining 29 were retrospective cohort studies. Table 17.1 summarize the extracted data from the included papers.

Table 17.1 Characteristics and outcomes of the included studies comparing MIS versus open PLIF and TLIF

Author (Year)	Design	Quality of evidence (GRADE)	Number of patients (MIS/ Open)	Diagnosis	Follow-up (mean, months)	OR time MIS (min)	OR time Open (min)	EBL MIS (cc)	EBL Open (cc)	LOS MIS (days)	LOS Open (days)	Non-union MIS (%)	Non-union Open (%)	Outcome MIS	Outcome Open	Complication MIS (%)	Complication Open (%)
Adogwa [16] (2011)	Retrospective	Low	15/15	DS	24	300	210	200	295	3	5	0	0	VAS back at 2 years: 5.5 (8.4 preop) VAS leg at 2 years: 5.5 (8.5 preop) ODI: 15.7 (36.9 preop)	VAS back at 2 years: 4.7 (9.3 preop) VAS leg at 2 years: 3.5 (8.2 preop) ODI: 17.1 (34.3 preop)	0	6.7
Archavlis [17] (2013)	Retrospective	Low	24/25	DS, IS	26	220	190	185	255	7	11	8.3	4	VAS back at 2 years: 2.5 (6.9 preop) VAS leg at 2 years: 2.7 (6.7 preop) ODI at 2 years: 23 (46 preop)	VAS back at 2 years: 2.8 (6.9 preop) VAS leg at 2 years: 2.6 (6.6 preop) ODI at 2 years: 23 (preop 48)	29	28

Brodano [18] (2015)	Retrospective	Low	30/34	DS	MIS: 23 Open: 25	144	102	230	620	4.1	7.4	0	0	VAS: 2.3 (7.8 preop) ODI: 10 (42 preop)	VAS: 2.6 (8.1 preop) ODI: 12 (46 preop)	3.3	8.8
Cheng [19] (2013)	Retrospective	Very low	50/25	DS, SS	60	244.6	278.8	392.5	535.5	4.8	6.1	8	0	VAS: 2.9 (7.1 preop)	VAS: 3.5 (7.6 preop)	10	12
Dhall [20] (2008)	Retrospective	Very low	21/21	DDD, DS	MIS: 24 Open: 34	199	237	194	505	3	5.5	4.8	0	NR	NR	5.7	3.8
Djurasovic [21] (2016)	Retrospective	Low	64/64	NR	24	263.55	278.69	262.4	614.06	NR	NR	NR	NR	ODI at 2 years: 19.69 (52.75 preop) SF-36 at 2 years: 42.90 (30.17 preop)	ODI at 2 years: 29.74 (45.13 preop) SF-36 at 2 years: 37.65 (28.97 preop)	NR	NR
Fan [22] (2010)	Prospective	Very low	28/31	DS, LDH, SI, SS	MIS: 14.4 Open: 14.2	203.6	194.5	496.4	887.7	9.5	15.2	NR	NR	VAS back: 1.8 (7.2 preop) ODI: 10.7 (69.2 preop)	VAS back: 3.4 (6.6 preop) ODI: 21.2 (69.2 preop)	20.7	17.9

(continued)

Table 17.1 (continued)

Author (Year)	Design	Quality of evidence (GRADE)	Number of patients (MIS/ Open)	Diagnosis	Follow-up (mean, months)	OR time MIS (min)	OR time Open (min)	EBL MIS (cc)	EBL Open (cc)	LOS MIS (days)	LOS Open (days)	Non-union MIS (%)	Non-union Open (%)	Outcome MIS	Outcome Open	Complication MIS (%)	Complication Open (%)
Fan [23] (2016)	Retrospective	Very low	24/36	DDD, DS, LDH, SI	MIS: 14.2 Open: 13.4	270.8	227.5	666.7	908.3	12.5	15.5	0	0	VAS back at 1 year: 1.7 (5.9 preop) VAS leg at 1 year: 1.2 (5.8 preop) ODI at 1 year: 18.7 (38.2 preop) SF-36 at 1 year: 62.39 (43.4 preop)	VAS back at 1 year: 2.0 (6.1 preop) VAS leg at 1 year: 1.6 (6.1 preop) ODI at 1 year: 18.4 (37.8 preop) SF-36 at 1 year: 61.7 (41.3 preop)	12.5	8.3
Gao [24] (2016)	Retrospective	Low	75/120	DS, LDH	12	191	150	195	298	NR	NR	0	0	NR	NR	6.7	4.2
Gu [25] (2014)	Prospective	Low	44/38	DDD, LDH, SI, SS	MIS: 20.6 Open: 20.0	195.5	186.6	248.4	576.3	9.3	12.1	6.8	7.9	VAS back: 1.9 (7.3 preop) VAS leg: 1.7 (7.6 preop) ODI: 16.5 (43.7 preop)	VAS back: 1.8 (7.4 preop) VAS leg: 1.8 (7.7 preop) ODI: 15.9 (44.3 preop)	11.4	12.1

Harris [26] (2011)	Retrospective	Very low	30/21	DS, SS	12	150	156	208	335	2.5	3.2	3.3	4.8	VAS at 1 year: 2.3 (7.78 preop) ODI at 1 year: 13.9 (45.7 preop)	VAS at 1 year: 2.4 (7.58 preop) ODI at 1 year: 6.4 (45.7 preop)	13.3	14.3
Isaacs [27] (2005)	Retrospective	Very low	20/24	DS	NR	300	276	226	1147	3.4	5.1	NR	NR	NR	NR	5	25
Kotani[28] (2012)	Prospective	Very low	43/37	DS	MIS: 32 Open: 40	172	176	181	453	NR	NR	2	0	JOA: 23.5 (11.1 preop) ODI at 3 months: 13.2 (52 preop) RMQ: 5.1 (12.2 preop)	JOA: 22.8 (12.6 preop) ODI at 3 months: 32.1 (48.9 preop) RMQ: 10.9 (13.7 preop)	2.3	0
Lau [10] (2011)	Retrospective	Very low	10/12	DS	MIS: 15.2 Open: 12.6	389.7	365.3	466.7	464.6	5	NR	NR	NR	NR	40	8.3	
Lau [29] (2013)	Retrospective	Very low	78/49	DDD, DS, LDH, SS	1	NR	NR	168.6	661	3.1	4.7	NR	NR	NR	NR	11.5	28.6
Lau [30] (2013)	Retrospective	Very low	142/140	DDD, DS, LDH, SS	NR	NR	NR	NR	NR	NR	NR	NR	NR	Facet violation (%): 3.2	Facet violation (%): 4.3	NR	NR

(continued)

Table 17.1 (continued)

Author (Year)	Design	Quality of evidence (GRADE)	Number of patients (MIS/ Open)	Diagnosis	Follow-up (mean, months)	OR time MIS (min)	OR time Open (min)	EBL MIS (cc)	EBL Open (cc)	LOS MIS (days)	LOS Open (days)	Non-union MIS (%)	Non-union Open (%)	Outcome MIS	Outcome Open	Complication MIS (%)	Complication Open (%)
Lee [31] (2012)	Prospective	Low	72/72	DS, LDH, SS	24	166.4	181.8	50.6	447.4	3.2	6.8	3	1.5	VAS back: 2.3 VAS leg: 1.6 ODI: 21.4 SF-36 PCS: 64.6	VAS back: 2.4 VAS leg: 2.0 ODI: 10.7 SF-36 PCS: 63.0	12.5	9.7
Mobbs [32] (2012)	Prospective	Very low	37/30	DS, SS	MIS: 11.5 Open: 18.7	NR	NR	NR	NR	5.4	9.8	NR	NR	VAS: 2.4 (7.9 preop) ODI: 25 (54 preop) SF-12: PCS 41, MCS 50	VAS: 3.3 (8.3 preop) ODI: 28 (52 preop) SF-12: PCS 36.9, MCS 50.9	5.4	33.3
Mukai [13] (2013)	**RCT**	Low	20/20	DS	12	167	149.2	207.7	247.5	NR	NR	10	5	NR	NR	NR	NR
Ntoukas [33] (2010)	Retrospective	Low	20/20	DDD, DS, LDH, SI, SS	12	275	152	135	432	5	10	0	0	VAS: 2 (8.5 preop) ODI: 15 (74 preop)	VAS: 2.5 (8.8 preop) ODI: 18 (72 preop)	5	0

Oh [34] (2013)	Retrospective	Low	22/46	DDD, DS, LDH, IS, SS	MIS: 25 Open: 28	NR	NR	163	412	NR	NR	9.5	8.8	VAS at 2 years: 2.6 (7.0 preop) ODI at 2 years: 21.1 (51.2 preop)	VAS at 2 years: 2.8 (7.1 preop) ODI at 2 years: 23.9 (55.5 preop)	14	11
Park [4] (2007)	Prospective	Very low	32/29	DS, LDH, SS	12	191.7	148.8	432.8	737.9	5.3	10.8	3.1	3.4	VAS back: 2.1	VAS back: 3.8	12.5	13.8
Parker [35] (2014)	Prospective	Low	50/50	DS	24	274	229	200	350	3	4	0	0	VAS back: 3.3 VAS leg: 3.0 ODI: 11.0 SF-12 PCS: 44.3 SF-12 MCS: 54.5 EQ-5D: 0.85	VAS back: 3.6 VAS leg: 2.7 ODI: 15.6 SF-12 PCS: 41.3 SF-12 MCS: 52.0 EQ-5D: 0.76	10	14
Pelton [36] (2012)	Retrospective	Very low	33/33	DDD, DS, SS	6	WC: 116 Non-WC: 110	WC: 184 Non-WC: 185	WC: 127 Non-WC: 224	WC: 338 Non-WC: 288	WC: 2 Non-WC: 2	WC: 3 Non-WC: 3	NR	NR	VAS back WC: 4.1 Non-WC: 3.8	VAS back WC: 5.9 Non-WC: 5.3	NR	NR

(continued)

Table 17.1 (continued)

Author (Year)	Design	Quality of evidence (GRADE)	Number of patients (MIS/ Open)	Diagnosis	Follow-up (mean, months)	OR time MIS (min)	OR time Open (min)	EBL MIS (cc)	EBL Open (cc)	LOS MIS (days)	LOS Open (days)	Non-union MIS (%)	Non-union Open (%)	Outcome MIS	Outcome Open	Complication MIS (%)	Complication Open (%)
Peng [37] (2009)	Retrospective	Very low	29/29	DS	24	216.4	170.5	150	681	4	6.7	NR	NR	ODI: 16.2	ODI: 17.5	6.9	13.8
Rampersaud [38] (2011)	Retrospective	Low	37/41	DS, SI	12	222	227.4	200.4	797.8	6.1	8.4	NR	NR	ODI: 18.9	ODI: 33.7	10.8	29.3
Rodriguez-Vela [39] (2013)	Prospective	Very low	25/25	DDD	36	NR	NR	NR	NR	NR	NR	NR	NR	VAT back: 3.4 VAT leg: 2.4 ODI: 12.1 SF-36: 59.4	VAT back: 4.6 VAT leg: 3.2 ODI: 18.1 SF-36: 52.5	NR	NR
Scheufler [40] (2007)	Retrospective	Low	53/67	DDD, DS	16	1 level: 104 2 level: 175	1 level: 132 2 level: 192	1 level: 55 2 level: 124	1 level: 125 2 level: 351	NR	NR	NR	NR	NR	NR	NR	NR
Schizas [11] (2009)	Prospective	Very low	18/18	DDD, DS, IS, SS	22	348	312	456	961	6.1	8.2	16.7	0	ODI: 33	ODI: 26	16.7	11.1
Seng [41] (2013)	Prospective	Low	40/40	DDD, DS	60	185	166	127.3	405	3.6	5.9	2.5	2.5	VAS back: 1.3 VAS leg: 0.8 ODI: 13.6 SF-36 PCS: 47.0 SF-36 MCS: 54.1	VAS back: 0.9 VAS leg: 1.0 ODI: 12.3 SF-36 PCS: 46.9 SF-36 MCS: 53.3	5	10

Singh [42] (2014)	Prospective	Low	33/33	DDD, DS, SS	6	115.8	186	124.4	380.3	2.3	2.9	NR	NR	VAS: 2.9	VAS: 5.2	NR	NR
Starkweather [43] (2008)	Prospective	Very low	17/18	SI	1.5	110	298	96	427	1.8	5	NR	NR	NR	NR	0	0
Sulaiman [44] (2014)	Retrospective	Low	57/11	DS	12	161	375	95	786	3.2	3.6	NR	NR	VAS: 3.2 ODI: 26.4	VAS: 5.1 ODI: 46.1	7	18
Terman [45] (2014)	Retrospective	Very low	53/21	DDD, DS, SS	MIS: 31 Open: 28	NR	NR	100	450	2	3	NR	NR	VAS: 4.7 ODI: 44	VAS: 4.3 ODI: 45	17	52
Tian [46] (2017)	Retrospective	Very low	30/31	DDD	25.6	159.2	113.6	142.2	213.3	4.5	5.6	3.3	6.4	VAS back: 1.3 VAS leg: 1.1 ODI: 17.2	VAS back: 1.2 VAS leg: 1.1 ODI: 18.2	6.7	6.5
Tsutsumimoto [47] (2009)	Retrospective	Very low	10/10	DS	24	148.3	155.8	282	352.6	NR	NR	0	0	NR	NR	NR	NR
Villavicencio [48] (2010)	Retrospective	Low	76/63	DDD, DS, LDH, SS	37.5	214.9	222.5	163	366.8	3	4.2	NR	NR	VAS: 3.4	VAS: 3.2	Major: 0 Minor: 22.2	Major: 9.5 Minor: 13.2
Wang [14] (2011)	**RCT**	Low	41/38	DS, LDH, SS	32.7	168.7	145	207.7	258.9	6.4	8.7	NR	NR	NR*	NR*	7.1	13.2
Wang [8] (2010)	Prospective	Low	42/43	DS, IS	26.3	156	142	264	673	10.6	14.6	2.4	2.3	VAS back: 0.9 ODI: 10.8	VAS back: 1.1 ODI: 12.2	9.5	7

(continued)

Table 17.1 (continued)

Author (Year)	Design	Quality of evidence (GRADE)	Number of patients (MIS/ Open)	Diagnosis	Follow-up (mean, months)	OR time MIS (min)	OR time Open (min)	EBL MIS (cc)	EBL Open (cc)	LOS MIS (days)	LOS Open (days)	Non-union MIS (%)	Non-union Open (%)	Outcome MIS	Outcome Open	Complication MIS (%)	Complication Open (%)
Wang [49] (2011)	Prospective	Very low	25/27	DS, LDH, SI, SS	27.5	139	143	291	652	NR	NR	4	3.7	VAS back: 1.3 VAS leg: 1.0 ODI: 12.4	VAS back: 1.3 VAS leg: 1.0 ODI: 11.5	16	29.6
Wang [50] (2014)	Prospective	Very low	42/39	DS, SI, SS	36.1	127	168	274	645	NR	NR	2.4	2.6	VAS back: 1.3 ODI: 18.2	VAS back: 1.5 ODI: 17.4	9.5	17.5
Wang [51] (2012)	Retrospective	Low	1667/4439	NR	NR	NR	NR	NR	NR	1 level: 3.4 2 level: 3.4	1 level: 3.6 2 level: 4.0	NR	NR	NR	NR	NR	NR
Wang [52] (2012)	Retrospective	Very low	52/22	DDD, DS, SS	NR	NR	NR	1 level: 145 2 level: 187	1 level: 400 2 level: 493	1 level: 3.9 2 level: 5.1	1 level: 4.8 2 level: 7.1	NR	NR	NR	NR	7.7	31.8
Wang [53] (2017)	Retrospective	Low	35/37	DDD, LDH	MIS: 35 Open: 37	152	103	136	364	4.7	8.6	NR	NR	NR*	NR*	0	9.38
Wong [54] (2014)	Prospective	Low	144/54	DDD, DS, SI	MIS: 45 Open: 46	123	225	115	485	2.8	4.4	7.5	6.5	VAS back: 2.3 VAS leg: 1.4 ODI: 26	VAS back: 4.0 VAS leg: 2.2 ODI: 33	8.3	24

Xue [15] (2012)	**RCT**	Low	37/43	DS, LDH, SS	25.3	1 level: 136.3 2 level: 200.2	1 level: 245.1 2 level: 262.4	1 level: 70.8 2 level: 100.2	1 level: 324.2 2 level: 500.2	1 level: 12.1 2 level: 20.2	1 level: 21.1 2 level: 22.6	8.1	7	VAS at 18 months: 2.1 (8.2 preop) ODI at 18 months: 15.4 (43.4 preop)	VAS at 18 months: 2.1 (8.5 preop) ODI at 18 months: 15.8 (45.1 preop)	21.6	11.6
Yee [55] (2014)	Retrospective	Very low	52/16	DDD, DS, LDH, SS	MIS: 33 Open: 32	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Zairi [56] (2013)	Retrospective	Low	40/60	DDD, DS	MIS: 27 Open: 30	170	186	148	486	4.5	5.5	2.5	1.7	VAS back at 2 years: 3.8 VAS leg at 2 years: 2.7 ODI at 2 years: 30	VAS back at 2 years: 3.8 VAS leg at 2 years: 2.7 ODI at 2 years: 30	2.5	8.3

The three randomized controlled trials (RCTs) are in bold

DDD degenerative disc disease, *DS* degenerative spondylolisthesis, *EBL* estimated blood loss (cc), *EQ-5D* EuroQoL-5D, *IS* isthmic spondylolisthesis, *JOA* Japanese Orthopedic Association score, *LDH* lumbar disc herniation, *LOS* length of stay (days), *MCS* mental component summary, *MIS* minimally invasive surgery, *NR* not reported, *NR∗* numerical values not reported (only figures), *ODI* Oswestry Disability Index, *OR time* operative time (min), *PCS* physical component summary, *RCT* randomized controlled trial, *RMQ* Roland Morris Questionnaire, *SF-12* Short-Form 12, *SF-36* Short-Form 36, *SI* spinal instability, *SS* spinal stenosis, *VAS* visual analogue scale, *VAT* visual analogue thermometer scale, *WC* workman's compensation

Level of Evidence

Based on the GRADE protocol, all of the included studies were rated as low or very-low quality due to various methodologic flaws. All three of the PRCTs, which were initially assigned a quality rating of high, were downgraded to a final rating of low quality. Similarly, none of the prospective studies met the GRADE criteria to be considered higher than low-level evidence due to inadequate sample size and effect size. The final GRADE ratings of each study are included in Table 17.1.

Clinical Course

A total of 9856 subjects were represented in the 48 included studies, with 3639 undergoing MIS PLIF or TLIF and 6217 undergoing an open approach. Of note, the large numbers are due to one administrative data study with 1667 MIS cases and 4439 open cases [51]. The most common diagnoses were degenerative disc disease and degenerative spondylolisthesis (Table 17.1). Mean follow-up time was 23–24 months in both MIS and open cohorts.

Perioperative Outcomes

A summary of perioperative outcomes is detailed in Table 17.1. The operating room (OR) time was reported in 39 of the 48 studies and significantly variable. The MIS cohorts experienced longer surgical times in 19 studies and shorter surgical times in 20 studies.

Estimated blood loss (EBL) was reported in all but five of the included studies [30, 32, 39, 51, 55]. Compared to the EBL in open approaches, the MIS PLIF and TLIF cases were associated with up to 89% less blood loss.

The post-operative hospital length of stay (LOS) was included as an outcome measure in 36 of the 48 studies. All studies that reported LOS showed shorter hospitalizations for patients who underwent MIS procedures.

Table 17.2 Summary of which approach (MIS versus open) is more favorable for shorter operative time, less blood loss, shorter hospitalization, lower non-union rate, lower complication rate, and better patient-reported outcome

	MIS	Open
Shorter operative time	X	
Less blood loss	X	
Shorter hospitalization	X	
Lower non-union rate	–	–
Lower complication rate	X	
Better patient-reported outcome	–	–

"X" indicates more favorable approach, and "–" indicates unclear evidence

Radiographic Outcomes

Rates of radiographic non-union were reported in 26 of the 48 studies (Table 17.1), 13 of which demonstrated higher non-union rates in the MIS group. The non-union rates ranged from 0 to 16.7% in the MIS cohorts; whereas, in the open cohorts, non-unions were reported in 0–8.8% of patients. The method and timing of fusion assessment and criteria for diagnosing non-union were highly variable among these studies. In addition, one study assessed intraoperative radiographic evidence of facet joint violation and demonstrated no statistically significant difference between the MIS and open approaches [30].

Complication Rates

Complications were reported in 38 of the 48 studies (Table 17.1), 15 (39%) of which showed higher complication rates in the MIS group. The complication rate in the MIS cohorts ranged from 0 to 40%, while the complication rate in the open cohorts ranged from 0 to 52%.

Villavicencio et al [48] further divided complications into "major" and "minor" subgroups. Major complications included screw or allograft malposition requiring reoperation, neurologic deficit lasting longer than 3 months, infection or other post-operative complications requiring hospital readmission, as well as switching from MIS to open procedure. Minor complications included screw or allograft malposition without a need for reoperation, transient (less than 3 months) neurologic deficit effectively treated with physical therapy and/or steroid injections, cerebrospinal fluid (CSF) leak, hematoma, and anemia. The open cohort experienced a higher rate of major complications; however, the rate of minor complications was higher in the MIS cohort (Table 17.1).

Patient-Reported Outcomes

Of the 48 included studies, 34 demonstrated some form of patient-reported outcome (Table 17.1). The visual analogue scale (VAS) for pain was most commonly utilized. Two studies [14, 53] included figures showing the patient-reported outcomes but did not report numerical values (labeled as NR∗ in Table 17.1). In the MIS cohorts, follow-up total, back, and leg VAS ranged from 0.8 to 5.5. Similarly, the follow-up total, back, and leg VAS ranged from 0.9 to 5.1 in the open cohorts. There was no statistically significant difference in final total, back, or leg VAS between the MIS and open cohorts in most of the studies. Less frequently reported patient-reported outcome measures included Oswestry Disability Index (ODI), EuroQoL-5D (EQ-5D), Japanese Orthopedic Association (JOA) score, physical component summary (PCS) and mental component summary (MCS) of the SF-12 and SF-36, Roland Morris Questionnaire, and visual analogue thermometer (VAT) scale. No

significant difference was observed in any of the studies on these measures at final follow-up between the open and MIS cohorts. Furthermore, the method and timing of evaluating patient-reported outcomes were highly variable.

Economic Outcomes

The studies that included economic evaluations demonstrated reduced hospital cost in the MIS cohorts [19, 35, 36, 38, 42, 44, 51, 52, 54]. The largest evaluation using data collected from the Premier Perspective Database from 2002 to 2009 [51] showed no significant difference in costs for one-level fusion, but MIS surgery was associated with a $2106 (5.8%) decrease in costs for two-level fusion. MIS consistently demonstrated lower direct costs compared with open surgery, with cost-savings ranging from 6.1% to 49.3%. Rampersaud et al [38] determined one-year cost utility using direct hospital costs and showed that the cost per quality adjusted life year (QALY) gained was $128,936 for the MIS cohort, compared to $232,912 for the open cohort. In addition, Parker et al [35] evaluated both direct and indirect health care costs over 2 years and found that the cost per QALY gained for MIS surgery was $50,017 versus $68,860 for the open cohort—demonstrating lower indirect costs associated with MIS surgery.

Patient Preferences

In considering treatment options for various spinal pathologies, spine surgeons and their patients must weigh the potential benefits against the potential risks of each approach. When deciding between open versus minimally invasive PLIF or TLIF, the literature does not provide a definitive superiority of one approach over the other.

Table 17.2 summarizes the consensus in the literature regarding which approach is more favorable for shorter operative time, less blood loss, shorter hospitalization, lower non-union rate, lower complication rate, and better patient-reported outcome. In terms of operative length, 20 out of 39 studies reported shorter surgical time for MIS, but 19 studies reported longer surgical time. Generally, less intraoperative blood loss and shorter hospitalization are associated with the MIS approach. Even though there are lower rates of major complications reported for MIS, the evidence for lower non-union rates and better patient-reported outcomes is not as strong.

Discussion

With a rapid increase in the cumulative data pertaining to MIS techniques in lumbar interbody fusion, we must not only understand their clinical implications but also realize their limitations. This up-to-date qualitative systematic review included 48 low to very-low quality comparative studies with heterogeneity among patients, small sample sizes, lack of consistent reporting, and subjective treatment allocation. Although there was no significant difference in the operative time, the EBL and LOS both favored the MIS approach. The rate of adverse events was similar between the

MIS and open cohorts; however, the incidence of medical complications was higher in the open cohort. In addition, there was no significant difference in the rates of non-union and complications between the two groups. The patient-reported outcome measures varied between studies, without any conclusive findings. Furthermore, a disadvantage to consider in MIS is the need for intraoperative fluoroscopy and the potential detrimental effects of radiation exposure [25]. On the other hand, MIS seems to be cost-saving from both the hospital and societal standpoint [35].

As with any literature review, our conclusions are limited by the strength and quality of the data analyzed. Without well-designed RCTs, it is possible that less difficult cases were treated with MIS techniques, which may ultimately impact patient outcomes and compromise the validity of the analysis. Furthermore, the definition of MIS is often ambiguous in many of these studies. Multi-center RCTs utilizing appropriate diagnostic, clinical, and surgical stratification as well as validated outcome measures are needed to perform a valid comparison between the MIS and open approaches and to definitively establish superiority of one technique over the other.

Conclusion

In conclusion, there is evidence, of limited methodological quality, in support of MIS PLIF and TLIF as a feasible and appropriate surgical option for treatment of degenerative conditions of the lumbar spine.

Box

1. What is known?
   Posterior (PLIF) and transforaminal (TLIF) approaches to lumbar interbody fusion were developed to improve fusion rates, maintain vertebral alignment, and relieve pain symptoms. More recently, minimally invasive (MIS) techniques for PLIF and TLIF were introduced with the goal of creating smaller surgical wounds, minimizing trauma to adjacent tissues, and promoting faster postoperative recovery.
2. What is new?
   MIS techniques are associated with less blood loss and shorter hospitalization, but without significant difference from open PLIF and TLIF in terms of operative time, complications, non-union rate, and patient-reported outcome. Multi-center randomized controlled trials utilizing appropriate diagnostic, clinical, and surgical stratification as well as validated outcome measures are needed to perform a valid comparison of the two approaches.
3. What are the consequences for clinical practice?
   In considering treatment options for various spinal pathologies, spine surgeons and their patients must weigh the potential benefits against the potential risks of each approach. When deciding between open versus minimally invasive PLIF or TLIF, the literature does not provide a definitive superiority of one approach over the other.

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Preoperative Preparation of Osteoporotic Patients for Instrumented Spine Surgery

18

Sebastian Hartmann and Heiko Koller

Introduction

The most common metabolic bone disease is represented by osteoporosis, a disease leading to changes in the cortical and trabecular bone structures resulting in low bone mineral density (BMD). This reduced bone quality might lead to fractures of the spine followed by wrist and hip fractures, influencing the morbidity and mortality of the affected patients. The disease was first classified in 1994 to assess the fracture risk and to implement a screening for postmenopausal osteoporosis. A dedicated scientific group established a standardized score, the T-score, which compares the measured BMD with the BMD of healthy young individuals. Later a revised fracture risk score evaluating the 10-year probability of fractures, called FRAX, was released. In general, the categories for diagnosis based on the T-score are:

- normal (T-score −1.0 and above)
- low bone mass, referred to as osteopenia (T-score between −1.0 and −2.5)
- osteoporosis (T-score −2.5 and below)
- severe osteoporosis (T-score −2.5 and below with fracture history)

The WHO committee has developed another classification system based on the bone mineral density. According to this scheme a BMD >833 mg/cm^2 measured at the hip is considered as normal bone, whereas a BMD between 833 and 648 mg/cm^2 represents osteopenia and a BMD lower than 648 mg/cm^2 is classified as

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osteoporosis. A BMD lower than 648 mg/cm^2 and a coexisting fracture stands for severe (established) osteoporosis.

In general, osteoporosis can be subclassified into 3 types. Type I represents postmenopausal osteoporosis and is therefore explained by a sudden lack of oestrogen in elderly women. Type II or aging osteoporosis can be found in elderly men and women and it is mainly caused by an increasing dysfunction of osteoblasts and therefore the reduction of bone formation. Type III osteoporosis is a secondary disease and therefore often caused by long-term use of drugs such as cortisone, rheumatological disorders or an unbalanced diet.

The worldwide prevalence of osteoporotic fractures amounts to 8.9 million, meaning an osteoporotic fracture occurs every 3 seconds [1]. Of those 8.9 million, approximately 60% represent spine fractures resulting in one vertebral fracture every 22 seconds [1]. Moreover, it has been shown that only a 10% loss of bone mass in the vertebrae can double the risk of vertebral fractures [2]. Although many of those fractures remain asymptomatic, osteoporosis in general has a high impact on the patient's everyday life: The disability due to osteoporosis has been shown to be greater than that caused by cancer (with the exception of lung cancer) [1].

A high rate of osteoporosis has been found in patients undergoing spine surgery. Approximately 15% and 50% of male and female patients suffer from osteoporosis (T-score <-2.5) [3] and half of the elderly patients experience a low BMD with increased fracture risk. Thus, the incidence of osteopenia and osteoporosis add an increasing number of fractures to be treated. This effect represents a current and future challenge to worldwide health care system, not the last because of increasing treatment costs.

Dual-energy X-ray absorptiometry (DXA) of the distal radius, the lumbar vertebral bodies or the femur head signifies the standard of reference for BMD measurement, nevertheless this method is not able to distinguish between cortical and trabecular structures within the bone. In case of degenerative bone changes, the BMD measurement might lead to increased but incorrect BMD results, so that the interpretation of lumbar spine DXA is limited [4]. As a result, patients with a normal BMD after DXA measurement may suffer from osteoporotic fractures, although the measured values signifies a normal BMD according to the WHO criteria of osteoporosis [5]. The literature provides evidence that patients with a vertebral fracture often suffer from low BMD in peripheral bones, so that the use of a high-resolution peripheral quantitative computed tomography (HR-pQCT) might predict osteoporotic fractures in the future [2, 6–8]. A correlation has been found between vertebral deformities due to osteoporotic fractures and the bone microstructure of the distal radius [9]. This is of high clinical impact, so that patients with a lower peripheral BMD might suffer from an increased risk of developing severe deformities due to a vertebral fracture.

In addition, human serum markers were identified to indicate osteoporosis: A significant correlation between osteoporosis and vitamin D (25-OH-D) or calcium supplements has been found. Low vitamin D may lead to increased serum levels of parathyroid hormone consequently ending in high circulating serum calcium concentrations due to increased bone loss. The longstanding use of proton pump inhibitors

(PPI) may lead to elevated serum levels of gastrin suggesting hypochlorhydria. Hypochlorhydria results in a decreased calcium uptake and consequently in a reduced bone mineralisation. In addition to that, several laboratory parameters including urinary deoxypyridinoline levels (DPD) or (specific bone) alkaline phosphatase (ALP) can indicate osteoporosis. Since the stability and anchorage strength of pedicle screws are directly dependent on the bone density of the target vertebral body, BMD is not only an important risk factor for implant-related complications (IRC) but may also be responsible for lower fusion rates [10, 11]. While bone quality plays a minor role in patients without spine instrumentations, the literature provides evidence, that fractures and implant-related failures following instrumented spine fusions are more common in osteoporotic patients than in patients with normal BMD. As a result, a high rate of proximal junctional kyphosis (PJK) and failure (PJF) and progression of spinal deformities are common in these patients often ending in revision surgeries [12].

In the current narrative review, the authors explore the specific importance in detecting preoperative osteoporosis in patients considered for spinal fusion surgery. The incidence of osteoporosis in spinal surgery, its medical prevention, surgical strategies as well as the mode of implant failure in osteoporosis and the problem of hidden osteoporosis in patients with ankylosing spinal disorders will be discussed.

The osteoporotic characteristics, also called ‘collagenosis’, seen in patients with pediatric or adult patients with spinal deformity due to skeletal dysplasia, syndromic disease (e.g., Marfans, Neurofibromatosis, osteogenesis imperfecta) or systemic disease (e.g., mucopolysaccharidosis) are not subject of the current chapter. However, collagenosis and a related poor bone quality in this patient group can pose similar challenges and need similar preoperative precautions as in the patient group with adult spinal osteoporosis discussed herein.

Methods

The authors performed a narrative literature review based on an extensive PubMed search. All studies published in English and German language with full-text availability were considered for inclusion. A continuous search string could not be identified due to the complexity of the theme and the cross subjecting to internal medicine. Additional information was found after identifying and screening the reference lists of the included articles. The articles collected were screened initially for relevance by title and abstract reading. After including the article, full-text reading was performed. According to the evaluated literature of osteoporosis and instrumented spine surgery, the manuscript has been structured with the following topics:

- Incidence of osteoporotic spines
- Medical therapy options prior to surgery in the osteoporotic
- Surgical strategies in osteoporotic patients
- Mode to failure of instrumented osteoporotic spines
- Fusion rates in osteoporotic spines
- Hidden osteoporosis

Results

Incidence of Osteoporotic Spines

According to the WHO criteria, osteoporosis is defined as a BMD below 2.5 standard deviations or more off the mean value for young healthy women (T-score of <−2.5 SD). It is estimated that approximately 20 million women and 5 million men in Europe suffer from osteoporosis with a rising incidence, causing annual costs of nearly €37 billion. Approximately 66% of these costs are used for the treatment of osteoporotic fractures not including the complications of spine revision surgeries [13, 14]. It has also been shown that osteoporotic patients undergoing spine surgery tend to have a longer postoperative stay in hospital and a higher 90 day readmission rate consequently leading to higher costs for the healthcare system [15]. Nearly one third of patients with low BMD suffer from an undiagnosed secondary cause of osteoporosis, which might be treated sufficiently in case of diagnosis [16]. Due to the increased incidence of spine surgeries in the elderly population, osteoporosis represents a comorbidity with enormous impact on the peri- and postoperative outcome of instrumented spine surgery. The literature provides evidence, that poor bone quality correlates significantly with an increased risk of spinal sagittal imbalance and IRC, resulting in increased perioperative morbidity and mortality [17–20]. Despite the rising incidence of osteoporosis and the fact that spine surgeons are often the "first contact" for patients with osteoporotic compression fractures, the impact this disease bears for the health systems seems to be neglected [21]. Only a paucity of patients receives adequate diagnostic work-up and pharmacological therapy after fracture, moreover, a significant decrease in the rate of treatment of osteoporosis with an increasing patient age was found [22–25]. Another factor leading to a failed diagnosis of osteoporosis is the misinterpretation of DXA scans. It has been found that the BMD measurement at the lumbar spine using DXA tends to be distorted by the sequels of degenerative disc disease with osteophyte formation and sclerotic osseous changes of the lumbar spine [26]. Therefore, particularly negative DXA scans of the lumbar spine are deemed not reliable to exclude or detect osteoporosis. The distal radius- or femoral neck BMD seem to be more consistent, so that a significant correlation of osteoporosis and poor bone quality in these localizations has been shown [9, 27, 28]. Quantified computed tomography (QCT) shows even better results for the measurement of bone quality, as it is possible to differentiate between cortical and trabecular bone mass [29]. Beside preoperative measurement of bone quality, there is a novel alternative of intraoperative assessment of bone strength by using the DensiProbe® test [30, 31]. This test uses the insertional torque of pedicle screws, which is known to be a reliable parameter for the strength of trabecular bone mass. Using this device it is possible to detect asymmetrical bone strength differences in the pedicles and to adapt the surgical strategy and implant selection specifically for osteoporotic vertebrae [30, 31].

The incidence of osteoporotic patients in spine surgery has been investigated in a study including 144 patients requiring spinal surgery with 27% of those patients suffering from osteoporosis and roughly 44% from osteopenia. Preoperatively,

approximately 38% of these patients received no anti-osteoporotic therapy and 74% had inadequate vitamin D status without appropriate substitution [9]. Another study conducted by Chin et al. showed even higher incidences: Among 323 female patients older than 50 years scheduled for spine surgery, 51% suffered from osteoporosis and another 41% of the patients had osteopenia [3]. The incidence of osteoporosis increases with age in females, whilst the incidence of osteopenia decreases with higher age. One explanation might be a further progression of bone mineral density loss, so that a shift of osteopenic patients towards osteoporotic patients occurs [3]. Similar rates have been found in a study including 2293 patients treated with spinal instrumentation. Approximately 45% of the patient cohort suffered from osteoporosis. It was found that osteoporosis significantly increased the risk of postoperative complications resulting in revision surgeries due to IRC [32]. In general, the rate of revision surgery for osteoporotic patients tends to be higher compared to the non-osteoporotic counterparts [33–35]. Other studies have shown that a high proximal junctional kyphosis angulation with an increased sagittal vertical axis (SVA) as well as osteoporosis can be potential predictors of postoperative complications in adult patients with spinal deformity and thus should be considered as possible risk factors for revision surgery [9, 28, 36, 37].

To treat the osteoporotic spine prior to any surgical intervention that uses implants, detection of osteoporosis is decisive. Secondary osteoporosis related to systemic disease and/or drug usage can be difficult to detect and patients shall be screened for this history prior to surgery (Table 18.1).

Medical Therapy Options Prior to Surgery

Preoperative optimization of BMD is essential for satisfying postoperative results, as many patients undergoing spine surgery do have decreased BMD. Reduced and pathologic BMD is connected to a higher likelihood of IRC [18, 38–41]. Despite the risk factors and possible consequences, spine surgeons seem to neglect the fact, that osteoporosis requires special preoperative planning and consequently adapting the operative strategies [21, 22].

Hypovitaminosis D or an insufficient calcium intake may lower the BMD, consequently leading to osteoporosis [42, 43]. In a study conducted by Stoker et al. it has been shown that 27% of the patients scheduled for spinal fusion showed vitamin D deficiency [44]. The supplementation of vitamin D leads to increased absorption of calcium and reduces the risk of BMD loss. When speaking about calcium supplementation there is clear evidence for the usage of calcium citrate malate, as it is not dependent on the gastric acid status, reduces the risk of developing kidney stones and is better absorbable by the gastrointestinal mucosa compared to calcium carbonate [45].

Hypochlorhydria reduces the calcium absorption. Decreased calcium absorption thus leads to decreased plasma calcium concentrations, which may ultimately worsen pre-existing osteopenia or osteoporosis. The long-term medication of

Table 18.1 Common causes for secondary osteoporosis (type III osteoporosis)

Cause	Study	Objective	Main findings
Ankylosing spondylitis	Magrey et al. [280]	Review regarding osteoporosis in patients with ankylosing spondylitis	Multifactorial, main cause=systemic inflammation mediated by TNF-α leading to RANKL induction and osteoclast activation
Glucocorticoid-induced	van Staa et al. [281]	Meta-analysis regarding the epidemiologiy of corticosteroid-induced osteoporosis	Corticosteroids cause transient decreases in serum calcium due to vitamin D inactivation of calcium absorption, induction of RANKL and macrophage stimulating factor (MCSF) and decrease in osteoprotegerin
Hyperthyroidism	John Howard Duncan Bassett et al. [282]	Overview of the pathophysiology of thyroid hormone in the bone	Increased bone remodelling frequency with maintained duration of resorption but reduced bone formation
Proton pump inhibitors (PPI)	Solomon et al. [283]	Comparison of BMD measurements between patients taking PPI, H2 receptor antagonists or no medication	Increased gastric pH leads to a calcium malabsorption and negative effects on skeletal homeostasis
Multiple drugs	Panday et al. [284]	Systematic review regarding drug-induced osteoporosis	Besides PPI and glucocorticoids, antiepileptic drugs, medroxyprogesterone acetate (hormonal contraceptives), aromatase inhibitors, gonadotropin-releasing hormone agonists (GnrHs), selective serotonin reuptake inhibitors (SSRIs), thiazolidinediones, calcineurin inhibitors, anticoagulants such as heparin and chemotherapeutic agents (methotrexate, ifosfamide) can be potential triggers for the loss of bone mass

proton pump inhibitors (PPI) may cause hypochlorhydria leading to calcium malabsorption. Therefore, a preoperative supplementation of calcium citrate malate in case of low plasma concentration is important for patients treated with PPI [46]. According to the recent literature, calcium supplementation has no negative impact on the cardiovascular system or increased risk of mortality or neoplasia [47–50].

In case of low BMD, several therapy options are available (Table 18.2). Today's first-line treatment option is Bisphosphonates. Due to hydroxyl- and phosphate components, Bisphosphonates have a high affinity for hydroxyapatite, second- and third-generation Bisphosphonates (Alendronate, Ibandronate, Risedronate and Zoledronate) contain nitrogen-side chains with the ability of even higher affinity to hydroxyapatite and a better skeletal accumulation. The biochemical mechanism of Bisphosphonates lies in the induction of osteoclast apoptosis due to the inhibition of farnesyl

Table 18.2 Patient's preferences regarding medical therapy options for osteoporosis[a]

Drug type	Approved indication[b]	Benefit arising from therapy	Risks arising from therapy
Anabolic agent			
Teriparatide	OPMW, OPM, GIOP	Ohtori et al. [60]: Fusion rate: Teriparatide vs. Bisphosphonate—82% vs. 68%, respectively Ohtori et al. [59]: Incidence of pedicle screw loosening: Teriparatide vs. Bisphosphonate vs. Control—7–13% vs. 13–26% vs. 15–25%, respectively Inoue et al. [62]: Mean insertional torque of pedicle screws: Teriparatide vs. Control—1.28 Nm vs. 1.08 Nm, respectively. Yagi et al. [61]: Incidence of PJK Type 2: Teriparatide vs. Control—4.6% vs. 15.2%, respectively	Position-dependent blood pressure change; hypercalcemia, nausea, joint aches, musculoskeletal pain
Antiresorptive agents			
Bisphosphonate	OPMW, OPM, GIOP, hypercalcemia of malignancy, Paget disease, bone metastasis	Nagahama et al. [53]: Fusion rate, cage subsidence, vertebral fracture: Bisphosphonate vs. Control: 95% vs. 65%; 5% vs. 29%; 0% vs. 24%, respectively Tu et al. [56]: Fusion rate, cage subsidence, vertebral fracture, pedicle screw loosening: Bisphosphonate vs. Control: 75% vs. 56%; 28% vs. 54%; 19% vs. 51%, 18% vs. 45%, respectively	Nausea, dyspepsia, abdominal pain, diarrhea, constipation, musculoskeletal pain, osteonecrosis of the jaw, atypical femoral fracture
Denosumab	OPMW, OPM, GIOP, high risk of fracture receiving androgen deprivation therapy for non-metastatic prostate/breast cancer in m/w	Cummings et al. [72]: Denosumab vs. Control: 68% reduced risk of new vertebral fractures, 20% reduced risk of new non-vertebral fractures	Hypocalcemia, weakness, musculoskeletal pain, anemia, diarrhea, skin irritations, osteonecrosis of the jaw, atypical femoral fracture

(continued)

Table 18.2 (continued)

Drug type	Approved indication[b]	Benefit arising from therapy	Risks arising from therapy
Raloxifene	OPMW, risk reduction of invasive breast cancer in OPMW	Cummings et al. [69]: Outcome analysis: Raloxifene vs. Placebo: Reduced incidence of breast cancer Kanis et al. [285]: Incidence of vertebral fracture: Raloxifene vs. Placebo: 42% risk reduction with the use of Raloxifen	Hot flushes, hyperhidrosis, headache, dizziness, lower limb cramps, joint ache, nausea, VTE
Calcitonin	Second-line therapy for OPMW (postmenopause >5y)	Chesnut et al. [74]: Incidence of vertebral fracture: Calcitonin vs. Placebo: 33% risk reduction with the use of Calcitonin	Nasal irritation, hypersensitivity skin reaction, headache, dizziness, nausea, vomiting, loss of appetite, back pain
Anabolic and antiresorptive agent			
Strontium Ranelate	Second-line therapy for OPMW and OPM	Reginster et al. [286]: Incidence of vertebral fracture: Strontium Ranelate vs. Placebo: 45% risk reduction with the use of Strontium Ranelate	Hypersensitivity skin reactions, musculoskeletal pain

OPM/OPMW Osteoporosis in men/postmenopausal women, *GIOP* Glucocorticoid-induced osteoporosis, *VTE* venous thromboembolism

[a]The choice of a suitable pharmacological therapy should be evaluated based on the individual patient's state of health and pathology

[b]Approved Indications by the FDA (exception: Strontium Ranelate)

pyrophosphate synthase (FPPS), a key regulatory enzyme in the mevalonic acid pathway, which is crucial for the production of cholesterol, other sterols, and isoprenoid lipids inside the osteoclasts [51, 52]. The majority of clinical and preclinical trials showed satisfying results regarding the use of Bisphosphonates for postoperative outcome in patients with osteoporosis. Undesirable side effects of Bisphosphonates are well known for either short- or long-term use including upper gastrointestinal complaints when given orally, nausea, acute-phase reactions (when given intravenously), severe chronic musculoskeletal pain, hypocalcaemia and ocular inflammation [53–56]. Nevertheless, rare side effects, such as osteonecrosis of the jaw and atypical femur fractures have been reported in patients with prolonged usage of Bisphosphonates [57]. Presently, the U.S. Food and Drug Administration (FDA) has recommended the usage of Bisphosphonates for 3 years, followed by a BMD re-evaluation or a clarification of possible complications or contraindications. The appropriate treatment period has not been demonstrated, thus a frequent follow-up is necessary, especially in patients at high risk for vertebral or non–vertebral fractures [58].

Teriparatide, a recombinant human parathyroid hormone (rhPTH), is the only pharmacological option acting solely as an anabolic agent. Compared to

Bisphosphonates, this therapy option has shown superior results regarding bone fusion rates after spinal surgery [59, 60]. In the studies mentioned, Teriparatide was taken on average 2 months before and 8 to 10 months after surgery. Due to the activation of PTH receptors located on the osteoblast cell surface and the coupling to downstream messengers, growth factors get induced and activate the anabolic bone remodelling process. The prophylactic usage of Teriparatide shows a significant BMD increment in the upper-instrumented vertebra (UIV) of long dorsal instrumented pedicle screw constructs and therefore a reduced risk of vertebral fractures after corrective surgery for adult spinal deformities. Additionally, the preoperative use of Teriparatide was shown to improve stability of pedicle screws due to an increase of volumetric BMD and fine bone structures, moreover, the incidence of PJK from bone failure was reduced in a study of Yagi et al. [61, 62]. Undesirable side effects have been reported but seem to be benign including lower limb pain, headache, nausea and dizziness [63]. The rapid decrease of BMD after the treatment of Teriparatide in postmenopausal women and eugonadal men with osteoporosis has been observed, so that the indication for immediate anti-resorptive therapy after Teriparatide might balance the resorptive component [64]. Currently, the FDA has limited the treatment period with Teriparatide to 24 months as a correlation between the use of Teriparatide and the development of osteosarcoma has been found in preclinical animal studies, whereas this could not be observed in humans [65, 66].

Strontium Ranelate, a new anti-resorptive and anabolic agent, could form an alternative for Teriparatide with longer half-life, but this treatment option is approved only as a second-line therapy [67]. Selective oestrogen receptor modulators (SERM) were initially used for hormone-selective breast cancer but showed positive effects for BMD increment and risks of fragility fractures. Today, Raloxifene is one of the most commonly used agents for osteoporosis of type I and shows satisfying results regarding bone loss and risk of vertebral fractures. Common adverse effects include hot flushes and lower limb cramps [68]. Deep venous thromboembolism is a rare complication; nevertheless, this treatment option has not been shown a negative cardiovascular effect [69, 70].

Denosumab, a human monoclonal antibody against receptor activator of nuclear factor-kB ligandin (RANKL), is another alternative to the upper mentioned therapy options. RANKL is a key mediator for osteoclast activation. Denosumab acts as an inhibitor for RANKL, which ultimately leads to a reduced BMD reduction [71]. With the use of anti-resorptive agents, it is possible to reduce the risk of a new radiographic vertebral compression fracture by 68% in postmenopausal women [72]. Possible side effects are similar to Bisphosphonates, although the risk of long-term adverse events seems to be slightly higher for Denosumab [73].

In case of incompatibility to the aforementioned medications, Salmon Calcitonin might be a second-line option, as this therapy option has a 40- to 50-fold better ability to inhibit osteoclast activity compared to the human type Calcitonin. In an adapted dose, a risk reduction of vertebral fracture and a BMD increment has been shown. Nevertheless, the use of Calcitonin as a first-line therapy or as a long-term option is limited due to its high costs and the unfavourable application form (nasally or intravenously) [74].

Surgical Strategies to Improve Fixation Strength in Osteoporotic Patients

Preoperative analysis of the osteoporotic patient and spine scheduled for surgery shall address the surgical fixation options to be considered in the individual patient. The anchorage quality of spinal implants is only as good as the bone density of the instrumented vertebral body. The literature provides evidence that the insertional torque, the pullout strength and the cutout torque of each fixation point are significantly lowered in osteoporotic spines [17, 33, 152].

This selected review of literature should give the reader a quick summary of the different treatment options of instrumented spine techniques in osteoporotic patients in order to improve the stability of the construct. The majority of the referenced studies are in vitro investigations, so that an uncritical transfer to the clinical use might not be able. Preoperative consultation of the osteoporotic spinal patient and surgical planning should address the different options and related drawbacks available with current techniques to improve fixation in osteoporotic vertebrae.

Screw Design Modifications and Insertion Techniques

Pedicle screw placement represents the daily routine for most spine surgeons. To choose the sufficient pedicle screw design in patients with lowered BMD is a major concern. The diameter and length of pedicle screws influences the pullout strength and might prevent screw loosening [153–156]. The area of the pedicle screw thread and the accompanied bone stock might be defined as the "flank overlap area" (FOA), which determines a sufficient predictor of appropriate pedicle screw fixation in poor bone quality vertebrae [157]. A constant increase in anchorage strength by choosing an increased diameter of approximately 1 mm was demonstrated [155]. Nevertheless, the diameter of the pedicle defines the diameter of the screw placed and spine surgeons should be aware of implanting larger screws than conventionally used leading to fractures of osteoporotic pedicles, especially without pre-tapping [158–160]. Beside the adjustment of the pedicle to the screw diameter, the length of the pedicle screw represents a high impact on the anchorage strength. Inserting a pedicle screw to 80% of the vertebral body length is said to provide appropriate fixation capabilities [161]. Whereas, no significant difference was observed in osteoporotic vertebrae by inserting a screw to 50% of the vertebral body depth or complete incorporation of vertebral body depth but without perforating the anterior vertebral wall [162]. If the anterior cortex is perforated to achieve a bicortical pedicle screw placement, a significant increase of pullout forces was determined [160, 162]. Care must be taken in order to anchor a pedicle screw in a bicortical fashion, so that incorrect placement might end in severe vascular, bowl or neurological injuries [161, 163–166]. An increased number of threads within the pedicle due to the purchase of longer screws increases the anchorage strength due to a larger FOA, especially in the often used caudal fixation point S1. The literature provides evidence, that a bicortical S1 screw fixation is superior compared to a unicortical technique. Zhuang et al. observed a significant increase of pullout strength with bicortical sacrum fixation in early-stage osteoporosis compared to a unicortical cement

augmentation of the pedicle screws [39]. Moreover, direct fixation into the apex of the sacral S1 promontory (tricortical fixation) represents a significant increase in peak insertional torque compared to a bicortical S1 pedicle screw implantation [167]. Lehman et al. added a "one to one" correlation of tricortical pedicle screw fixation and bone mineral density [167]. In contrast, a "windshield wiper" effect was observed with the use of a bicortical screw placement in lumbar segments leading to a shift of the center of rotation to the distal screw end. This effect might result in screw toggling ending in pedicle fractures, so that bicortical screw fixation might be reserved for sacrum use only [162]. Another technique to reduce the extrapedicular screw distance is described as "screw hubbing", a technique with incorporation of the screw until the head touches the dorsal laminar cortex. Pedicle screws are exposed to rotational and bending moments. These moments increase with a longer extrapedicular distance, especially in case of undersized screws. As a consequence, the pedicle screw is subjected to a center of rotation shift into the pedicle leading to a "teeter totter" effect with the pedicle acting as a fulcrum, screw toggling might occur [168]. Additionally, "hubbing" the head of the pedicle screw against the dorsal laminar cortex delivers a load-sharing effect reducing the ability of the craniocaudal microtoggling motions. Despite the theoretical advantages, Paik et al. observed a significant decrement of pullout strength with the use of "hubbed" screws compared to conventional pedicle screws. Paik et al. added the possibility of iatrogenic fractures of the dorsal lamina, transverse process or the superior articular facet [168]. Also, with hubbing the polyaxial advantageous characteristics of pedicle screws can be diminished, as hubbing will lower the screw head range of motion. Another option is a screw adaptation after insertion or simple a "screw turnback". Under some instances, screws must be turned back after insertion due to rotational or translational manoeuvres or just adapting the rod to the screws. Biomechanical investigations in osteoporotic vertebrae with cement augmented screws turned back after insertion showed, that the pullout strength were comparable to unaugmented screws. As a consequence, adjusting the screw depth after insertion in augmented screws should not be advocated [169, 170]. In general, the size of the pilot hole of pedicle screws plays a major role to ensure appropriate screw anchorage. Oversized initial pilot holes may lead to inappropriate screw fixation resulting in early screw loosening, whereas undersized pilot holes increase the insertional torque, so that pedicle fractures, especially in osteoporotic vertebrae, may occur. The optimal size of the initial pilot hole is difficult to define and probably varies from patients to patients with different bone quality. The average diameter of a probe is approximately 3–6 mm with a conical shape. To evaluate the appropriate size, Battula et al. defined the "critical pilot size hole". This size is represented by the diameter of a pilot hole, which contributes to a sufficient anchorage of the screw, but otherwise prevents over-dimensioning with subsequent screw failure [171]. In a biomechanical evaluation, Battula et al. observed the "critical pilot size hole" as a diameter of 71.5% of the outer pedicle diameter to prevent screw failure and to ensure an appropriate insertional torque. Additional to selecting the appropriate initial pilot hole, the topic of "pre-tapping" the pilot hole before screw insertion or the use of "self-tapping" screws is of great interest. Most of the pedicle screws used are

"self-tapping" screws with the ability to cut the thread path, so that insertion of the screw is simplified, which leads to a reduction of the operative procedure's complexity. On the other side, the pedicle is exposed to rotational frictions with the use of "self-tapping" screws leading to a high insertional torque, so that pedicle fractures might occur in osteoporotic bones [171]. In contrast, the efficiency of pedicle pre-tapping is discussed critically. Biomechanical studies reported decreased pullout forces in osteoporotic spines with a significant stronger load to failure in self-tapping screws [172–174]. Interestingly, the significant differences of pullout forces of "self-tapping" compared to "pre-tapped" screws could not be proven in the thoracic spine. No consistent technique for measuring pedicle screw fixation strength and as a consequence choosing the appropriate screw size is available yet. Helegson et al. determined the ideal screw size based on the insertional torque, so that an intraoperative assessment of an insertional cut off value of 2.5 in-lbs insertional torque led to significant higher pullout forces by choosing the appropriate screw 1 mm bigger than the used tapper [175].

In the last decades, a lot of investigations have been performed to increase the pullout forces of pedicle screws. The thread design or the thread pitch of the pedicle screw has been evaluated intensively. The cross-sectional shape defines the type of the thread, so that V-shaped and square-shaped threads consisting of the similar thread pitch on both sides with a flat angle or a rectangular angle, respectively, are available. In contrast, a buttress-shaped thread is made of two different angles and this design is commonly applied in nonmedical usage to convert rotational to linear motions. To summarize, the V-shaped thread design revealed to have significant advantages compared to buttress-shaped or square-shaped threads independently of the bone density [176]. Additional attempts to extend the fixation strength of pedicle screws have been performed. From a theoretical point of view, a higher number of thread gears in cortical bone regions (pedicle) might lead to an increased fixation of screws. These screws consist of two different sizes of thread gears with a smaller one at the proximal part and a larger one at the screw tip. Although dual-threaded screws require an increased insertional torque than standard screws in bone and low density foam, this thread design failed to prove superiority in pullout tests and cyclic fatigue loading protocols [173, 177]. The majority of the studies presented are in vitro studies, so that one to one transfer into the clinical routine may not be possible. The same is true in literature by evaluating the different screw shapes and modifications due to a conical or cylindric shape, expandable screws or special screw coating. In case of a conical screw shape design, either the core or both, the core and the thread can be conical allowing a gradual increment in diameter in the proximal direction. This might lead to a high amount of compression strength in the posterior part of the screw resulting in increased pullout strengths [106, 178, 179]. In contrast, other investigators did not find a significant increment of pullout forces [106, 176, 178, 180]. Interestingly, Kwok et al. proved an increased insertional torque, but the concomitant pullout strength has not been influenced by the conical shape of the screw [179]. Anatomically, a conical screw shape matches to the elliptical shaped cross section of the pedicle with a decrease in diameter anteriorly. Approximately 60% of the pullout strength is based on the geometry and the

cortical bone of the pedicle and approximately 15–20% depends on the cancellous bone within the vertebral body [105, 108, 162, 169].

Beside the proposed techniques to enforce pedicle screw fixation in osteoporotic bone including longer and thicker screws, under-tapping of the initial pilot hole, appropriate screw shape or cement augmentation techniques and screws with a distal expansion mechanism were developed. These screws perform in a similar manner to a "barb", so that the pullout forces are increased after secondary three-dimensional clamping of the screw. In contrast to the described techniques above, expandable screws do not increase the initial insertional torque, but the increased pullout forces are a result of the enhanced contact area between the expanded pedicle screw and the surrounding bone [108, 181, 182]. The three-dimensional expansion of the screw compresses the low-density cancellous bone of the osteoporotic vertebra resulting in a region with increased density around the screw. Koller et al. evaluated the difference of standard 6.0-mm pedicle screw and 6.0-mm screws with distal expansion mechanism. The distal expansion mechanism covered 20% of the shaft screw length. The expandable screw increased the failure load by 20% compared to a standard screw with identical diameter and length [181]. Cook et al. revealed the same results. The group presented an increased pullout resistance of 20% compared to a conventional screw, whereas in low bone density vertebrae the pullout resistance enlarged to 50% [108]. Transferring these results to the clinical routine, a low rate of screw loosening has been observed in the population with physiological BMD as well as in osteoporotic patients [183, 184]. However, with an increasing use of these screws, the concerns also increased in case of screw failure resulting in revision surgery.

The majority of the available screws consist of a titanium alloy or stainless steel. Coating of pedicle screws with a thin surface of hydroxyapatite (HA) was proven to increase bone-implant contact and screw fixation within the pedicle and the vertebral body [185–187]. Hasegawa et al. performed mechanical tests in dogs, which had HA coated screws implanted for 10 days. The research team compared HA-coated to non-coated pedicle screws in each contralateral pedicle of one vertebra and reported an increase of pullout strength by approximately 60% after sacrificing the dogs [187]. Nevertheless, the revision of HA-coated pedicle screws revealed to be difficult due to a 20-fold higher removable torque required compared to conventional screws [188].

Cement Techniques

Most studies dealing with enhancing the screw purchase are of in vitro biomechanical nature and only a few clinical trials are available. Two main different testing purposes are available including axial pullout forces with tensile forces acting on the screw and cyclic loading toggling tests with cranio-caudal toggling moments leading to load to failure results. In case of pedicle screws, the physiological forces and moments acting on the screw until bony fusion occurs are predominantly bending forces, so that cyclic cranio-caudal toggle displacements represent a quasi-physiological testing purpose. Nevertheless, only a paucity of the published studies uses this test procedure. The literature provides evidence, that the use of cement

augmentation techniques increases vertebral bone density and consequently enhances pedicle screw fixation. Contrastingly, screw performance in osteoporotic patients is reduced with a high likelihood of implant-associated complications [17, 104, 107, 109, 189–191]. The most frequent indications to perform cement augmentation of pedicle screws are osteoporosis. Beside simply injecting cement into the vertebral body, important factors have to be considered in order to select the right injection technique, to regulate the time of cement injection or screw placement after the cement is placed, to adjust the appropriate cement volume and to adapt the cement type or the used screw type. The possibility of the cement-related complications must be considered. Cement injection might be possible after the initial pilot hole is prepared [103]. Afterwards a conventional screw is placed in a solid bone cement stock [103]. With the use of a fenestrated screw, the cement is injected through the screw leading to a cement surface around the screw limited throughout the screw fenestrations [103]. It might be safer to use a cement-augmented fenestrated screw in order to have the bone surrounding the screw compressed and consequently the risk of cement extravasation might be limited. Final and clear differences between these two methods have not been clarified, whilst the use of fenestrated screws characterizes a possible faster and safer alternative [103, 169, 192, 193]. The third technique is limited to the use of vertebroplasty or kyphoplasty, whereas no differences between these two techniques have been found [194]. In case of PMMA injection, the curing time does not influence the pullout forces whether the screw is placed immediately after the cement injection or after complete curing [195, 196]. Theoretically, a "soft cement" usage immediately after activating might lead to a better cement-bone integration due to the associated low viscosity until curing occurs. Hoppe et al. consequently postulated, that the failure mode in "soft cement screw injections" is more likely to be at the bone-cement interface compared to a screw-bone failure mode in already cured "hard cement" [197]. The appropriate cement volume has been determined around 2–3 mL, so that a too small cement volume can lead to insufficient fixation, whereas too much leads to an increased risk of inadvertent extravasation with spinal canal compression or cardiovascular complications [102, 139, 198]. The mostly used cement still remains Polymethylmethacrylate due to the low cost and good biocompatibility with good and relative safe results in the last decades. As a disadvantage of PMMA, the bioinert characteristics prevent osteoconductive and osteoinductive properties [193]. Additionally, the exothermic reaction might lead to temperatures between 50 °C and 110 °C leading to thermal necrosis in the surrounding bone or soft-tissues. One might argue, that these high temperatures might mitigate bone fusion as a result of osseous necrosis. Nevertheless, use of PMMA augmented spinal fixation significantly increased bony fusion in patients with osteoporotic bone compared to non-augmented screws [101, 108, 139, 193, 194, 199–201]. Liu et al. revealed similar forces for pullout of expansion screws compared to pullout of PMMA-augmented screws [202]. In general, the average increment of pullout forces comparing non- to augmented screws in osteoporotic vertebrae was reported to be 10- to 14-fold higher. Based on the possible drawbacks of PMMA cement, a new calcium phosphate (CaP) cement has been developed with improved osteoconductive and

osteoinductive characteristics, which serve as a scaffold for osseointegration. Calcium sulphate (CS) and calcium triglyceride (CT) are further alternatives with short reabsorption time and the risk of inadvertent extrusion [203, 204]. Of note, PMMA has performed better in pullout tests and more experience exists for its use compared to CaP cement [204, 205].

Alternative Techniques

Beside the anatomical direction through the pedicle with use of standard pedicle screws inserted in a convergated direction, the so called "medialized cortical screw trajectory (mPact)" was shown to result in similar as well as increased pullout forces than conventional pedicle screws. This technique was introduced in the last decade and described as a dorso-medial to ventro-lateral screw trajectory to include cortical bone areas of the pedicle and the pars interarticularis [206]. As a consequence, better bone quality is included compared to conventional pedicle screws engaging the already decreased cancellous bone of osteoporotic vertebrae [207]. For this technique screws in a smaller diameter and shorter length are used, hence this technique revealed significant higher insertional torque and pullout strengths [207–209]. Biomechanical and clinical studies in osteoporotic spines according to that topic are lacking. The risk for pedicle breaches with this cortical bone catching technique might be increased. A randomized trial of Lee et al. investigated the use of conventional pedicle screws and the new cortical screw trajectory and revealed no significant differences in case of fusion rates as well as pain and functional outcome [210]. Hence, significantly less LBP was observed with less blood loss, shorter operative time and smaller skin incision compared to their counterpart [210]. Beside the above mentioned, other techniques including triangulation (connection of the screws to build a triangle), lamina hooks (mostly added at the cranial level of fusion constructs) or cross-linking of the implanted rods are used. Use of advanced screw design such as the hollow screw or S1-alar screws were also shown to increase fixation strength in the sacral bone [211]. With use of the S1-alar screw, 2 screws with connection to one polyaxial rod can be connected to a standard posterior screw-and-rod system. Significant improved fixation strength under cyclic loading was shown for the S1-alar screw technique compared to use of common S1-pedicle screws [211].

"Rod contouring" is another option to reduce the preloading forces of a pedicle screw. Long thoracolumbar constructs to treat spinal deformities often need rod adaptation to allow an appropriate screw/rod match. With the help of pre-contouring rods, the corrective manoeuvres are easier to perform, nevertheless "rod persuasion" devices are often necessary to gain an optimal fit of the rod within the screw head. This leads to an increased preloading of the screw and creation of recoil forces that impact the screw-bone interface. Particularly in the osteoporotic spine, this can increase the likelihood of screw failure associated with screw pullout. In a biomechanical study, pedicle screws reduced to the rod generated significantly decreased pullout strength and decreased "work energy to failure" in normal and osteoporotic vertebrae [212]. This means, that especially in osteoporotic patients, rod persuading against the screw with the help of "rod persuasion devices" should be prevented in order to gain sufficient screw anchorage [212].

Mode of Failure in Osteoporotic Spines

Biomechanics and Sagittal Alignment

Understanding the biomechanics of the osteoporotic bone supports the surgeon in preoperative planning and consulting the patient of surgical options, risks and back-up strategies if surgery of the osteoporotic spine might be the index treatment.

Due to the bone mass reduction of osteoporotic vertebrae as well as increased age and associated comorbidities, it is challenging for spine surgeons to treat these patients in case of instrumented spine surgery. These VCF may result in increased low back pain (LBP) with high impact on the daily activities resulting in an increased mortality and morbidity [75–77]. Spinal vertebral compression fractures (VCF) represent the major form of osteoporotic spine alterations with a prevalence of 520,000 new VCF for 2010 in Europe [13, 78–81].

Initially osteoporotic VCF present as harmless fractures rarely causing neurologic deficits, but often these fractures reveal the beginning of a "suffering cascade" finally leading to segmental and global changes in spine alignment with hyperkyphotic deformities and spinal stenosis resulting in sagittal imbalance with severe degenerative alterations (Fig. 18.1) [79, 81–84]. Spinal reconstructive surgery in the elderly frail patients with cumulation of multiple fractures can be a task and significant burden for both the patient and the physician in charge. The altered spinal curvatures with hyperkyphotic deformity of the thoracic spine or loss of lordosis of

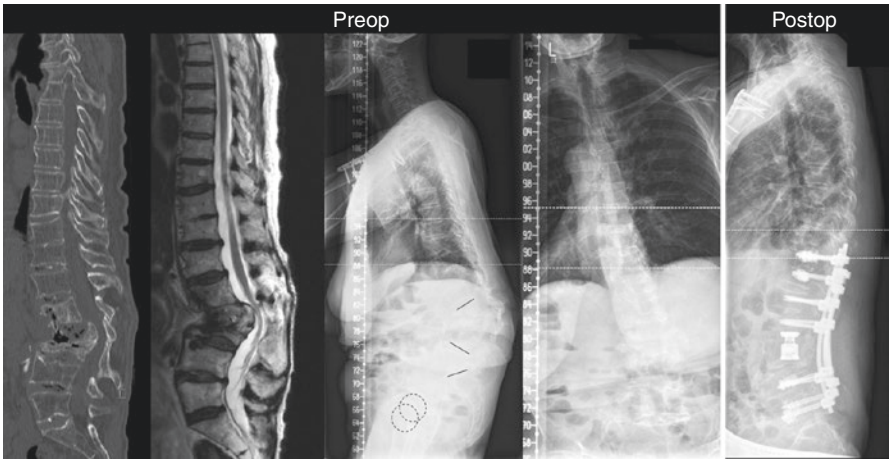

Fig. 18.1 Example of surgical challenges and sequels with multilevel spinal osteoporotic vertebral compression fractures in a frail patient. This 78 years-old patient suffered from Parkinson's and presented with a history of fall-related humerus and radius fracture. The patient was classified ASA 3 and had no prior history and presented with disabling and immobilizing pain. Treatment first with Teriparatide and 2 months later spinal surgery with decompression for spinal stenosis with resection of L3 and partial L4 vertebra was performed from a posterior approach. Distal fusion level was L5 to avoid cranial stress-rising from sacroiliac advanced fixation using e.g. S2-alar screws or iliac screws in this frail patient with severe osteoporosis (T-score: −4.1). Patient experienced an uneventful course without adjacent level fracture and achieved walking ability again as per the 1 year follow-up

the lumbar spine and the resulting pathophysiological load transfer anteriorly increase the risk of adjacent level and future fractures [82, 85].

Immediately after an osteoporotic VCF has occurred, the risk to sustain a second subsequent fracture is significantly increased in postmenopausal women, whereas only one third of all spine fractures are recognized [77, 86, 87]. Among 381 postmenopausal women who suffered from a VCF, 19.2% had another VCF within the next year [88]. Low BMD, low body mass index (BMI) and intradiscal cement leakage were possible risk factors for the development of an adjacent VCF after vertebroplasty in osteoporotic patients [89].

Increased thoracic kyphosis as a result of vertebral fractures or even in degenerative alterations without a major sagittal imbalance are risk factors for developing new vertebral fractures independent of the bone status of the patient [87]. Progressive kyphosis of the affected regions finally leads to a biomechanical shift of the load axis in sagittal plane anteriorly, which in turn leads to an increased lever arm, so that pathological forces with increased spinal compressive loadings occur (Fig. 18.2). In the first step, postural compensatory mechanisms such as hyperlordosis of the unaffected lumbar spine, posterior tilting with pelvic rotation, hip extensions, flexion of

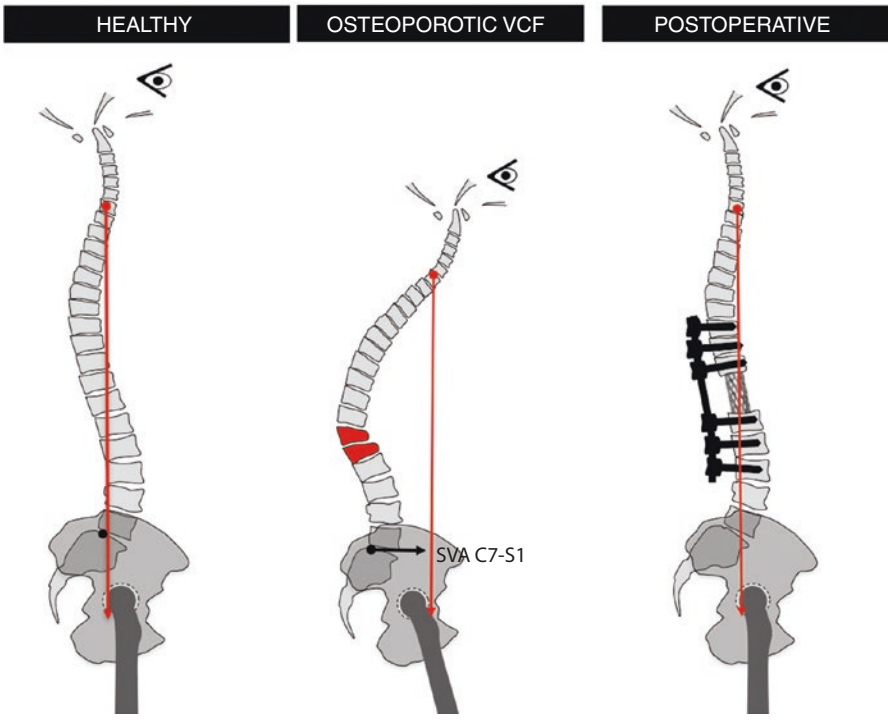

Fig. 18.2 Mechanical consequences of osteoporotic VCF on sagittal alignment and balance as well as loading conditions. With increased SVA, posterior element structures and muscles are facing increased efforts to maintain sagittal balance while the anterior elements, discs and vertebrae, are overloaded. Surgical reconstruction yields to reverse these mechanics and disrupt an otherwise vicious circle

the knees and ankles appear [90–94]. When these compensatory mechanisms have been fatigued and the patient cannot compensate for a regional kyphosis due to an already existing VCF or loss of lordosis and increase of thoracic kyphosis as a result of the degenerative aging process of the lumbar spine, changes of physiologic vertebral loading conditions finally can lead to VCF. Especially the loss of the lumbar lordosis in elderly patients and an increase of thoracic kyphosis particularly in sarcopenic patients causes a shift of the SVA anteriorly and increases the risk for VCF.

Besides the altered sagittal alignment in degenerated spines and the changes in load bearing capacities, it has been hypothesized that the increased fracture probability in patients with low BMD may be slightly counterbalanced by disc degeneration. Morphological studies have shown, that the hydrostatic pressure in healthy discs observed in stress plots is located within the nucleus homogenously. For the most part, the transmission of force is derived via the nucleus pulposus and finally distributed radially to the annulus [95]. In case of osteoporotic vertebral bodies, this leads to stress peaks at the weak center of the vertebral body, where compression fractures might occur. The nucleus pulposus of degenerated discs looses the capability of hydrostatic compressive loading, consequently the nuclear pressure is lowered and stress peaks in the annulus fibrosus appear. Due to that, the increased fracture risk in osteoporotic vertebral segments might be balanced by the material capabilities of the degenerated disc and osteoporotic vertebrae adjacent to a degenerated disc might have a lower risk to fracture [95–97].

Beside these simple initial of VCF, the complications following instrumented spinal surgery in osteoporotic patients often include the end-level failure, screw

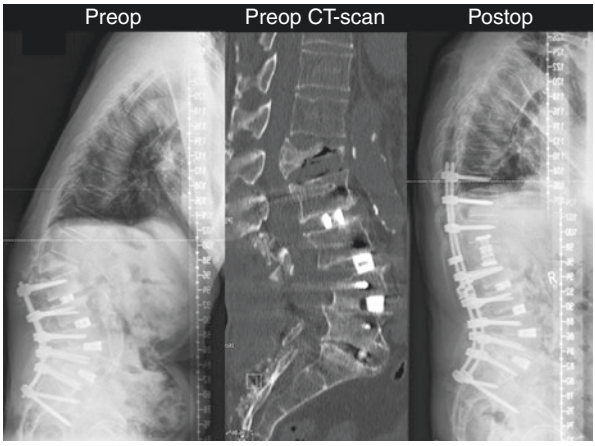

Fig. 18.3 Example of a 77 year old male patient with history of posterior multilevel fusion L2 to the pelvis who presented with new onset pain at 6 months postoperative due to adjacent level osteoporotic VCF and stenosis as well as severe PJK. Treatment was performed with posterior revision fusion, VCR of L1 and extension of the fusion to the lower thoracic spine as well as pharmacological treatment with Teriparatide

loosening or pull-out, pedicle fractures or pseudarthrosis with PJK (Fig. 18.3) [18, 41, 98–100]. With anterior approaches and anterior column spinal treatment in osteoporotic patients, screw cut-out or subsidence of cages is a common challenge.

Implant Failures

The literature provides evidence, that high-density trabecular bone is associated with improved implant anchorage within a vertebra [101–106]. Due to an insufficient bone stock, the risk of implant failures is increased, so that the goal of a solid fusion after spinal instrumentation might not be accomplished. Most common modes of failure in posterior instrumentations of low-density bone are represented by screw pullout and loosening [104, 107–110]. DeWald et al. reported in a retrospective study of 38 patients with five-level fusions, that early complications (<3 months) were pedicle and vertebral compression fractures (13%), whereas pseudarthrosis due to instrumentation failure (11%), adjacent-level disc herniations (4%) and severe junctional kyphosis (26%) represented late complications (>3 months). Rod- or screw breakage is rare, as the screw fixation in osteoporotic patients is limited due to a weak screw-bone surface and, thus, repetitive load bearing on the screws leads to loosening at the surface of the screw within the bone long before a screw breakage occurs. Screw and rod breakage are usually observed in patients with sufficient BMD due to overloading of the posterior structures until bony fusion appears.

End-Level and Adjacent Level Failure

Proximal junctional kyphosis (PJK) adjacent to a long segmented spinal instrumentation is a commonly observed complication particularly in osteoporotic patients. According to the literature, the incidence of PJK ranges between 17% and 39% in patients with adult scoliosis, approximately 27% in patients with adolescent scoliosis, over 30% in Scheuermann's kyphosis and approximately 37% for patients treated for adult spinal deformity including three-column osteotomies [111–115]. The incidence varies not only due to the treated disease and the follow-up but also upon the definition of PJK. Yagi et al. classified PJK resulting from disc and ligamentous failure as type 1, from bone failure is categorized into type 2 and type 3 represents implant/bone interface failure [116]. Type 2 is said to be the most problematic one, which often requires revision surgery [116]. In a survey among SRS members, PJK was found to be a "very important issue" and the majority of the attendees agreed with the definition of a "kyphosis at the top of the fusion where the kyphosis Cobb angle between the upper instrumented vertebrae (UIV) going up two vertebrae is $\geq 20°$" [117]. In contrast, proximal junctional failure is usually defined as a "failure at top of instrumented fusion, where neurological deficit, pain, PJK, hardware prominence or other issues necessitates revision surgery" [117]. Park et al. evaluated 160 patients with adult spinal deformity and long instrumented fusion and reported about 17% of PJK and 18% of PJF with a median postoperative time to development of 17 months and 3 months, respectively [18]. The PJK/

PJF-free survival time was assessed as a median of 70 months [18]. The failure modes of PJF included fractures at the UIV or UIV + 1 or screw pullout [18]. Beside others (increased age, stop at T11/L1, increased preoperative SVA, large corrections), osteoporosis was determined as a major risk factor for the development of PJF [18]. Other studies confirmed osteoporosis as a risk factor for PJK without addressing the failure rate according to revision surgery [116, 118, 119]. The greatest risk to develop PJF seems to be in patients with severe sagittal imbalance, osteoporosis and a high grade of surgical curve correction [18, 41, 118, 119]. Additionally, a high body mass index (BMI) was found to be an independent risk factor for PJK [18]. Optimizing spine balance to unload vertebrae is considered the key factor for effective outcome of adult spinal deformity corrections and lumbar-instrumented fusions [120–124]. Miyakoshi et al. evaluated 39 patients with postmenopausal osteoporosis and symptomatic thoracolumbar or lumbar kyphosis [125]. These participants received corrective spinal surgery with multilevel posterior lumbar interbody fusion and were matched to 82 patients with postmenopausal osteoporosis without vertebral fractures and no indication for surgery [125]. Significant improvements of global spinal alignment and quality of life (QOL) were found in the operated group 6 months postoperatively, whereas the baseline levels of the non-operated group were not reached [125].

Proximal junctional kyphosis is identified to appear in osteoporotic patients more often compared to the normal population, so that long-term results might be impaired [126, 127]. The ideal target alignment in these elderly patients has yet to be defined as the physiologic global sagittal alignment changes with aging. Different strategies to prevent end-level and adjacent-level failure are available, but only a paucity of them has shown to significantly minimize this complication effectively. A higher preoperative pelvic tilt and a higher postoperative thoracic kyphosis are predictive for the development of PJK and thus should be observed precisely [128].

The application of cement within the UIV and UIV + 1 was shown to reduce adjacent segment kyphosis and failures significantly [40, 129–131]. Especially in osteoporotic patients, the application of cement-augmented techniques within strategic vertebrae cranially as well as caudally seems to be sufficient [129, 131]. These findings were also proved in a biomechanical cadaveric study, so that the prophylactic cement augmentation at the UIV and UIV + 1 decreases the incidence of proximal junctional failures after long posterior spinal instrumentation [132]. Notably, the postoperative failures associated with the prophylactic cement augmentation of strategic vertebrae can sometimes be worse than the PJK complications seen without use of cement. These cement complications range from thromboembolic sensations, mechanical compression of nerve structures to exothermic effects with damage to the nutrient vessels within a vertebra or intraspinal cement extravasation. Especially, the effect of cement leakage might often be underestimated. According to the literature, the incidence of cement-extrusion ranges between 5% and 23% [133–136]. Not only direct cement embolic events cause postoperative cardiovascular complications, an animal study revealed the displacement of fatty tissue into the venous system by injecting cement into the vertebral body, which may result in a

fatty embolism [133–136]. The appropriate cement volume seems to be approximately 28% of the fractured body or less volume in case of single vertebral body fractures treated with percutaneous vertebroplasty, in contrast, the appropriate volume of cement augmented pedicle screws has not been clarified yet [137]. No significant differences in pullout forces between screws augmented with 4.0 mL or 1.5 mL were found, however, high-volume augmented pedicle screws after cyclic loading revealed to be disadvantageous compared to moderate augmented screws [138]. Pishnamaz et al. concluded that high-volume augmentation should be avoided [138]. According to that, other biomechanical studies did not find differences in the axial pullout forces between low- and high volume cement-augmented screws [101, 139]. Hart et al. found that approximately 15% of non-augmented patients showed failures in the proximal junctional segment with vertebral body collapse, whereas no failures were found in the cement-augmented group [140].

It has been concluded, that the construct stability and stiffness depends on the bone mineral density of the patients without any relationship to the number of augmented vertebral bodies [141]. As a consequence, the appropriate treatment or prophylactic strategy might be the use of anti-osteoporotic therapy prior to the surgical procedure [41]. One option might be the use of Teriparatide starting before surgery, which showed improvement of volumetric BMD and fine bone structures at the UIV + 1 with a reduced PJK incidence in one study [61]. Inappropriate selection of the UIV and UIV + 1 may also lead to an increased risk of PJK and PJF. The proximal fusion level should be preferred according to the status of the UIV and UIV + 1 within the coronal and sagittal alignment, the adjacent disc spaces, balance of the shoulder and the amount of the coronal and/or sagittal curve due to a correct definition of the apical segment of the curve [41].

Several other techniques can lower the risk of proximal junctional failure particularly in the osteoporotic patients. These include the selection of the fusion level with a special focus on the condition of the supposed end-level and rigidity of adjacent discs and ligaments, the application of a so called ‘soft-landing’ with using dual diameter rods, hooks, and bands crossing the UIV + 1 and UIV + 2 as well as the use of soft-tissue preserving instrumentation techniques for the most upper instrumentation levels [142–151].

Optimize Sagittal Balance to Unload Vertebrae

Moderate to severe kyphosis represents the most common spinal deformity in osteoporotic patients. Scoliotic deformities result in a combination of a coronal as well as sagittal imbalance. The severity of symptoms rises in a linear fashion with progressive sagittal imbalance [121, 213, 214]. An operative procedure to realign and correct the sagittal and coronal deformity leads to a significant improvement of the clinical symptoms of the affected patients [120, 121]. Relevant LBP is commonly associated with increased kyphosis in osteoporotic patients. The prevalence of LBP is given with a relatively high range and is stated between 30% and 80%

depending on the methods of the different studies and the age and pain definitions of the included patients [215–218]. The treatment of spinal deformities in osteoporotic patients is still challenging as the anchorage of spinal implants is worse compared to normal patients. Associated diseases of these predominantly elderly patients do not necessarily make perioperative treatment easier, so that the indication should be performed precisely and if possible, major osteotomy procedures should be avoided [82]. On the other side, optimizing spine balance to unload vertebrae is considered the key factor for effective outcome of adult spinal deformity corrections and lumbar-instrumented fusion [120–124]. As stated above, PJK and PJF are known to occur more often in osteoporotic patients and seem to be increased with the amount of surgical rebalancing necessary [126, 127]. Accordingly, in the osteoporotic patients planning of optimal surgical realignment as well as preoperative and intraoperative measure to prevent complications from osteoporosis must be planned well in advance. A treatment algorithm of the authors is presented (Fig. 18.4) to reduce the incidence of osteoporosis related complications in adult spinal deformity.

VCF are common in osteoporotic patients. Accordingly, preoperative assessment in the spinal patient with osteoporosis includes biplanar full-spine standing radiographics to detect any spine alignment alteration both from recent and remote VCF.

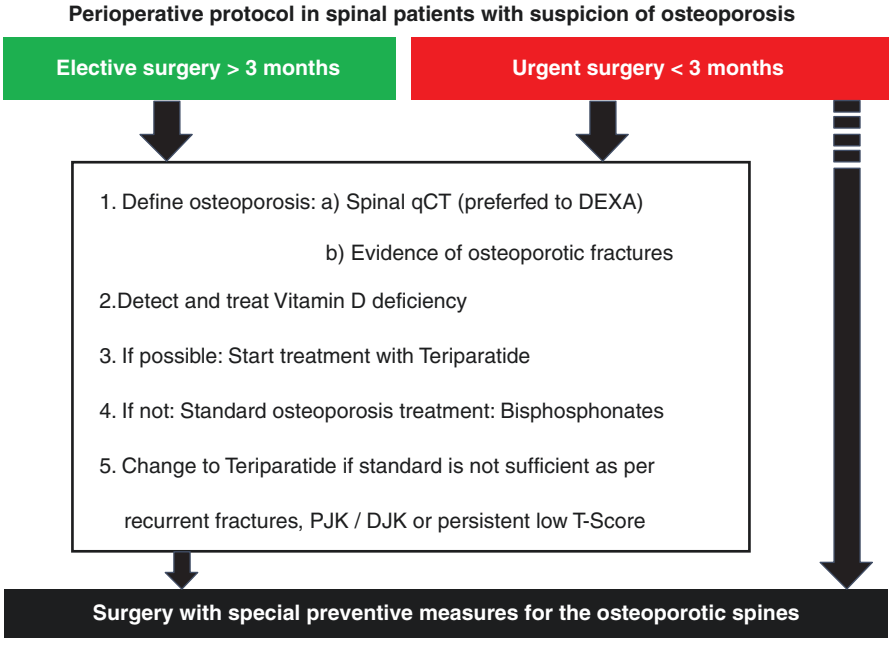

Fig. 18.4 A practical treatment algorithm for patients with osteoporosis scheduled for spinal surgery as per the author's experience

Fusion Rates in Osteoporotic Spines

Pseudarthrosis is one of the main challenges in modern spine surgery. The non-fusion rate ranges between 3% and 35% according to the literature [10, 219, 220]. Possible risk factors for non-fusion were discussed including obesity, diabetes, chronic steroid use, smoking status, malnutrition, postoperative sagittal imbalance or poor surgical technique due to an insufficient removal of intervertebral disc material [221–224]. There is still a lack of data according to fusion rates in osteoporotic patients and the knowledge how to increase bony fusion. Current findings regarding the correlation between the bone quality and spinal fusion rate show a trend towards non-union especially in female patients, a high age and low BMD [10, 225]. Compared to healthy patients with normal BMD, the non-fusion rates in osteoporotic patients tend to be roughly 30% higher [12]. In contrast, increased BMD measurements are significantly correlated with the development of a solid fusion and a reduced risk of screw loosening [38]. A significant correlation between osteoporosis and the development of IRC was shown. Especially the bone-screw interface and prolonged stress on the instrumented spine as a result of bony non-union is responsible for that. Despite this fact, the incidence of non-union in osteoporotic patients after spine instrumentations is underestimated and the literature provides evidence that the rate of postoperative complications, such as PJK, IRC and VCF is twice as high compared to bone-healthy patients. Although studies exist that have shown no significant influence on patient-reported outcome, which might be related to the heterogeneity of the study cohort radiographically, the postoperative treatment course and the morbidities of the patients [12, 33], chronic spinal non-union can be a source of significant pain and disability. Additionally, the radiological modality determining and measuring bony fusion is responsible for the wide range of fusion rates reported. The standard of reference for radiographic evaluation is computed tomography (CT) with multiplanar reconstructions (MPR), beside that, plain radiographs and either single-photon emission computed tomography (SPECT) or positron emission tomography (PET) combined with a CT have shown to be sufficient imaging options with different accuracy [12, 226, 227]. In general, pseudarthrosis accounts for approximately 40% of the indications for revision surgery [228]. The results of revision surgery are often unpredictable in osteoporotic patients, moreover, patient-reported outcome does not necessarily correlate with the fusion rate in revision surgery in this patient group [229, 230]. There is an increased interest in the impact of pharmacological treatment on the fusion rate. Bisphosphonates, an antiresorptive first-line therapy for osteoporosis, has been assumed to decrease the fusion rate due to a decreased bone remodelling process if the drug is taken at the time of surgery and postoperatively. Presently, it has been shown that Bisphosphonates do neither increase nor decrease the fusion rate compared to control groups [53, 55, 56, 231]. Patients treated with Teriparatide, an anabolic agent, showed a nearly twice as high fusion rate compared to patients without medication [219]. The superiority of Teriparatide over Bisphosphonates regarding the fusion rate has also been shown in several studies [60, 232]. The main characteristics of the studies regarding osteoporosis and fusion rate are shown in Table 18.3.

Table 18.3 Main findings regarding fusion rate in osteoporotic patients

Study	Objective of the study	Number of patients/ mean age	Diagnosis	Mean bone quality (baseline)	Findings
Schreiber et al. [10]	BMD measurement using Hounsfield Units (HU) in CT	28/68	Degenerative disc disease, scoliosis, anterior/lateral spondylolisthesis, radiculopathy, foraminal stenosis	T-Score: −1.42	• Fusion rate: 73% • Non-union mostly in women and patients with low BMD • Fusion associated with higher BMD compared to prox. vertebral body
Ebata et al. [219]	Effect of Teriparatide on the fusion rate	74/72	Female patients >49 years with BMD <80% of mean or previous vertebral compression fracture and lumbar degenerative disease	T-Score: −2.33	• Fusion rate with Teriparatide: 69% • Fusion rate without medication: 35.1%
Chen et al. [231]	Effect of bisphosphonates on the fusion rate	69/64	Osteoporotic patients with single-level degenerative spondylolisthesis	BMD: 0.484	• No significant difference regarding solid fusion (failed fusion—bisphosphonates vs. control: 9% vs. 14%)
Bjerke et al. [12]	Incidence of osteoporosis-related postoperative complications	140/68	Primary surgery for thoracolumbar/ lumbar fusion	–	• Fusion rate: – Normal BMD: 81.4% – Osteopenia: 81.6% – Osteoporosis: 53.8%

Hidden Osteoporosis

In addition to "de novo" osteoporosis, several diseases, especially rheumatic diseases, are associated with a reduced bone density. Among them, ankylosing spondylitis (AS, aka Bechterew's disease) is linked to an increased risk of osteoporosis and incidence of vertebral and extravertebral fractures and is considered the main representative of the group of ankylosing spinal disorders (ASD) [233]. The worldwide

prevalence of AS is stated with approximately 0.1 to 1.5% and is more common in European males [234–236]. A study conducted by Vasdev et al. showed that roughly 29% of patients diagnosed with ankylosing spondylitis suffered from osteoporosis [237]. In contrast to "de novo" osteoporosis, the onset of AS is predominantly at the age of 30 years with a highly genetically associated factor due to HLA-B27 gen complex [238–240]. In case of typical symptoms according to a disabling pain at the sacroiliac joints accompanied with common radiological signs of progressive ossification of the spinal column, no longer genetic diagnosis is necessary. These ossifications entail bridging bone formations (syndesmophytes) of the spine, with high fracture susceptibility even after a fall from standing or sitting positions [239, 241–244]. The cervical spine is of utmost risk for fractures accounting approximately 53% followed by the thoracic (42%) and the lumbar spine [245]. In contrast to AS, patients with DISH do not suffer from a decreased bone mineral density in general, as the study of Sohn et al. described [246]. However, stress-shielded areas in the vertebral body in a DISH patient with all three columns fused can cause challenges with vertebral body fixation due to loss of bone quality and regional osteoporotic bone.

A complication in AS patients is often described as "Anderrson lesion" and leads to localised vertebral or discovertebral necrotic lesions with non-union after vertebral fractures of the spine described by Andersson in 1937. The repeated stress on fractured vertebral bodies due to a long ankylosed lever arm accompanied with fracture associated kyphosis may lead to a focal stenosis often mimicking and misdiagnosed as an infection [247–249].

Patients with ASD often have delayed diagnosis of fractures, which might be a result of minor trauma with only moderate pain as well as an insufficient radiodiagnostic evaluation of the osteoporotic radiopaque bone. Osteoporosis accompanied with altered anatomy of ASD patients and the affected cervico-thoracic junction often masks fractures, so that these may be overlooked in ASD patients [250, 251]. Studies revealed a delay in diagnosis in ASD patients of approximately 10–50% leading to a secondary deterioration with an associated decline in neurological function [241, 242, 252–255]. High level of suspicion of vertebral fractures shall be applied in patients with hidden osteoporosis and history of spinal trauma and back pain.

The surgical treatment of these patients is complex and complicated by the medical comorbidities. The mortality rate of surgically treated patients accounts approximately 7–25% [241, 242, 245, 253, 256–258]. Lukasiewicz et al. reported, that 50% of patients out of a cohort of 939 patients with ASD fractures were treated surgically. Fracture care is different to the normal and healthy population and the selection criterions based on the conventional "fracture care" might not be transferred to ASD patients [241, 245, 257, 259]. Caron et al. found a mortality rate of surgically and conservatively treated patients after 1 year of 32% and 51%, respectively. According to that, a special modifier for fractures of ASD patients was added to the current AO classification [260, 261]. In the case of spinal instrumentations after ASD fractures, the high loads of long lever arms of the auto-fused segments must be taken into account [262]. Long lever arms in combination with the decreased BMD,

especially in AS patients, require long dorsal instrumented constructs often in combinations with antero-lateral approaches and additional decompression [258, 263–266]. The literature revealed that most of the patients have been treated with multilevel posterior segmental fixation due to extended bilateral fixation points above and below the affected levels, especially in case of cervical fractures [241, 242, 244, 252, 255, 256, 258, 267–269]. Due to ankylosed spinal segments accompanied with osteoporotic fractures, some patients may develop progressive kyphotic deformities with severe symptoms such as gait disturbance, difficulties in preventing the horizontal view and deterioration in digestive functions due to the compression of abdominal organs [270, 271]. In these cases of fixed kyphotic deformities, osteotomy procedures might be the treatment of choice with satisfactory outcomes and acceptable complications [270]. Kim et al. performed 292 corrective osteotomies in AS patients and described these surgical methods as effective with a good radiological and clinical outcome [270].

Discussion

Osteoporosis represents an increasing problem with high socio-economic impact [13, 15, 20, 78]. Although spine surgeons are not directly familiar with the pharmacological therapy, there is a need to rethink about the future decades, especially as a large number of patients with spinal disorders are presented to orthopaedic-, trauma surgeons or neurosurgeons [9, 42]. The incidence of undiagnosed osteoporosis in patients admitted to instrumented spine surgery is alarming [9]. Due to high complication rate, revision surgeries for postoperative mechanical complications are more complex compared to the initial procedure. Consequently, the indication for spinal instrumentations in osteoporotic patients should therefore be scrutinized and, above all, longer fusions should be subjected to a precise "risk/benefit" analysis [82]. In case of elective long instrumented spine procedures, preoperative BMD measurements followed by pharmacological therapy might be the future treatment, not at least to economize the financial burden of the disease and to prevent potential life threating complications in these elderly and comorbid patients. Dual-energy X-ray absorptiometry (DXA) or just the occurrence of a fragility fracture represents the standard of reference in diagnosing low bone density. DXA may not gain insights into the three-dimensional bone architecture, so that differences between cortical and trabecular structures may not be accomplished. In the present of osteoporosis and vertebral fractures, similar defects of peripheral bones were observed, so that the use of quantitative computed tomography (pQCT) might improve the diagnosis of osteoporosis and predict vertebral fractures [6, 7].

Studies revealed, that 50% of woman and 15% of men older than 50 years suffer from osteoporosis [3, 9]. The annual number of spinal fusion discharges increased 2.4-fold (137%) between 1998 and 2008 with a mean age for spinal fusion of 54 years and an in-hospital mortality rate of 0.25% (United States) [272]. Ultimately, this means that most of our patients seen in the outpatient clinic scheduled for spinal surgery suffer from some form of decreased bone density. In terms of numbers, this

means that approximately 43% and 27% of patients scheduled for spine surgery suffer from osteopenic or osteoporosis, respectively. Schmidt et al. showed that only 11% had received anti-osteoporotic therapy, whereas 38% of these patients had the appropriate indication for therapy but had not get any.

Osteoporosis can be classified into three types. In any of the these cases, a preoperative check-up in collaboration with a specialist of internal medicine might be helpful to indicate pharmacological treatment and adaption to the patient's type of disorder preoperatively (Table 18.2). This does not necessarily mean that every patient below the age of 50 years needs a strict medical osteoporotic assessment, however, the medical history (radius fractures, vertebral fractures, family medical history, gynaecological problems, daily drug intake) should provide a potential indication for further diagnostic steps. Often, in preoperative X-ray or CT scans, evidence of reduced bone density may be predicted. Beside pharmacological therapy options, it is important to keep the non-pharmacological therapy such as physiotherapy, adequate supplementation of calcium and vitamin D, physical activity and lifestyle change in mind. Especially physiotherapy may lead to some behavioural improvement to decrease the risk of fall [273, 274]. Due to the high impact of bone quality on the postoperative outcome, preoperative screening and medical therapy will become essential in order to implement a primary prevention of mechanical complications prior to spinal surgery.

The first step in medical therapy should be a supplementation of calcium and vitamin D, as it has a favourable application form, low costs and has shown satisfying results. The choice of Bisphosphonates as a first-line therapy has to be evaluated thoroughly in collaboration with an internal medicine specialist, as side effects are common and other medications such as Teriparatide have been shown to have equal effects on BMD and the prevention of vertebral fracture with more benign side effects. Denosumab, Raloxifene and other treatment options such as Calcitonin and Strontium Ranelate are not recommended unless there is no other option. Long-term data with increased patient cohorts are needed to prove the quality of these drugs. The literature provides evidence, that Teriparatide reduces the risk of all new vertebral fractures by approximately 65% and the risk of moderate to severe vertebral fractures by 90% in postmenopausal women with already existing vertebral fractures compared to placebo medication [275]. The authors added, that the increment of bone density was already seen after Teriparatide has been discontinued and thus the BMD increasing effect was proven beyond the application period [275]. Nevertheless, the regulatory indication for Teriparatide in the authors' country is limited to postmenopausal osteoporosis of the woman, osteoporosis of the man, and in glucocorticoid-induced osteoporosis when vertebral body fractures have already occurred despite adequately guided antiresorptive therapy for more than 2 years. The primary goal of spine instrumentations is ultimately bony fusion, which, in turn, depends on a stable anchoring of the screws, especially immediately after the operation. Due to that, antiresorptive or anabolic drugs might be an option for that. Bisphosphonates failed to increase bony fusion, whereas Teriparatide showed a nearly twice as high fusion rate compared to patients without medication [53, 55, 56, 219, 231]. Comparing both medications, Teriparatide shows a significantly

increased fusion rate according to recent data (Table 18.2) [60, 232]. A low fusion rate in patients suffering from osteoporosis is an issue with increasing impact. At present, there is an intense focus on preoperative pharmacological optimization and new surgical techniques in order to minimize the risk of failed fusion and IRC. In case of revision surgery, low bone quality represents not only a higher risk factor of perioperative complications but forms another challenge planning an adequate surgical procedure according to the amount of spinopelvic alignment correction. PJK is one of those problems with an incidence of approximately 20% after adult spinal deformity [116]. Several risk factors are described, although the treatment of osteoporosis is thought to be essential preventing IRC. Especially bone strength represents the major factor in balancing the increased junctional stress after long instrumentations in adult spinal deformity patients. This fact might be obvious in case of paediatric spinal deformities, which show a significant reduction of the PJK incidence in patients with probably normal BMD values [116, 276, 277]. Although the overall PJK risk was not significantly lowered, Yagi et al. observed a significantly increased rate of PJK with bone failures often requiring revision surgery [116, 278, 279].

Several studies showed a direct correlation between the BMD and screw anchorage quality, so that a few surgical pearls to optimize spinal fusion outcome in osteoporotic patients are available (Table 18.4). Beside the different techniques of increasing screw anchorage, fusion level and fusion length selection, end-level instrumentation techniques may also play a major role in preventing complications.

Table 18.4 Recent findings regarding the effect of surgical strategies for the optimization of implant stability

Study	Study characteristics	Surgical strategy	Results
Screw diameter			
Hsu et al. [155]	Polyurethane foam with high or low density	3 different screw models with 3 different diameters each	• Higher pullout strength was observed with higher diameter in all screws types
Cement augmentation			
Kueny et al. [193]	39 osteoporotic, human vertebrae	4 categories: screw only, screw with increased diameter, prefilled augmentation and screw injected augmentation	• Screw injected augmentation showed increased pullout force and fatigue force • Screws with increased diameter by 1 mm showed similar results to screw injected augmentation
Expandable pedicle screws			
Koller et al. [181]	17 human cadaveric vertebrae	6.0 mm standard fashioned pedicle screws vs. 6.0 mm pedicle screws with a distal expansion mechanism	• Significant higher failure load was demonstrated for expandable pedicle screws (910.3 ± 488.3 N vs. 773.8 ± 529.4 N)

Table 18.4 (continued)

Study	Study characteristics	Surgical strategy	Results
Hydroxyapatite (HA)-coated screws			
Ohe et al. [287]	6 ovariectomized pigs representing osteoporotic spine and 2 sham-operated for control	Three types of pedicle screws: untreated, sandblasted and HA-coated pedicle screws	• HA coated pedicle screws showed significant higher peak torque
Hasegawa et al. [187]	2 female, ovariectomized beagle dogs	Instrumentation L1-L6, left side uncoated screws, right side hydroxyapatite coated screws	• Pull out force was significantly higher for hydroxyapatite coated screws (165.6 ± 26.5 N vs. 103.1 ± 30.2 N)
Bicortical screw fixation			
Matsukawa et al. [209]	Postoperative CT scan assessment of 50 adults	Cortical bone trajectory	• Insertional torque was 141% higher compared to the traditional monocortical technique
Zhuang et al. [39]	25 human cadavers	Left: bicortical screw fixation; right: unicortical cement-augmented screw fixation	• Bicortical and PMMA-augmented fixation showed similar results for higher BMD • PMMA-augmented screw fixation showed better results for vertebrae with lower BMD

Nevertheless, these strategies present secondary preventive techniques in osteoporotic patients. Hence, referral to an endocrinologist or specialist familiar with medical anti-osteoporotic drug therapy prior to spine surgery might be an issue for primary complication prevention.

According to clinical routine, it is not possible to subject each patient to a detailed endocrinological referral, nevertheless, in the case of scheduled and extended spinal fusion or in case of pre-existing comorbidities (ankylosing spinal diseases), the use of preoperative evaluations and subsequent anti-osteoporotic therapies should be applied. A practical treatment algorithm of the senior author can be one way to lower the risk with osteoporosis related postoperative complication (Fig. 18.4).

Box 1: Incidence of osteoporotic spines

1. What is known?	An increasing incidence of osteoporotic patients has been observed in the last years
2. What is new?	A large number of patients scheduled for spine surgery suffer from osteopenia or osteoporosis. Most of them have not received adequate medical treatment by time
3. What are the consequences for clinical practice?	A preoperative bone mass density evaluation followed by an adequate therapy may be sufficient. The preoperative planning and postoperative care may be adapted accordingly

Box 2: Medical therapy options prior to surgery

1. What is known?	Anti-resorptive drugs (Bisphosphonates) are the standard of care in osteoporotic patients (T-score <−2.5) and the indication of anabolic drugs (Teriparatide) is currently only intended and possible for a small number of patients
2. What is new?	The prophylactic usage of Teriparatide shows a significant BMD increment in the upper-instrumented vertebra (UIV) of long dorsal instrumented pedicle screw constructs. Teriparatide improves stability of pedicle screws due to an increase of volumetric BMD and fine bone structures, so that the incidence of PJK with failure can also be reduced
3. What are the consequences for clinical practice?	The indication of Teriparatide should be expanded, so that a larger group of patients may be addressed. Further studies have to reveal a safe clinical use compared to anti-resorptive agents

Box 3: Mode of failure in osteoporotic spines

1. What is known?	Osteoporotic patients suffer from a high incidence of vertebral compression fractures. These fractures might lead to hyperkyphotic deformities often requiring spinal surgery with instrumentation and osteotomies
2. What is new?	Fractures of the UIV, UIV + 1 and screw pullout at that level represent the most common mode of failure
3. What are the consequences for clinical practice?	Continuous radiological controls (long-standing lateral and anteroposterior X-ray, CT) to assess the cranial and caudal adjacent segments are important for early detection of changes in the sagittal profile

Box 4: Surgical strategies to improve fixation strength in osteoporotic patients

1. What is known?	Cement augmentation of pedicle screws is the gold standard to improve fixation strength in low bone density patients. The majority of the referenced studies are in vitro investigations, so that an uncritical transfer to clinical use might not be able
2. What is new?	An underestimated high complication rate by using cement augmentation techniques is described but still represents the treatment modality of choice
3. What are the consequences for clinical practice?	Optimizing spine balance, cement augmentation techniques of UIV and UIV + 1 and pre-tapping in osteoporotic spines might be options to reduce the complication rate. Cement augmentation techniques of all screws within the “heavy metal construct” might often be an overtreatment, as cement extravasation often occurs

Box 5: Optimize sagittal balance to unload vertebras

1. What is known?	There is a linear dependence between progression of sagittal deformity and clinical symptoms
2. What is new?	Optimizing spine balance to unload vertebrae is considered the key factor
3. What are the consequences for clinical practice?	In case of long posterior instrumentations in combination with osteotomies, preoperative anti-osteoporotic pharmacological therapy to improve screw anchorage might be rational. Nevertheless, major osteotomies with long posterior constructs should be avoided

Box 6: Fusion rates in osteoporotic spine

1. What is known?	A high non-fusion rate is reported. This might be even higher in patients with osteoporosis, which increases the stress on the implants and consequently leads to implant-related complications in an "a priori" weak vertebra
2. What is new?	Teriparatide revealed approximately twice as high fusion rates compared to patients without medication and is significantly superior to Bisphosphonates
3. What are the consequences for clinical practice?	Teriparatide application prior to instrumented spine surgery might not only increase fusion rates. Drug approval regulatories should therefore expand the indication for Teriparatide, as long as additional RCTs confirm a reliable and safe use

Box 7: Hidden osteoporosis

1. What is known?	An association between ankylosing spinal disorders and osteoporosis has been found, whereby ankylosing spondylitis forms the main representative of this group. A high cervical and thoracic fracture rate associated with a delayed diagnosis has been reported
2. What is new?	Overlooked fractures are common and might lead to secondary deterioration. Late complications are represented by fracture-associated and non-fracture associated sagittal deformities
3. What are the consequences for clinical practice?	In case of suspected fractures in these patients, high-resolution imaging techniques of the whole spine are advocated. Fixed kyphotic deformities might be treated with osteotomy procedures leading to satisfactory outcomes and an acceptable complication rate

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Cubital Tunnel Syndrome: Primary Decompression or Transposition of the Ulnar Nerve at the Elbow

19

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Introduction

Cubital tunnel syndrome (CuTS) results from compression of the ulnar nerve within its fibroosseous tunnel at the elbow. It is the second most common nerve entrapment syndrome (carpal tunnel syndrome being the most common). Knowledge of the pathoanatomy in this region can allow an appreciation of patients' symptoms and nerve pathology. Numbness and tingling in the ulnar nerve distribution may be intermittent, constant and/or associated with weakness of the forearm or hand muscles. The severity of the neuropathy can, in addition to careful physical examination, be evaluated by electrodiagnostic studies (EDS) and imaging (ultrasound (US) or magnetic resonance imaging MRI) of the nerve at the elbow. Deformity or enlargement of the nerve, the stability of the nerve with elbow flexion and changes in the fascicular arrangement of the nerve on US can be consistent with clinical symptoms and may aid in the diagnosis and selection of a treatment plan.

When considering the patient who presents with symptoms of primary ulnar neuropathy at the elbow it is important to consider the common situations that are associated with ulnar nerve dysfunction at this location. We tend to consider these patients as having one of the following conditions or a combination of these scenarios:

1. Intermittent numbness and tingling
2. Constant numbness without weakness
3. Numbness with weakness

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4. Dynamic symptoms (such as those occurring during elbow flexion and extension) related to an unstable (subluxation or dislocation) ulnar nerve (also evaluate for medial triceps snapping)
5. Mass effect on the nerve (i.e., anconeus epitrochlearis; ganglion or osteophyte with arthritis (also evaluate for elbow joint contracture))
6. Weakness without numbness (evaluate for wrist level pathology)

Following careful evaluation of the history and physical examination and a confident diagnosis, the options for treatment must be evaluated by the surgeon and the patient to decide upon an appropriate plan. The general options for treatment include patient education, avoidance of exacerbating activities or positions, and extension splinting for mild symptoms and either simple decompression (SD) or an anterior transposition (AT), whether it is submuscular (SMAT) or subcutaneous (SCAT), for persistent symptoms or weakness.

1. Simple Decompression
   (a) Open in Situ (with stable ulnar nerve in flexion/extension)
   (b) Open or endoscopic
2. Anterior Transposition
   (a) Subcutaneous
   (b) Submuscular (or intramuscular or transmuscular)

The information we have to make decisions regarding the best treatment whether conservative or surgical is often not clear. Many studies have varying degrees of information or agreement on the severity of the neuropathy at presentation which also limits the conviction of any outcome related to a surgical procedure. Outcome measures are often lacking and many studies and reports are retrospective and therefore may offer lower quality, although valuable data.

In situ decompression has been favored for simplicity, lower morbidity and equivocal outcome compared to most transposition procedures. Because of several recent comparative studies with similar outcomes, in situ decompression has gained in popularity by some surgeons. Anterior transposition of the ulnar nerve has a similar expected outcome and historically has been completed more commonly for associated nerve instability or worse preoperative ulnar nerve function. Most decisions regarding the chosen surgical procedure though lies largely with the experience and training the surgeon has with these procedures. As there has not been a clear recommendation regarding which procedure should be considered for CuTS, this has resulted in a variety of surgical procedures performed.

Gelberman [1] described the effect of elbow flexion on increasing intraneural pressure and concluded that additional measures to decrease the pressure may be required (medial epicondylectomy or transposition). Similarly, Dellon [2] described that the intraneural pressure was only reduced in all elbow positions with a submuscular transposition (cadaver model). These studies also complicate our understanding of the mechanical change required at the time of surgery as we see many patients

improve with a simple decompression alone which suggests that the change in pressure or perfusion with decompression alone was indeed adequate to improve nerve function.

More severe numbness or weakness or an unstable nerve may benefit from anterior transposition. One argument for primary transposition for more severe deficits is the idea that providing decompression and decreased stretch-associated elevated intraneural pressure (and resulting ischemia) may be better, because if an SD does not result in improvement, then the additional time to return for surgery and again wait for recovery may jeopardize motor recovery due to the extended time and motor end-plate degeneration.

The decision for submuscular transposition is also highly variable. This procedure may risk elbow pain, hematoma or wound problems or elbow instability although it does have the ability to place the nerve in a position with expected lower intraneural pressure in a position similar to the median nerve. It is more commonly performed in revision surgery when a SD is no longer an option due to scarring or a tortious course of the nerve.

Currently, surgical treatment of ulnar neuropathy at the elbow remains controversial regarding SD or AT. This chapter was constructed to answer the question—what high quality evidence exists to provide both the patient and the surgeon a statistically significant rate of clinical and electrodiagnostic improvement, coupled with the lowest morbidity, for primary CuTS?

Methods

The methods for this study included evaluating meta-analyses for primary CuTS in adults that have been based upon higher quality data related to SD and AT. An online search was completed (English language, PubMed, Medline, Google Scholar) to identify meta-analyses performed for decompression or transposition of the ulnar nerve since 2000. Search words included “RCT” and “prospective” and “ulnar nerve decompression” and “transposition” and excluded “revision” or “fracture” or “distal humerus”. Meta-analyses where then reviewed to identify the quality of the included data so that a GRADE approach could be used to determine if a strong or weak recommendation could be associated with SD or AT. There were several common studies within each meta-analysis as the overall number of RCTs on this topic are relatively small. These studies though do represent the best core comparative data that has yet been available for analysis on this subject.

Results

We identified several studies that were available to compare higher quality data since 2000 and also included two additional studies that were not included within the existing meta-analyses. Details of these studies are outlined in Table 19.1.

Table 19.1 Comparative studies since 2000

Author	Search details	Type and number	Outcome
Zlowodzki et al. [3]	Medline, EMBASE, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, CINAHL; and annual mtg AAOS 2004–6, AAPS 2005–6, AANS 2001–6, ASSH 2001–6. 458 studies identified; 43 retrieved; 39 excluded	*4 RCT total: 335 pts* *All EDS confirmed* 2-SD v SCAT (117pts) 2-SD v SMAT (218pts) Three of four studies with clinical grading (261pts) Two studies - NCV comparison (100pts) 49 SD/51 AT:	*No difference in outcome with primary clinical grading as outcome* STD mean diff in effect size −0.04; 95% CI −0.36 to 0.28; p = 0.81 *No difference*; mean diff in effect size 0.24 (95% CI −0.15 to 0.63; in favor of SD (p = 0.23; I2 = 0%, p = 0.9)
Macadam et al. [4]	RCT and comparative observational studies: SD or SCAT/SMAT f/u > 6 months PubMed, Medline, OVID MEDLINE, EMBASE, Cochrane Database of Systemic Reviews, Cochrane Central Register of Controlled trials, abstracts of AAOS, COA, ASES, CSPS, ASPS, AAHS, ASSH, AANS 1214 titles, excluded 1113; 26 duplicates excluded, additional exclusions then leaving Ten full text articles *Quality assessed by Detsky quality index*	Ten studies (four prospective, two prospective-randomized (2005, 2006)) 449 SD vs 457 AT AT: 342 SC; 115 SM	No significant difference in outcome Odds 0.75; 95%CI (0.542, 1.040) Subgroup analyses: Improvement with *SD* 0.751,95% CI 0.542–1.040 *SD vs SCAT* OR 0.836 95% CI 0.562–1.242, p = 0.374 *SD vs SMAT* 0.596 (95% CI 0.341–1.044, p = 0.071. *Improvement with SD alone with graded quality index* *Hi quality* studies: OR 0.685 (95% CI 0.435–1.076, p = 0.101 *Lower quality* studies: OR 0.829 (95%CI 0.518–1.325, p = 0.433)
Chen et al. [5]	2268 RCT or prospective study retrospective study, cross sectional study; Pubmed/Medline Science direct, Cochran library, Google scholar 1536 after dups 1508 excluded 28 reviewed 16 excluded (3 review, 1 no data, 12 no SD/AT comparison) *Jadad > 3 all included studies*	Twelve articles/ Thirteen studies 1009 pts 500 SD 509 AT	*No significant difference* OR 0.91; 95% CI 0.67–1.23, p = 0.536 *Incidence of complications lower for SD vs AT* (four studies: 150 SD, 72 AT) OR 0.32; 95% CI 0.17–0.60, p = 0.05

Table 19.1 (continued)

Author	Search details	Type and number	Outcome
Caliandro et al. [6] (an update from 2010 and 2012)	RCT/quasi RCT	Seven studies/476 patients SD vs SC AT 4/327 pts ME vs AT: 1/47pts SCAT vs SMAT: 1/48pts Endoscopic vs open: 1/54 (56 nerves)	No difference in any comparison *SD v AT—No difference* Clinical improvement RR 0.93, 95% 0.80 to 108 (mod quality) Neurophysiologic improvement: Mean diff in m/s 1.47, 95%CI −0.94 to 3.87 *Transposition had increased wound infection* RR 0.32, 95% CI 0.12 to 0.85 (mod quality)
Staples et al. [7]	Prospective cohort study	One study / 125 pts 47 SD vs 78 AT	No long term differences. *Significant findings: narcotic use at 4–8 weeks for AT and higher rate of surgical morbidity and patient reported disability—* although most resolved beyond 8 weeks

Discussion

This review includes the outcome of approximately 2800 procedures and a nearly equal number of patients who received a SD versus a form of AT. The exact degree of preoperative ulnar nerve dysfunction is not known to be exactly comparable and there is also inherent variability in many perioperative details including the surgical procedures, anesthetic (general or regional), duration of ischemia, use of tourniquet, degree of intraneural blood flow after transposition, postoperative protocols and of course variability in the measurement postoperative exam based upon the patient and the examiner. All of these factors influence the postoperative data and should be considered when interpreting the outcome.

This review of the good or high quality data does not indicate when the conversion from nonoperative to surgical treatment is recommended for CuTS. Improvement though with either SD or AT is likely for the majority of patients. There is no compelling evidence that an anterior transposition should be favored, including in cases of poor nerve function. There is no clear benefit to SMAT versus SCAT. There is an elevated risk of wound problems (pain, hematoma) with transposition. Endoscopic procedures also have a higher association with hematoma compared to open decompression and also may be associated with medial antebrachial cutaneous nerve (MABC) numbness.

Macadam et al. [4] used the Detsky Quality index for their review and did not show any improved outcome beyond the outcome with a SD with their high quality data.

Caliandro et al. [6, 8, 9], updating their previous 2010 and 2012 Cochran Database reviews, demonstrated moderate quality data with a clinical improvement (RR 0.93, 95%CI 0.80–108) and also reported on studies that measured similar postoperative neurophysiologic improvement (mean difference in m/s 1.47, 95%CI −0.94 to 3.87) with SD or AT. They also demonstrated that anterior transposition had an increased wound infection risk (RR 0.32, 95%CI 0.12–0.85). They concluded that the two procedures were equally effective, including when there was severe nerve impairment.

Chen et al. [5] completed their review with the studies that included Jadad scores >3 for all included studies and reviewed over 1000 patients and found no significant difference between outcome with SD versus AT. They also found a higher incidence of complications with AT. They recommended SD due to the lower rate of complication.

Zolodowski et al. [3] reviewed only RCTs (335 patients) and in the three of the four studies there was an associated clinical grading of 261 patients and two studies that also reviewed NCVs. There were no differences in outcome with primary clinical grading as outcome and there was no difference in NCV results when comparing SD versus AT. They also concluded that SD was a reasonable alternative to an AT for ulnar nerve compression at the elbow.

One additional level 1 study by Zarezadeh et al. [10] has shown elevated postoperative pain with submuscular transposition compared to subcutaneous transposition and Staples et al. [7] have also reported upon the increase in morbidity with transposition compared to SD. Fortunately, though, there were no long-term differences and despite a significant finding following AT with narcotic use at 4–8 weeks and a higher rate of surgical morbidity and patient reported disability, most of these issues reportedly resolved beyond 8 weeks.

Chimenti and Hammert [11] also reported in their evidence based algorithm in 2013 that different surgical procedures had similar outcomes and that lack of standardized grading systems and outcome measures made it impossible to recommend a specific procedure. While anterior transposition was more common with revision surgery, there was no literature with significant findings to support this approach.

Song et al. [12] reported on the cost-utility for treatment of ulnar neuropathy of the elbow. They modeled SD as the main procedure and modeled four conditions. This presumed (1) SD with AT for salvage, (2) SCAT followed by SMAT for salvage, (3) medial epicondylectomy with SMAT for salvage, and (4) SMAT with a poor outcome as an endpoint. They used an analytical model based upon meta-analyses along with medical cost (in 2009 US dollars) and found that SD as an initial procedure was the most cost-effective procedure.

The limitations of meta-analyses are well known and the measure of the data used for comparison is critical to a useful recommendation for a patient to have a meaningful improvement with a surgical procedure. The studies reviewed here though do represent the best current comparison of the existing data regarding SD versus AT.

Other presenting findings though must be considered when deciding upon a surgical procedure to treat a compressed ulnar nerve at the elbow. As this chapter has been written from the standpoint of a primary surgical procedure at the elbow, when there is a mass effect it should be considered whether a SD will alleviate that effect. This may require removal of the mass (ganglion, osteophyte) and may also require transposition to place the nerve in a position to minimize ongoing nerve irritation/friction (instability of ulnar nerve or compression by the medial triceps). Radiographs and US or MRI are also available to evaluate and augment the diagnosis after physical examination and prior to surgery. Anterior transposition must include protection of the MABC and a tension-free transposition with appropriate release of any tissue restricting the ulnar nerve from the medial arm down through the FCU and also must include excision of the medial intermuscular septum.

Conclusion

The current data offer a strong recommendation for either SD or AT for surgical treatment of ulnar neuropathy at the elbow. The recommendation for considering an AT compared to a SD is weak and is based upon equal effectiveness of a SD, lower morbidity of SD and the cost-effectiveness of a SD. Despite these findings, each patient must be addressed individually and the options and best evidence reviewed with them prior to deciding upon surgery and prior to obtaining informed consent.

Authors' Preferred Approach

Our approach is generally to consider an open SD as the initial surgical procedure. This consists of unroofing of the ulnar nerve through the cubital tunnel. We avoid circumferential neurolysis as this can lead to ulnar nerve dislocation. For more severe cases or cases with a dislocating ulnar nerve, a SCAT is chosen. We reserve SMAT for salvage in the majority of cases.

Box

What is known?

1. SD and AT are equally effective procedures for treating UNE.
2. Surgical morbidity is higher for AT but often resolves by 8 weeks.

What is new?

1. SD is equally effective as AT, including with more severe neuropathy
2. SD has been shown to be cost-effective

What are the consequences for clinical practice?

1. These data can be shared with patients to guide an informed decision when considering a surgical procedure
2. SD will be effective in most patients with a stable ulnar nerve.
3. Results in severe CuTS may be suboptimal regardless of procedure.

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Open Versus Endoscopische Cubital Tunnel Release

20

Brigitte E. P. A. van der Heijden and Henk J. Coert

Introduction

Cubital tunnel syndrome is a symptomatic ulnar nerve dysfunction at the elbow region probably caused by a combination of compression, traction and friction. Static and dynamic factors are involved, leading to ischemia or mechanical compression, secondary to repeated elbow flexion, anatomic variants of muscles and ulnar nerve subluxation. It is the second most common form of nerve entrapment after carpal tunnel syndrome [1].

Clinical Presentation and Diagnosis

Diagnosis of cubital tunnel syndrome is made through a combination of history, physical examination, and confirmatory nerve conduction testing [2, 3]. Paresthesia is anticipated in the little finger and ulnar half of the ring finger. Sensory disturbance on the dorsal ulnar hand confirms compression proximal to the Guyon canal based on the origin of the dorsal cutaneous branch of the ulnar nerve in the distal forearm. Weakness of the interosseus, the adductor pollicis, and the ulnar lumbrical muscles, which occurs with advanced disease, may cause characteristic posturing in the hand (Wartenberg sign, Froment sign, and claw hand deformity, respectively). Routine clinical provocative testing includes ulnar nerve percussion at the retrocondylar groove (Tinel sign) and the elbow flexion test. Stability of the ulnar nerve is assessed posterior to the medial epicondyle from extension to flexion. Nerve conduction

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studies (NCS) may be used to confirm a clinical diagnosis of cubital tunnel syndrome but false negatives are possible as a result of variable compression of fascicles, because remaining large fiber function may produce conduction values that are within normal limits. Also NCS fail to produce predictions on the outcome after treatment [4].

Cubital tunnel syndrome may be categorized as mild, moderate, or severe disease. Common grading systems include modified McGowan and Dellon classifications [5, 6] (Fig. 20.1). Patients with mild disease report subjective sensory symptoms without objective loss of 2-point sensibility or muscular atrophy (McGowan 1 and Dellon 1). Cubital tunnel syndrome of moderate severity imparts weakness on pinch and grip without atrophy (Dellon 2 and McGowan 2A). The presence of atrophy and intrinsic muscle strength of only 3/5 defines McGowan 2B disease. Most studies however do not differentiate between McGowan 2A and 2B. Patients with severe cubital tunnel syndrome have profound muscular atrophy and sensory disturbance (McGowan 3) and weakness that inhibits active finger crossing (Dellon 3).

Treatment [2, 7, 8]

The first approach is non-operative, especially in patients with mild to moderate symptoms, in whom education of the cubital tunnel syndrome and exercises, avoiding applying direct pressure to the medial aspect of the elbow on firm surfaces, nighttime elbow splinting preventing flexion of the elbow beyond 50°, limitation of motion between 40° and 70° or maneuvers for the arm and neck for improving the gliding of the ulnar nerve may provide symptomatic benefit. Untreated, chronic cubital tunnel syndrome can lead to permanent loss of sensibility, muscle weakness, and secondary joint contractures. Therefore, when conservative management fails, surgery is indicated. Different validated outcome measurements can be used to determine the effect of the operation of which the modified Bishop rating scale (Fig. 20.2) and McGowan classification (Fig. 20.1) are most commonly used. The Bishop's rating scale evaluate overall improvement, severity of residual symptoms, work status, strength and sensibility. The outcome is defined as poor (0–2), fair (3–4), good (5–7) or excellent (8–9).

Open Release Versus Endoscopic Release

It is still not known which surgical technique is preferred for treating primary idiopathic cubital tunnel syndrome: open or endoscopic release. The Dutch National Guideline of Ulnar Nerve Neuropathy (2011) recommends simple open release [8, 9].

Endoscopic release of the cubital tunnel has been first described by Tsai and later modified by Hoffmann [10, 11]. Theoretical advantages of this technique are the short incision, low risk of damage to the posterior branch of the medial antebrachial

	McGowan Classification System	Mc Dellon Classification		
Grade	**Description**	**Sensory**	**Motor**	**Tests**
0	No symptoms	No symptoms	No symptoms	No symptoms
1	Minimal lesions, paresthesia and dysesthesia, no wasting or weakness of ulnar intrinsic muscles	Paresthesias come and go, vibratory percecption increased	Subjective weakness, clumsiness or loss of coordination	Elbow flexion test and/or tinel's sign may be positive
2	Intermediate lesions, weakness and wasting of interossei, although some voluntary power is retained	Paresthesias come and go, vibratory percecption normal or decreased	Measurable weakness in pinch and/or grip strength	Elbow flexion test and/or tinel's sign are positive. Finger crossing may be abnormal
3	Severe lesions, paralysis of interossei and marked weakness of the hand	Paresthesias are persistent, vibratory perception decreased, abnormal two-point discrimination	Measurable weakness in pinch and grip strength plus muscle atrophy	Elbow flexion test and/or tinel's sign maybe present. Finger crossing usually abnormal

Fig. 20.1 Classification system of symptoms of cubital tunnel syndrome

Fig. 20.2 Outcome Bishop rating scale

Bishop score (Score: 8 to 9 excellent; 5 to 7 good; 3 to 4 fair; 0 to 2 poor)		
Severity of residual symptoms		
	Asymptomatic	3
	Mild	2
	Moderate	1
	Severe	0
Improvement	Better	2
	Unchanged	1
	Worse	0
Work Status	Working in previous job	2
	Changed job	1
	Not working	0
Strength	Grip≥80% (compared with other hand)	1
	Grip≤80% (compared with other hand)	0
Sensibility	≤6 mm static two-point discrimination	1
	>6 mm static two-point discrimination	0

cutaneous nerve, reduced manipulation of the nerve and less extensive soft tissue dissection, all factors predictive of faster recovery [12].

In this chapter a review of literature is given in which the results and complications of the endoscopic release and simple open decompression of the cubital tunnel are compared.

Research question: What are the effects of open in situ decompression and endoscopic decompression of the ulnar nerve?

- P: adults (age ≥ 18 year) diagnosed with idiopathic cubital tunnel syndrome
- I: Operative treatment of the cubital syndrome by open in situ decompression or any kind of endoscopic release
- C: comparison between open in situ release and endoscopic release
- O: any objective measurement of clinical outcome, Bishop outcome table, McGowan outcome table, satisfaction, pain, return to work, complications.
- S: randomized controlled trials, prospective or retrospective comparative studies, case-control studies

Materials and Methods

Types of Outcome Measures

Primary Outcomes

Primary outcome was defined as clinical improvement which was defined as either an "excellent" or "good" outcome on postoperative Bishop score (Fig. 20.2) or McGowan scale (Fig. 20.1). When self-administered scales were used, it was evaluated if statistically significant changes were reported regarding the main scores in the questionnaires. Subsequently, data were dichotomized into "improved or not improved" for the clinical improvement outcome, regardless of the differences between the tools used. If a study evaluated more than one cubital symptom outcome measurement, a better score on at least one of the outcome measurements was enough to be considered as an improvement.

Secondary Outcomes

For secondary outcomes the following items were evaluated:

- Satisfaction
- Pain
- Ability to work
- Complications

Search Methods for Identification of Studies

A systematic review of the literature was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. All articles till April 2018 describing open in situ decompression or endoscopic decompression for idiopathic cubital tunnel syndrome were retrieved with no limitations for year of publication. Electronic databases of PubMed, Embase, Cochrane Library and Clinical Trials (clinicaltrials.gov) were searched with medical subject headings and key words, including "cubital tunnel syndrome," "ulnar neuropathy," ulnar neuritis," "ulnar nerve entrapment," "open decompression," "simple decompression," "in situ decompression," "endoscopic decompression," and "surgical decompression." All relevant articles were identified, independent of language used. The Dutch National Guideline for cubital tunnel syndrome was also used concerning choice of key words and articles used. Biomechanical studies, studies on animals or cadavers, technical notes, letters to the editor and instructional courses were excluded.

Inclusion/Exclusion Criteria

The following inclusion criteria were applied: (1) idiopathic ulnar nerve entrapment at elbow confirmed clinically and/or electrophysiologically, (2) studies comparing

results and complications of open in situ decompression versus endoscopic decompression, (3) studies including objective and well-described outcomes and (4) sample size >10 patients and (5) adult patients (≥18 year). Exclusion criteria included any study that did not included both the open and endoscopic cubital tunnel release. Articles that met inclusion criteria following title and abstract review were selected for full-text review.

Data Extraction and Management

Two authors (Van der Heijden and Coert) independently assessed the abstract of each publication. When it was not possible to include or exclude an article based on the abstract, a full-text version of the article was downloaded. If the abstract was not available, the article was excluded from the study. Of all potentially relevant studies full texts were studied to determine to include it or not. In addition, we retrieved the reference list of each selected article to identify additional studies missed at the first electronic search. The review authors then independently extracted data from included studies and assessed risk of bias with a data extraction form specifically designed for this purpose.

Baseline data including age, sex, population size, baseline severity, and follow-up time period for each study were collected. Primary outcome data were collected by means of the Bishop score, the McGowan scale or validated questionaire. Secondary outcome measures pain, satisfaction, return to work and complication rates.

The risk of bias for randomized controlled trials (RCTs) was evaluated with the Cochrane Collaboration's Risk of Bias Tool. The Cochrane Tool incorporates the selection bias, performance bias, detection bias, attrition bias, reporting bias and other risk of bias. The items were judged as "low risk", "unclear risk" or "high risk". A modification of the Newcastle-Ottawa Scale was used to evaluate the quality of observational studies, including retrospective controlled studies and prospective cohort studies. The original Newcastle-Ottawa Scale contains the assessment of selection (exposed cohort, no exposed cohort, ascertainment of exposure, outcome of interest), comparability and outcome (assessment of outcome, length of follow-up, adequacy of follow-up). We added the detection and attrition and other bias in accordance with the Cochrane Tool (BIJLAGE 1). Discrepancies between authors were resolved by consensus.

Statistical Analysis: Meta-Analysis

Two previous review studies with meta-analysis of open versus endoscopic cubital decompression were done in 2016 [13] and 2018 [14]. In the study of Ren et al., RevMan statistical software, version 5.1 (Cochrane Collaboration, http://ims.cochrane.org/revman) was used to analyze the study data. The Cochrane Handbook's Q test and I^2 statistic were used to determine the heterogeneity among the studies. If there was significant heterogeneity ($P < 0.05$, $I^2 > 50\%$), random-effect models were

used. Otherwise, fixed-effect models were applied if there was no significant heterogeneity ($P \leq 0.05$, I^2 0%). Relative risks (RRs) and 95% confidence intervals (CIs) were calculated for dichotomous variable. In the study of Buchanan et al., baseline data were analyzed using IBM SPSS Version 22.0 software (IBM Corp., Armonk, N.Y.). Odds ratio with a 95% confidence interval were used for each outcome variable. A random effects model with inverse variance weighting to calculate I^2 values was performed if heterogeneity testing between study variability was >50%. Forest plots were constructed for each group. Publication bias was presented graphically using a funnel plot and Egger regression test. The statistical analyses were performed using RevMan version 5.0 (Nordic Cochrane Centre, Copenhagen, Denmark). Since 2015 no new clinical study comparing OR and ER has been done. Both review studies performed meta-analysis of the same studies for the following outcome parameters: clinical outcome, satisfaction, pain and complications (overall complications, hematoma and reoperation). In this study we combine the results of both review studies. No new meta-analysis was done.

Results

Study Selection

A total of 114 studies were identified at the first search and after removing duplications. Only seven studies were selected based on the abstract, one study was excluded as the full text was not available. Finally, six publications relevant to the topic were included, one RCT and five observational studies (Fig. 20.3).

Study Characteristics

Among the studies selected, five were observational and one was a randomized controlled trial. Of the five observational studies, three were retrospective and two were prospective comparative. The characteristics of the six included studies are presented in Table 20.1. All studies included patients with the diagnosis of idiopathic cubital syndrome based on history and clinical examination; i.e. positive Tinel's sign, sensory loss in the area innervated by the ulnar nerve, pain over the medial epicondyle, weakness of the muscles innervated by the ulnar nerve and a positive elbow flexion test. In all studies an EMG was performed pre-operatively to confirm the diagnosis of cubital tunnel syndrome. The severity of the cubital syndrome was assessed by the grading system of McGowan or Mc Dellon (Fig. 20.1). Although patient groups were not exactly the same, most patient had moderate severity of cubital syndrome. The duration of follow-up ranged from 6 to 139.2 months. The effect of the surgical intervention was measured mainly by the modified Bishop rating scale (Fig. 20.2) or McGowan classification (Fig. 20.1). Only two studies recorded patient satisfaction as a separate measurement using a numeric analogue scale. Four studies determined post-operative pain.

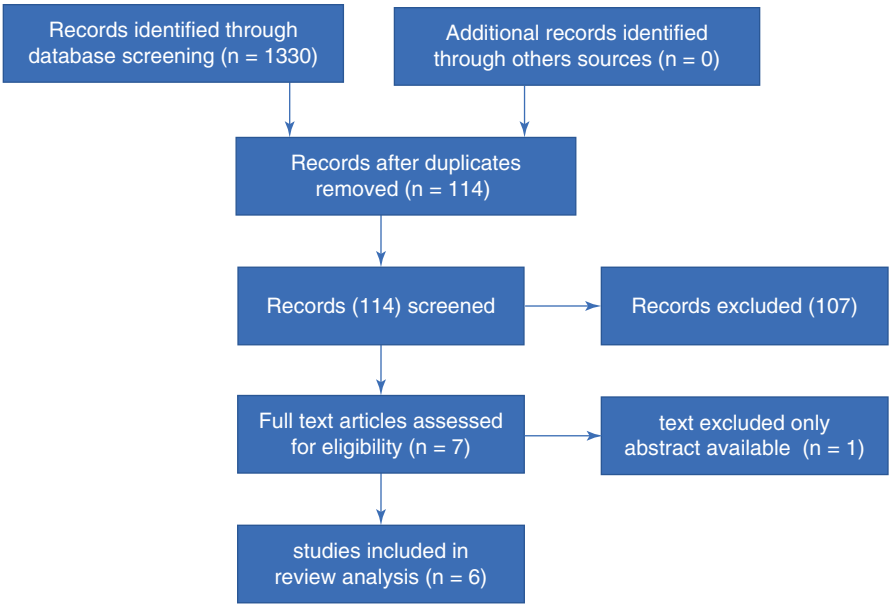

Fig. 20.3 Prisma flow diagram

Assessment of Bias in Included Studies: Level of Evidence [15, 16, 17]

Different scoring scales were used to analyse the level of evidence since both observational and randomized control trials were used in this review (Tables 20.2 and 20.3). The Newcastle-Ottawa Scale is designed to assess the risk of bias of observational studies. A modification of this scale was used in this review. All studies showed a low risk of bias on the Newcastle-Ottowa scale except that of Saint-Cyr, Bacle and Bolster which showed moderate risk. The study of Schmidt et al., which is a RCT, was evaluated according the Cochrane collaboration scale (Table 20.2) and GRADE (Table 20.3); According to GRADE, the quality of the body of evidence on a specific outcome is based on five domains: limitations in the design and implementation (risk of bias), inconsistency (heterogeneity), indirectness (inability to generalize), imprecision (insufficient or imprecise data) and publication bias. The level of evidence of the study of Schmidt et al. was downgraded with two grades because of unclear allocation and imprecision (low number of patients). Observational studies have the lowest score on the GRADE scale (5).

Clinical Outcomes

Besides, In the article of Saint-Cyr data given about patient characteristics considered all patients, without giving separate data for each surgical technique used. Therefore, data of Saint-Cyr could not be used for further analysis.

Table 20.1 Study characteristics

Data		Watts and Bain [18]		Saint-Cyr et al. [19]		Dützmann et al. [20]		Bolster et al. [21]		Bacle et al. [22]		Schmidt et al. [23]	
Operation		OCTR	ECTR	OCTR	ECTR	OCTR	ECTR	OCTR	ECTR	OCTR	ECTR	OCTR	ECTR
Study methods	Study design	Prospective comparative		Retrospective comparative		Retrospective comparative		Prospective comparative		Retrospective comparative		Randomized control trial	
Participants	Sample size (number)	15	19	58	12	59	55	22	20	48	143	27	29
	Inclusion criteria	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	Exclusion criteria	Yes	Yes	Yes	Yes	Yes	Yes	nm	nm	Yes	Yes	Yes	Yes
	Patient characteristics												
	Age	36 (21–74)	49 (22–70)	45.6 all[a]	45.6 all[a]	51 (20–82)	44 (17–76)	49.9 (13.3)	49.9 (11.6)	48 (24–71)	56 (28–84)	47.9 y (612.88)	50.3 y (610.71)
	Gender (%M)	40%	68%	52% all[a]	52% all[a]	58%	53%	50%	45%	nm	nm	59%	59%
	Profession	nm	nm	28% laborer[a]	28% laborer[a]	nm	nm	nm	nm	nm	nm	Yes	Yes
	Symptoms pre OK												
	Classification	McGowan	McGowan	Dellon/ SSS[a,b]	Dellon/ SSS[a,b]	McGowan	McGowan	Dellon	Dellon	McGowan	McGowan	mMcGowan	mMcGowan
	Function	Yes	Yes	Yes	Yes	McGowan	McGowan	DASH	DASH	McGowan	McGowan	Yes	Yes
	Sensation	Yes	Yes	Yes	Yes	McGowan	McGowan	Dellon	Dellon	McGowan	McGowan	Yes	Yes
	Duration	nm	nm	345 days[a]	345 days[a]	nm	nm	20.8 months	15.7 months	nm	nm	20 months	14.2 months
	EMG pre OK (% positive)	100%	100%	13%	13%	100%[c]	100%[c]	82%%	95%	100%[c]	100%[c]	74%	90%

(continued)

Table 20.1 (continued)

Intervention	Conservative treatment	nm	nm	Yes	Yes	nm	nm	nm	nm	nm	nm	nm	nm
	Length of incision (cm)	nm	nm	nm	2–3	6–8	1.5–2	2.7	2.4	3	1.2	3	3
	Length of decompression distal/proximal (cm)	nm	nm	nm	nm	nm	nm	12.4/12.1	15.2/12.5	Few cm	7.0/7.0	5.0/3.65	10.0/6.03
	Length of operation (minutes)	nm	nm	nm	nm	27.7	29.6	32.4	41.5	nm	nm	44.63	70.45
Follow up	Duration (time)												
	Shortterm	No	No	2 days-11.2 years[a]		3, 6[d]	3, 6[d]	7.1	6.7	No	No	3–6	3–6
	Longterm	12 months	12 months	2 days-11.2 years[a]		24 months	24 months	6 months	6 months	94 months (66–110)	94 months (66–110)	12 months	12 months
	Loss to FU (number)	2	1	5[a]	5[a]	nm	nm	6	12	6	52	nm	nm

Outcome data	Primary outcome												
	Validated scale	Validated questionaire		mBishop	mBishop	mBishop	mBishop	Bishop	Bishop	McGowan/ self report	McGowan/ self report	mBishop	mBishop
	Function	Yes	Yes	Yes	Yes	mBishop	mBishop	DASH	DASH	McGowan/ self report	McGowan/ self report	Yes	Yes
	Sensation	Yes	Yes	Yes	Yes	Mbishop	mBishop	Bishop	Bishop	McGowan/ self report	McGowan/ self report	Yes	Yes
	EMG post OK	No	No	No	No	Yes	Yes	No	No	No	No	Yes	Yes
	Secondary outcome												
	Satisfaction	60%	79%	No	No	No	No	86%	80%	No	No	No	No
	Pain	Yes/VAS	Yes/VAS	No	No	Yes (days)	Yes (days)	Yes/vas	Yes/VAS	No	No	Yes (NAS)	Yes (NAS)
	Ability to work	Yes (y/n)	Yes (y/n)	Yes (days)	Yes (days)	Yes (days)[d]	Yes (days)[d]	No	No	No	No	No	No
	Complications	40%[d]	11%[d]	nm	nm	32.10%	10.80%	0.05%	0.00%	0%	0%	4%	24%
	Rehabilitation post OK	nm	nm	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No	No

nm Not mentioned

Return to work: y/n patients are asked if they have been returned to their original work or not or days after surgery they returned to work

[a]No numbers were given for the separate groups

[b]*SSS* severity of symptom score: pain, sign of Froment, sign of Wartenberg and clawing

[c]Patients with a negative EMG were excluded

[d]Significant difference of groups (OR-ER)

Table 20.2 Overview of assessment of risk of bias of studies

Newcastle-Ottowa scale		Watts and Bain [18]	Saint-Cyr et al. [19]	Dützmann et al. [20]	Bolster et al. [21]	Bacle et al. [22]	Cochrane		Schmidt et al. [23]
Selection	Representativeness of the exposed cohort (ER)	Low risk	Low risk	Low risk	Low risk	Low risk	Selection bias	Random sequence generation	Unclear risk
	Selection of the non exposed cohort (OR)	Moderate risk	Moderate risk	Low risk	Moderate risk	Moderate risk		Allocation concealment	Unclear risk
	Ascertainment of intervention	Low risk	Low risk	Low risk	Low risk	Low risk	Performance bias	Blinding of participants and personnel	Low risk
	Demonstration that outcome of interest was not present at the start of the study	Low risk	Low risk	Low risk	Low risk	Low risk		All outcomes	
Comparability	Comparability of cohorts on the basis of the design or analysis	Low risk	High risk	Low risk	Low risk	High risk	Detection bias	Blinding of outcome assessments	Low risk
Outcome	Assessment of outcome	Low risk	Low risk	Low risk	Moderate risk	Moderate risk		All outcomes	
	Was follow-up long enough for outcomes to occur	Low risk	High risk	Low risk	High risk	Low risk	Attrition bias	Incomplete outcome data	Low risk
	Adequacy of follow-up of cohort	Low risk	High risk	Low risk	Low risk	Low risk		Clinical or neurophysiological outcome	
Detection	Was the timing of outcome assessment similar in all groups	Low risk	High risk	Low risk	Low risk	Low risk	Reporting bias	Selective reporting	Low risk

Attrition	Was the dropout rate described and acceptable	Low risk	Low risk	Unknown	Moderate risk	Moderate risk	Other bias	Are other sources of potential bias	Low risk
	Were all participants analyzed in the group to which they were allocated	Low risk	Low risk	Low risk	Low risk	Low risk			
Other	Are other sources of potential bias unlikely	Low risk	Low risk	Unsure	Low risk	Low risk			
Overall		*Low risk*	*Moderate risk*	*Low risk*	*Moderate risk*	*Moderate risk*	*Overall*		*Low risk*

Table 20.3 Overview of quality of studies using different scoring modalities

Study	Level of evidence[a]	Cochrane	New-castle	Grade
Watts and Bain [18]	2	nvt	low	5 (no RCT)
Saint-Cyr et al. [19]	3	nvt	moderate	5 (no RCT)
Dützmann et al. [20]	3	nvt	low	5 (no RCT)
Bolster et al. [21]	2	nvt	moderate	5 (no RCT)
Bacle et al. [22]	3	nvt	moderate	5 (no RCT)
Schmidt et al. [23]	1	low risk	nvt	3

[a]Level of evidence based on study design

Strength	Level	Design	Randomization	Control
High	Level 1	Randomized control trial (RCT)	Yes	Yes
		Meta-analysis of RCT with homogeneous results	No	
	Level 2	Prospective comparative study (therapeutic)	No	Yes
		Meta-analysis of Level 2 studies or Level 1 studies with inconsistent results	No	
	Level 3	Retrospective Cohort Study	No	Yes
		Case-control Study	No	Yes
		Meta-analysis of Level 3 studies	No	
	Level 4	Case Series	No	No
	Level 5	Case Report	No	No
		Expert Opinion	No	No
Low		Personal Observation	No	No

Primary Outcome: Proportion of Participants with a Clinically Relevant Improvement in Function Compared to Baseline

Data were dichotomized into "improved or not improved" for the clinical improvement outcome, regardless of the differences between the tools used. A clinical improvement was found in 87% of patients treated with endoscopic decompression and 82% of those treated with open decompression in the period from 6 to 12 months after surgery (Table 20.4). All included studies except two [18, 22] used the modified Bishop scale. Therefore the meta-analysis was done for only three of the five studies performed [20, 21, 23]. There was no significant difference in postoperative clinical improvement at the last documented postoperative follow-up between simple and endoscopic decompression.

Secondary Outcome: Satisfaction, Pain, Return to Work and Complications

Comparison of "Satisfaction" Between Open and Endoscopic Release

Only two studies [18, 21] measured satisfaction as a separate outcome. In the study of Watts et al., the patients were asked after 12-months of follow-up to complete a questionnaire administered by an independent observer. The degree of satisfaction was recorded using yes/no answers and was scored by the patient using a 100-mm visual analog scale (VAS). In the study of Bolster et al. patient satisfaction was evaluated pre- and postoperative at 6 months of follow-up by using a visual analogue scale (VAS)-scale (0–10). Both studies did not find significant different scores for patient satisfaction between OCTR and ECTR. Since the two studies used

Table 20.4 Functional outcome after open versus endoscopic cubital tunnel release

Studies	Operation	PRE-OK (Dellon/McGowan)			POST OK (mBishop)				Post OK dichotomized outcome	
		Mild	Moderate	Severe	Excellent	Good	Fair	Poor	Improvement	No improvement
Watts and Bain [18]	ECTR	53	26	21	Validated questionaire				79	21
	OCTR	27	40	33	Validated questionaire				60	40
Dützmann et al. [20]	ECTR	13	27	60	56	33	9	2	89	11
	OCTR	14	27	59	54	24	20	2	78	22
Bolster et al. [21]	ECTR	27	45	27	73	18	9	0	91	9
	OCTR	25	69	6	87	7	7	0	93	7
Bacle et al. [22]	ECTR	48	44	8	75	18	7	0	93	7
	OCTR	20	53	27	70	25	5	0	95	5
Schmidt et al. [23]	ECTR	0	72	28	76	7	3	14	83	17
	OCTR	4	56	41	70	11	0	19	81	19
Total	ECTR	28	43	29	70	19	7	4	86.6	13
	OCTR	18	50	33	70.25	16.75	8	5.25	81.5	18.6

Watts has no Bishop score: dichotome score concerns satisfaction
Bacle concerns subjective improvement scores

different methods of satisfaction measurement and durations of follow-up no meta-analysis was done.

Comparison of "Postoperative Pain" Scores Between Open and Endoscopic Release

Comparison of postoperative pain between ECTR and OCTR was conducted in four studies [18, 20, 21, 23]. Dützmann et al. measured the durations (in days) of postoperative pain. The other three studies used a numeric scale to measure the preoperative and postoperative pain. Meta-analysis was performed for those studies which used the numeric scale and data were used of the last documented postoperative follow-up. Although pain reduced significantly after the operation for both OCTR and ECTR, no significant difference was found for the mean reduction in visual analogue scale score between OCTR and ECTR.

Comparison of "Ability to Work" Scores Between Open and Endoscopic Release

It was not possible to do a meta-analysis concerning the outcome "ability to work". Although "ability to work" is one of the scorings items of the Bishop score, studies only provide a total Bishop score without showing the scores on the separate parts (i.e. ability to work) The study of Watts et al. only explicitly showed data about the fact if patients could return to their original job or not or did not work at all. They found no difference in scores after 12 months of follow-up between open and endoscopic surgery. Dützmann et al. evaluated the time to return to full activity after surgery and they found that this was significantly different between the open and endoscopic groups. Whereas 76.4% of the patients returned to their full functionality within the span of 2–7 days after endoscopic surgery, only 18.6% reached this result in the open group. The majority of patients in the open group required ≥7 days to return to full functionality in the operated arm ($P \leq 001$, Mann-Whitney U test). A correlation between these results and the duration of postoperative pain experienced by the patients showed a borderline significance, with the P value being slightly above 0.05 (P = .06; Pearson coefficient, 0.185; 95% confidence interval, 0.12–0.358). However, a trend could be observed. A higher percentage of patients (65%) had already ceased to have postoperative pain 3 days after endoscopic surgery compared with 49% in the open group (P = 0.08, Mann-Whitney U test).

Comparison of "Complications" Scores Between Open and Endoscopic Release

All five included studies [18, 20–23] reported complications after ECTR of OCTR such are infection, scar tenderness/pain, hematoma, subluxation of the ulnar nerve and reoperation (Table 20.5). In the study of Watts and Dützmann patients endured more scar tenderness and numbness around the elbow after the open procedure compared to the endoscopic procedure. Schmidt et al. found that endoscopic release resulted in more hematoma compared to the open release. In the study of Bolster and Bacle no significant differences for complications between ECTR and OCTR were found. Data of the five studies were pooled and consisted of 437 patients of which 171 received

Table 20.5 Overview of complications found after open and endoscopic cubital tunnel release

	Watts and Bain [18]		Dützmann et al. [20]		Bolster et al. [21]		Bacle et al. [22]		Schmidt et al. [23]	
Complications	OCTR	ECTR	OCTR	ECTR	OCTR	ECTR	OCTR	ECTR	OCTR	ECTR
Infection	0	0	1 of 59	0	0	1	0	0	0	0
Wound desiccation	0	0	0	0	0	0	0	0	1 of 27	3 of 29
Pain new	1 of 15	1 of 19	0	0	0	0	0	0	VAS, %?	VAS, %?
Scar tenderness	2 of 15	0	4 of 59	0	0	0	0	1	0	0
Hematoma	0	1 of 19	0	2 of 55	0	0	0	0	1 of 27[a]	7 of 29[a]
Numbness around elbow	3 or 15	0	14/59[a]	0[a]	0	0	0	0	0	0
Subluxation nerve	0	0	0	4 of 55	0	0	0	0	2?	2?
Re-operations	0	1(hematoma)	0	4 (2 hematoma/ subluxation)	0	0	1 (recurrence)	0	5 (residual/ recurrence)	3 (residual/ recurrence)
Total	6 of 15[a]	2 of 19[a]	19/59	6 of 55	0	1	1 (recurrence)	1	7 of 27	13 of 29

[a]Significant difference between OCTR and ECRT of the same study

OCTR and 266 ECTR. Ren et al. found moderate heterogeneity among studies (P 1/4 0.01, I^2 1/4 68%) and used the random-effect model. The overall estimate indicated that the pooled RR was 0.88 (95% CI 1/4 0.24e3.29, P 1/4 0.85), suggesting that the difference in complications in general was not statistically. Buchanan et al. distinguished different kind of complications: scar pain, hematoma and reoperation. After meta-analysis [18, 23], significant less scar tenderness was found in the ECTR group compared to OCTR group (p = 0.002). However, endoscopic cubital tunnel release caused a significant more postoperative hematoma than did the open release (p = 0.003, [18, 20, 23]). The rates of reoperation for endoscopic and open cubital tunnel release were 4.9% and 4.1%, respectively (p = 0.90). The primary reasons for reoperation in the endoscopic cubital tunnel release cohort were hematoma (50%) and persistent/recurrent symptoms (50%). The primary reason for reoperation in the open cubital tunnel release cohort was persistent/recurrent symptoms (100%).

Discussion

Endoscopic ulnar tunnel release (ECTR) has been introduced as an alternative treatment modality for cubital tunnel syndrome since the 1990s [10]. In theory, it offers outcomes similar to open cubital tunnel release (OCTR) while providing the additional benefits of a minimally invasive approach. It aims to minimize incision size, hereby reducing the potential risk of cutting the medial branch of the antebrachial cutaneous nerve (MABC) which may cause prolonged scar pain and hypesthesia [24–26]. ECTR may provide better view of the entire course of the ulnar nerve and make complete release of distant potential compression sites possible. Furthermore, it requires no special instrumentation apart from the endoscope and has a relatively short learning curve [11]. Drawbacks of ECTR include higher risk of hematoma, ulnar nerve subluxation, and theoretical risk of iatrogenic ulnar nerve injury with blind introduction of the endoscope.

Our systematic review demonstrated that endoscopic and open decompression are equally effective in improving clinical function and overall improvement of clinical symptoms (86% and 79%, respectively). No significant differences were found for patient satisfaction and reduction of pain.

The ability to work after short term (3–6 months) and long-term follow-up did not differ between ECTR en OCTR. There was only one study which evaluated days of recovery concerning ability to work [20]. It was found that patients of the ECTR group returned earlier to their work than did patients of the OR group; the majority of the patients returned to their full functionality within the span of 2–7 days after endoscopic surgery, the majority of patients in the open group required ≥7 days. An explanation for the faster recovery during the first few days after surgery for the ECTR group compared to the OCTR group could be the difference in length of incision and accompanying soft tissue damage (6–8 cm for the OCTR group and 1.5–2 cm for ECTR group). In contrast, studies performed later [21–23] uses almost the same length of incision for both the ECTR and OCTR. This might be one of the reasons that no differences were found for clinical outcomes and complications, since the OCTR more and more became comparable to the endoscopic technique.

Our systematic review showed an overall complication rate of 8% and 16% in ECTR and OCTR, respectively. Hematoma was the most common complication in the ER group (50% of complications seen with ECTR) compared with 4% in the OCTR; however, <25% of those required surgical evacuation. Despite the fact that some form of preventive steps to reduce hematoma formation has been described (tourniquet release, bipolar cauterization, closed suction drains, compressive dressing), the incidence of hematoma persisted to be higher in endoscopic release. An explanation can be the fact that more length of ulnar nerve is released compared to the open release and that in the inherent narrow surgical field less hemostasis can be performed. On the contrary, numbness around elbow and medial forearm likely related to MABC nerve injury was the most common complication in the OCTR group (63%) compared with 0% in the ECTR. Interesting to note is that this complication was especially seen in the older studies [18, 20] in which the incision of the open technique was longer that in the studies done afterwards. More important, the relatively high complication rate of MABC injury has led to the development of reducing the incision in the OCTR. The study of Buchanan showed that an open release leads to more scar tenderness than did the endoscopic release. There was no difference in the rate of reoperation. Hematoma or recurrence were the main reasons for reoperation in the ECTR group, while in the OCTR group recurrence was the main reason.

Hoffmann and Siemionow demonstrated multiple compression sites of the ulnar nerve up to 9 cm distal to the midpoint of the retrocondylar groove. Release of those bands would require a radical in situ decompression or a complex transposition, and hence, according to Hoffmann, an endoscopic release would offer a greater advantage of releasing those bands without complex soft tissue dissection. However, this review shows a relatively "short" length of decompression used in the open decompression technique is not associated with a worse outcome or a higher failure rate than in the endoscopic technique. Moreover, Schmidt et al. could not find any relevant constrictions more than 4 cm distally from the bony sulcus in their patients.

Limitations of this Review Study

Only one randomized controlled trial has been performed comparing the standard open release of the cubital tunnel with the endoscopic release. The study was of midhigh grade level because the random sequences allocation was unclear. Another disadvantage was the relatively low number of patients and therefore low power to find differences in outcome between operation techniques used. Two review articles have been written in which outcome parameters between ECTR and OCTR were compared and meta-analysis was performed as written in the results section. However, one has to wonder if this analysis should be done with data which have been obtained by different methods and at different durations of follow-up. Only one of the studies used was a randomized control trial and other studies were of low grade quality with low level of evidence.

Conclusion

Concerning the operation technique, some showed that open decompression is faster and safer. On the other hand, Dützmann et al. did not found any difference in operation time. As with all new techniques, operation time and risks will decrease when getting more experience. The learning curve of ECTR is said to be relatively short [11, 20, 26, 27]. Although it would be expected that the learning curve of OCTR is more steep than that of ECTR, it has never been analyzed. It might even be the other way around. Considering the small incision of the open decompression nowadays and the limited view for only the surgeon, it might be that the endoscopically technique, which is much more common today for young surgeons and gives a good view for all of the operating staff, is much easier to be learned than the open technique. Another advantage of the endoscopic technique is the possibility of patients to watch and images can be recorded (table of overview operation techniques).

Overview of techniques

	Open release	Endoscopic release
Advantage	Cheap (instruments)	Good view for patient and operating team
	Relative fast	Recording possibilities
	Local anesthesia possible	Extended release possible
Disadvantage	Less view	More expensive (instruments)
	Only view for surgeon	Learning curve
	Restricted release possibility	General of regional anesthesia
Risk	Lesion of cutaneus nerve	Hematoma

Box

What is known?

Different operation techniques are possible for treating primary idiopathic cubital tunnel syndrome and it is still not known which surgical technique is preferred. Open simple release is frequently recommended.

What is new?

Endoscopic and open decompression are equally effective in improving clinical function and no differences in complications rate were found. Note that the open decompression techniques more and more resemble the endoscopic technique in using a small incision and device to keep open the wound. The main difference is the distance over which the ulnar nerve is released.

What are the consequences for clinical practices?

Both the endoscopic or open release can be used in clinical practive for treating primary idiopathic tunnel syndrome. The distance over which the ulnar nerve must be released mostly of the time need not to be more than 4 cm distal and proximal from the cubital tunnel itself and must be evaluated intraoperatively if more release is necessary.

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Surgical Treatment of Meralgia Paresthetica

21

Elias B. Rizk and Russell A. Payne

Introduction

Meralgia paresthetica (MP) is a neuropathy of the lateral femoral cutaneous nerve (LCFN) resulting in pain, dysesthesias and decreased sensation over the anterolateral thigh [1]. It was first reported by German pathologist, Martin Berhardt, in the late nineteenth century. Vladimir Karlovich Roth observed the same phenomenon in cavalry soldiers with tight belts and termed it meralgia paresthetica from the Greek words for thigh (meros) and pain (algos) [2–5].

The LCFN is a pure sensory nerve that arises from the lumbar plexus and is primarily composed of fibers from the L2 nerve roots though multiple other lumbar roots can also contribute fibers. Significant variability in the course of the nerve has been noted in the literature. [1, 6, 7] Most commonly, it arises from the lateral margin of the psoas muscle, crosses the fascia of the iliacus muscle. It then courses under the inguinal ligament within 2 cm of the ASIS tip and medial to the sartorius muscle. The LCFN is usually found deep to the superficial fascia of the thigh inferolateral to the ASIS. Next it pierces the fascia to provide cutaneous innervation to the anterolateral thigh [1, 6]. The wide variation in the not only the course of the nerve but also the branching pattern has led some to advocate considering the area within 3cms of the ASIS as a "danger zone" [8].

MP is generally considered a compressive neuropathy of the LFCN at the inguinal ligament. It most commonly affects middle aged males and has been classically associated with increased body mass index, diabetes mellitus, pregnancy, tight fitting clothing, increased intra-abdominal pressure, surgical procedures, various toxicities and direct trauma [9, 10]. The exact cause is thought to be multifactorial and can differ depending on patient's age and gender [11].

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Histopathological evaluation of involved nerves reveals findings consistent with a compressive neuropathy such as reduced myelinated fiber density, perineurial thickening, subperineurial edema and regenerating nerve clusters [12–14].

As with other peripheral nerve disorders, diagnosis is largely clinical [15]. Patients complain of burning and/or numbness and tingling in the anterolateral thigh. Examination reveals sensory disturbance in the LCFN distribution which includes the skin of the anterior and lateral parts of the thigh as far as the knee. Pain is exacerbated by standing and walking and oftentimes relieved by sitting down [10, 16]. Provocative maneuvers such as the pelvic compression test have can be used to help distinguish MP from lumbosacral radicular pain [17]. Magnetic resonance imaging and/or ultrasound can be used to rule out masses compressing the nerve or presence of a nerve tumor. Additionally, several studies have looked at the morphology and size of the LCFN in order to diagnose MP [18–20]. Electrodiagnostic testing may prove useful but is limited especially in the obese [21–23]. Injections with anesthetic and/or steroids have been utilized for the dual purpose of both diagnosis and treatment [19, 24–27].

Treatment is often conservative and aimed at addressing the precipitating factor. Common approaches include losing weight and wearing loose fitting clothing. Pharmacotherapy utilizing anti-inflammatories and neuropathic agents are also employed. Cases refractory to life style modification and pharmacotherapy are often treated with ultrasound guided injections of anesthetic and/or corticosteroid [19, 25–28]. Others have described ultrasound guided alcohol neurolysis [29]. Additionally there is a growing body of literature documenting the use of pulsed radiofrequency ablation to treat MP [30–32].Those refractory to these treatments are referred to neurosurgeons for surgical treatment. Though other techniques such as LCFN transposition have been suggested, the mainstays of surgical treatment for MP are neurectomy (NR) and neurolysis (NL) [20, 33–45]. Which of these treatments is best supported in the literature?

Methods

We conducted a computerized search of MEDLINE (PubMed; all years). Eligible studies included those that compared NL to NR as a treatment to MP refractory to conservative therapy. The primary outcome measure considered was symptom resolution. The search terms “meralgia paresthetica” AND “surgery” were used. Only English language articles were evaluated. All patients regardless of age were included. All papers regardless of publication date were considered. The titles and abstracts of these papers were then reviewed and those comparing NL to NR were included in our analysis. The bibliographies of these papers were also evaluated in order to find additional papers that might have been missed in the initial search. Each of the eligible papers was then evaluated and assigned a level of evidence according to the American Academy of Neurology grading scheme. We then used the grading, recommendations, assessment, development and evaluations (GRADE) system to evaluate the body of evidence as a whole [46].

Results

Our initial search returned 143 articles (Fig. 21.1). After screening titles and abstracts, we found only seven English language articles comparing NL to NR. All of the articles were observational studies. There were no randomized, controlled trials.

> This was a non-randomized prospective cohort study of those with idiopathic MP refractory to conservative therapy who underwent surgical treatment with NL or NR. The primary outcome measure was pain resolution as defined by Likert score at 6 weeks after surgery. Patients determined which procedure they underwent. Surgery and follow up were

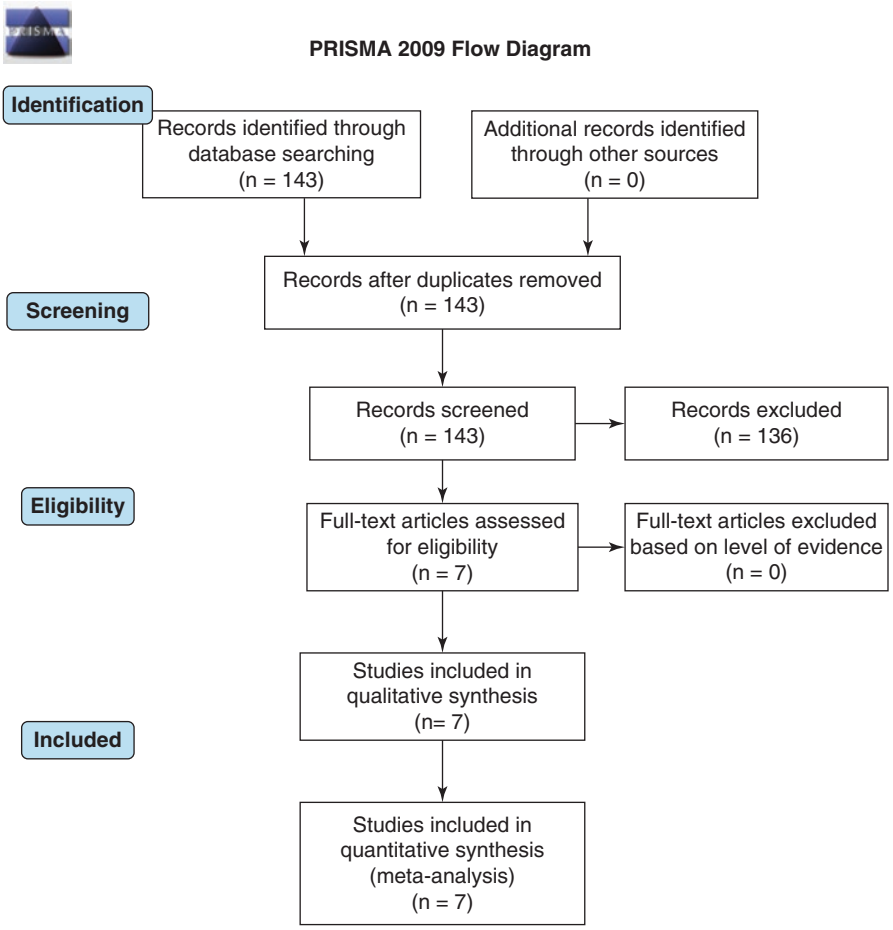

Fig. 21.1 PRISMA 2009 Flow Diagram. From: Moher D, Liberati A, Tetzlaff J, Altman GG, The PRISMA (2009). Preferred Reporting Items for Systematic Reviews and Mata-Analyses: The PRISMA statement. PLoS Med 6(6):e1000097. https://doi.org/10.1371/journal.pmed.1000097. For more information, visit www.prisma-statement.org

conducted by the authors of the study. Twenty-two patients underwent a total of 23 surgeries (15 NR and 8 NL). Fourteen of the 15 (93.3%) neurectomies and three of eight neurolysis (37.5%) resulted in successful pain reduction (Likert 1 or 2). Five of the failed NL patients went on to achieve complete symptom relief after NR. The authors conclude that NR is superior to NL in providing pain relief. de Ruiter and Kloet [33].

This was a retrospective cohort study analyzing the records of those who had undergone either NL or NR for treatment of idiopathic MP refractory to conservative therapy. The primary outcome measure was symptom relief. This was recorded, by means of a questionnaire, as complete, partial or no relief of symptoms. The surgical procedure was determined by the prevailing technique at the time. Surgery and follow up were conducted by authors of the study. Average follow up in the NR patients was substantially longer (93 months) than those in the NL group (16 months). Sixteen patients underwent a total of 22 procedures (12 NR and 10 NL). There were two patients who underwent bilateral procedures and another four patients that had a NR performed after failed NL. This study reported that 75% of those undergoing NR and 60% of those undergoing NL the first time had complete pain relief. The authors conclude that NR is superior to NL at ameliorating symptoms related to idiopathic MP. de Ruiter et al. [34].

This was a retrospective cohort study of those who had undergone either NL or NR for MP refractory to conservative treatment. Primary outcome was symptom resolution and patient satisfaction as defined by a patient questionnaire. Unlike previously mentioned studies, cases with varying etiologies were included (trauma, post-surgical, idiopathic). All cases were performed by the same surgeon. Follow up was performed by the treating surgeon as well as by an independent examiner. Average follow up was 98 months. There were 167 procedures performed on 160 patients (7 bilateral). These included 153 NL and 14 NR. One hundred and fifty-three patients underwent NL while only 14 under NR. Three of those who underwent NR did so after failed NL. Ten underwent NR after a neuroma was found. One underwent NR because of considerable narrowing. Seventy eight percent of those who underwent NL had relief of symptoms and satisfaction after surgery. This is compared with 35.7% of those who underwent NR. Benezis et al. [47].

Retrospective chart review of a series of patients who presented with idiopathic MP. The vast majority of patients responded to conservative therapy. Those who didn't underwent surgical intervention. Out of 79 diagnoses of MP, only three underwent for surgery (2 NR and 1 NL and transposition). All surgical patients reported resolution in symptoms. Follow-up was at least 1 year. This paper was not designed to detect which type of surgical intervention was superior, rather it was detailing an institutions experience with treatment of MP. Haim et al. [35].

Retrospective cohort study evaluating patients with MP refractory to conservative therapy who underwent surgery. Primary outcome measure was symptom relief defined as complete and persistent relief of all symptoms, partial relief of symptoms or failure to relieve symptoms. Patients randomly underwent either NR or NL. The details of this randomization are not explained. Ten patients underwent NL while 11 patients underwent NR. The surgeries were done by five neurosurgeons, four of which performed both NL and NR. Mean followup for NL and NR was quite different at 46 months and 116 months respectively. In the NR group, 9/11 experienced complete relief and 2/11 had partial relief. There were no failures. In the NL group, 3/10 experience complete relief and 3/10 had partial relief. There were four failures. The authors conclude that NR is superior to NL. van Eerten [36].

This is a non-randomized prospective cohort study collecting data from 14 consecutive non-obese patients with idiopathic MP. The procedure, either NR or NL, was chosen by the patient in clinic. Primary outcome measure was relief of presenting symptoms and characterized as either complete relief or incomplete relief. Patients were seen 1 week postoperatively. If there was incomplete relief, then they were reviewed again at 3 month intervals. All out-

comes were assessed within 18 months of the procedure. There were 14 surgeries performed on 14 patients (9 NR and 5 NL). All patients received 18 month follow up. In the NR group, 9/9 reported complete resolutions of symptoms, while 5/5 patients in the NL group reported symptoms recurrence within 1–9 months. The authors conclude that NR is superior to NL. Emamhadi and Sheikhvatan [40].

This is a case series of those with MP treated by a single surgeon. A total of 15 cases were treated in 14 patients (1 bilateral case). Primary outcome was symptom relief. Treatment was initiated with injections. There was resolution of pain in five case with nine patients experiencing persistent discomfort. Seven of these patients opted for surgical intervention. Follow up ranged 3–6 years. A total of eight surgeries were performed on seven patients (4 NL and 8 NR). All those who underwent NL had symptom recurrence by 2 years while those who had undergone NR had sustained relief. Ivins [44].

Level of Evidence

Previous publications have endeavored to answer the questions of whether NL or NR is superior in the treatment of MP [37, 48]. The low quality of the evidence available makes this question difficult to answer. As of the writing of this chapter, there have been no randomized, controlled trials comparing surgical treatments of MP. Much of the literature is composed of case reports and surgical case series with a lesser number of cohort studies. In our analysis, we included papers that reported outcomes for both NL and NR. Two of these papers were prospective cohort studies. The remainder were retrospective cohort studies or case series. Only Van Eerten randomized patients to NR or NL. Unfortunately, the details of the randomization/concealment as well as the method of outcome assessment are not presented in the paper. The most common drawback to the studies was that outcomes were assessed by an unmasked treater. In fact, only Benezis et al. utilized an independent examiner when performing follow up and assessing outcomes. This is a concern because it clearly introduces bias into the outcomes assessment and lowers the class of evidence. Another challenge we encountered when evaluating the evidence was that the groups being compared were at times dissimilar or the characteristics of the groups were not stated. We found this to be case in the articles authored by Benezis et al., Haim et al., and Van Eerten et al. Upon grading the evidence according the AAN scheme, we found that all of the articles were class IV evidence with significant heterogeneity between studies when considering inclusion criteria (idiopathic MP versus all etiologies) and outcomes assessment (definition of successful treatment). When evaluating the overall body of evidence, we found it to be of *very low* quality. We therefore did not perform a meta-analysis.

Patient Preferences

Both NL and NR require similar surgical approaches and are both performed by peripheral nerve surgeons. Advocates of NL refer to the success of NL as a treatment of other compressive neuropathies such as carpal tunnel and cubital tunnel syndrome. One of the proposed benefits is that it prevents nerve sectioning and the resultant anesthesia over the LCFN distribution which might be disconcerting to patients.

Those recommending NR over NL point to the abnormal histology of the LCFN in MP and refer to it as a "pain generator." In their assessment, NL of this abnormal nerve will not produce relief of symptoms. An additional NR procedure may then become necessary thereby exposing the patient to multiple surgeries.

Discussion

Our literature review revealed seven studies which compared NL to NR. Only one of these studies conducted by Benezis et al. reports that NL is superior to NR. In this study, NR was reserved for those who had neuroma formation within or deformation of the LCFN thereby making the two treatment groups dissimilar. However, the overall body of evidence is still of *very low* quality and this prevents us from being able to make a clear recommendation of NR or NL in the treatment of MP.

Traditionally, both NR and NL have been employed when treating MP. NR was first described in 1885 by Hager [49]. Both NL and NR are mentioned in papers discussing treatment of MP dating back to the early and mid twentieth century [5, 16, 41]. There are several authors that report substantial benefit after NL with success in up to 77–88% of cases [17, 38, 39, 50–52]. Others report poor outcomes with NL [53]. Similarly, NR success has been reported as high at 96% while others have documented poorer outcomes [24].

Recently, there have been several articles published re-introducing LCFN transposition as a treatment to MP [42, 43]. The data for this technique is sparse when compared to that of NL and NR and we did not include it in this analysis.

Conclusion

The poor body of evidence precludes us from recommending one surgical technique over the other.

Box

What is known?

MP is a painful mononeuropathy involving the LCFN. It usually resolves without need for surgical intervention. When refractory to conservative therapy, surgery in the form of NL or NR has been successfully reported in the literature.

What is new?

Conservative therapy utilizing ultrasound, injections and radiofrequency ablation show encouraging results. Recent publications have re-introduced the possibility of LCFN transposition though there is little published on this subject.

What are the consequences for clinical practice?

The poor body of evidence precludes us from recommending one surgical technique over the other. Though each technique has its advocates, both techniques are generally considered acceptable and report reasonable success rates.

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Evidence in Neurosurgery: Perspectives

22

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The previous chapters of this book have shown that becoming an evidence-based neurosurgeon is not a simple task. Both the editors and the authors have tried to take the next step in the synthesis of higher-level evidence for practicing neurosurgeons. The chapters are organized around common clinical scenarios taken from real-life experience. The results show that some scenarios are more common and subsequently comprise more high quality evidence, whereas others are extremely rare resulting on only a few retrospective case series. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) was used in this book for grading the quality of evidence [1]. GRADE provides a comprehensive framework for evaluation of the quality of evidence in systematic reviews and clinical guidelines, succeeding the hierarchical levels of evidence classification system which has been widely used for the past decades [2].

A recent international survey among 177 neurosurgeons aimed to explore the availability of evidence and its value within clinical practice also showed that all

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levels of evidence seemed to be used by the majority of neurosurgeons and all agreed that this is mainly due to a lack of evidence [3]. According to 84.4% of the neurosurgeons, neurosurgery is amenable to evidence; however, nearly half of the respondents believed that neurosurgery is less based on evidence than other medical specialties. Fifty-nine percent of the respondents considered the neurosurgical guidelines in their hospital to be based on high-quality evidence, most of whom considered their own treatments to be based on high-quality (level I and/or level II) data (84.3%). Yet, only 55% of neurosurgeons who did not consider the hospital guidelines to be based on high-quality evidence, considered the evidence for their clinical practice high-quality. Furthermore, neurosurgeons commented that randomized controlled trails (RCTs) are expensive and difficult to perform, whereas well-designed prospective comparative studies could be equally informative and easier to run. They therefore concluded that dismissing study designs other than RCTs when developing neurosurgical guidelines is holding back neurosurgery.

Numerous factors can be identified in neurosurgical trials which have contributed to overall low level of evidence, low prevalence of RCT's and poor quality of design and reporting in available RCT's [4]. First of all, the majorities of studied diseases are too rare and heterogeneous which has caused multiple RCT's to be terminated prematurely due to challenges in enrollment [5]. In addition, many general concepts in neurosurgery have been proven effective in practice and have been passed down by mentors to residents during training periods without being investigated properly. Therefore, the fundamental principle of equipoise, defined as uncertainty regarding the relative merits of diagnostic, prevention or treatment options making randomization ethically permissible, [6, 7] is extremely hard to achieve, and bias in selection of patients by treating neurosurgeons for participation in studies has posed a great challenge for generalisability of trial results. These factors have ultimately led to an overwhelming amount of retrospective cohort studies and case series with selected patient population and small sample size in attempt to provide some evidence for treatments not amenable to study in RCT's [4].

Randomized Clinical Trials

In the past century RCTs have reshaped medical practice as they have provided a way to evaluate therapeutic interventions in a more accurate and bias-free fashion [8]. Before the introduction of randomization in design and analysis of experiments in 1920s by Ronald Aylmer Fisher and formal RCT methods in the 1940s by Austin Bradford Hill, case reports, case series and clinical demonstrations were the most commonly used methods to prove an intervention to be effective [9, 10]. Initially, RCTs were criticized for withholding new potentially promising interventions from control groups and high demand for resources. However, the rapid growth of pharmaceutical industry after the Second World War and experiences with new drugs leading to irreversible damage to patients (such as thalidomide) have eventually led to the rise of RCTs to the top of methodological hierarchy and being identified as the gold standard of knowledge [8, 11].

RCTs have several advantages which have contributed to their popularity. In a well-designed trial, randomization reduces the potential for confounding by even distribution of known and unknown factors in intervention and control groups which contributes to strong internal validity and reduction of selection bias. Blinding helps to control what researches and participants know about allocation of interventions which reduces the potential for treatment bias. Therefore, both blinding and randomization in RCTs help distinguish intervention effects from confounding.

Despite this, RCTs have a number of limitations. RCTs usually require collaboration between multiple centers and take years to plan, execute and to analyze the collected data. Keeping this in mind, it is hard for RCTs to keep up with fast pace of innovation in medical field. Take for example the flow diverter case from chapter seven for ruptured and unruptured intracranial aneurysms. Flow diverters were first introduced almost a decennium ago as a treatment strategy for aneurysms with unfavorable configuration which are unsuitable for clipping and have high recanalization rates with coiling. Until now there have been six attempts to study flow diverters in an RCT with only two trials publishing their results [12, 13]. One of the published trials was stopped prematurely due to safety concerns, however, a lot of criticism was expressed towards its design [13]. The other four unpublished trials were stopped prematurely due to challenges in enrolment [5, 14–16]. In the meantime, the experience with flow diverters has rapidly increased, and a lot of effort has been made to further improve the device, making the results of previous RCTs not entirely applicable to the current situation. A lot of centers have already adopted the use of flow diverters as standard care for complex aneurysms based on numerous cohort studies and case series showing favorable results. The quality of evidence for flow diverters is generally low, yet, a moment of equipoise has already passed in clinical practice, rendering this treatment unsuitable for studying in an RCT.

The other major limitation of RCTs concerns the financial aspects. The time and resources consuming nature of RCTs has made them an extremely costly enterprise with the reported costs varying between USD 43 and 103.254 per patient, and USD 0.2–611.5 millions per RCT [17]. The expenses of large clinical trials have been growing for years without clear increase in quantity of high quality evidence [18]. High expenses in clinical trials have contributed to two unwanted effects, such as RCTs tend to be initiated in industrialized countries, which influences the interventions studied, and the RCT costs have been used as an excuse to raise the price of drugs [8, 19, 20].

The chosen study endpoints need to be feasible in the time constraints of an RCT, which does not necessarily reflect the outcomes of interest for the target population [21]. Moreover, high costs and long execution time can lead to selection of populations more at risk for assessed outcomes in order to get sufficient number of patients for various endpoints, or selection of low-risk populations to speed up the inclusion rate and to achieve the required sample size for trial endpoints. A nice case illustrating the issue is presented in chapter four on surgical resection in elderly glioblastoma patients. Despite the high proportion of elderly patients in general glioblastoma population, they are often excluded from trials due to an increased chance of baseline comorbidities, postoperative complications, prolonged recovery time or

therapy-induced side effects. Unfortunately, this has made the proper management strategy for glioblastoma patients with advanced age unclear with a risk of denying them a potential treatment option. Considering the growing relevance of this population, authors encourage enrolment of elderly patients in trials when feasible.

In surgical trials a number of additional methodological challenges arise affecting feasibility and generalisability. The nature of surgical interventions is complex: each patient has unique characteristics, each surgeon has different experience and skills, great variety of choices can be made considering anesthesia, premedication, instrumentation and postoperative care [8, 22]. Delivery of a surgical intervention also relies on the other members of a surgical team consisting of nurses, anesthesiologists or technicians. All of this factors can influence the outcomes and add complexity to interpretation of the results [23]. Standardisation has been used to in some extent control for these factors, with trials being performed at sites with experienced physicians and trained teams with highly selected participants, leading to concerns about overestimation of benefits and underestimation of harm of a particular surgical intervention [24]. Moreover, treatment preferences of surgeons and patients are known to influence willingness to participate in a randomized trial and impact the recruitment process [25]. This has led to the opinion that a more pragmatic approach is required to reflect real-world clinical practice and to evaluate the effectiveness of surgical innovations [26].

Other important considerations in surgical trials are learning curve and effect of clustering. A surgeon's experience increases as a trial on a new intervention progresses. Clustering means that variation in outcomes may be smaller in patients treated by the same surgeon or center than patients treated by different surgeons or centers. These effects are well-studied and reporting guidelines for non-pharmacological trials are well-established. [27–31] Despite this, a recent study on reporting of considerations of a learning curve and clustering effects in published RCTs has shown that considerations in published trials for both effects are often unclear [32]. In addition, methods of reporting varied greatly, adherence to reporting guidelines was poor and statistical analysis was rarely adjusted to reflect on stratification in randomization process. These findings strengthen the concerns about the quality of surgical research which is used to guide clinical decisions.

Alternative Study Designs

In the past years, a number of solutions and methodological alternatives have emerged to address the above-mentioned issues. The focus has shifted to designs which integrate research and daily clinical practice. With rising concerns about generalisability of study results from explanatory trials, pragmatic trials have been gaining popularity [26]. The concept of a pragmatic trial is quite old, as it has been proposed in 1967 by Schwartz and Lellouch who introduced a distinction between explanatory and pragmatic trials [33]. An explanatory trial is designed to measure efficacy of an intervention under "ideal" conditions to confirm a hypothesis, while a pragmatic trial is measuring effectiveness in real world clinical practice [26, 34,

35]. Pragmatic trials have been used for policy decisions as they are designed to reflect daily practice. The core design characteristics of pragmatic trials are minimization of selection criteria for trial participants, the reduction of complexity of study procedures and follow-up visits and freedom to study more types of intervention in one study. An intervention should be delivered in context of normal clinical practice by regular health workers. One of the examples of a pragmatic design in neurosurgery is the RESCUEicp trial addressing the role of decompression craniectomy for severe and refractory intracranial hypertension after TBI presented in chapter two, where the choice for hemi-craniectomy or bifrontal craniectomy was left at the discretion of the neurosurgeon [36].

In addition, patient-reported outcomes (PROMs) are more likely to be used in pragmatic studies [35]. Electronic patient records have increasingly been used for data collection minimizing data collection requirements and trial costs. This lean design has its drawbacks, as relying on clinical practice can increase heterogeneity of clinical findings and therefore reduce the probability of answering the research question. For example, the protocol of RESCUEicp trial allowed decompression craniectomy in the medical group where the original treatment failed to control ICP, leading to 37.2% of patients receiving the additional surgery. This has probably influenced the observed treatment effect. Besides, data collection from electronic patient records is prone for missing data.

Theoretical concepts of pragmatic and explanatory trials represent two ends of the same trial spectrum, and many trials have characteristics of both designs to provide a balance between internal and external validity as high quality evidence is required to inform clinical practice [37]. As degree of pragmatism across the trials may vary, PRECIS-2 tool has been developed to help this assessment and to provide guidelines to the process of trial design [38].

Another pragmatism-driven design which integrates research into clinical practice is comparative effectiveness trial (CET). In CET the effect of different treatment modalities is compared during use in clinical practice in order to guide decision making and to support quality improvement [39]. CETs combine the minimally intrusive character of observational studies as study procedures are limited to minimum, while preserving the advantages of experimental design, such as (cluster)randomization. Care providers have an important role in CET, as they should be engaged in defining the objectives of research and they should agree to comply to treatment delivery protocols. Moreover, integration of CET into clinical care system requires active participation of care providers for patient recruitment and consent procedure. This poses a potential disadvantage of this method, as consenting procedure might be time consuming and discouraging for trial participation for clinicians [40]. Reducing the time and effort for patient identification and in some cases obtaining a waiver for informed consent form have proven to be effective measures for this issue [41]. Involvement of clinicians in assessment of participants for trial eligibility introduces greater population heterogeneity in comparison to assessment by research staff. However, the results might be more informative for general practice [39]. Just like in pragmatic trials, data can be collected from electronic patient records.

Adaptive trial design is one of the methods to make RCTs more efficient. This design allows for modification of the trial course according to pre-specified rules based on the results of the accumulated data reducing the resource use, limiting the number of participants assigned to inferior treatments and limiting the completion time of the trial. [42–44] Different strategies for adaptive trial designs are known, such as dose-response modeling in exploratory trials, and seamless phase 2–3 designs, sample-size re-assessment, adaptive population enrichment and dropping of inferior treatment arms in confirmatory trials [45, 46]. Various concerns have been raised about the Type I error and operational bias in unblinded trials, therefore extensive statistical planning is required to control for these issues [44]. Adaptive designs have predominantly been used in pharmacological trials since surgical trials are susceptible for operational bias due to their mostly unblinded nature.

With increasing need for real-world data to inform healthcare policy decisions, many trialists and clinical researches have become interested in registries. In registries data is collected in a standardized way under conditions of common clinical practice ensuring high external validity [47, 48]. Patient- and physician reported data are usually collected. [49, 50] An increasing number of registries has been developed in the past years for administrative, policy and research purposes facilitated by advancement of the quality of electronic health records advances. Registries are low cost, they collect a massive amount of patient data and they do not require a lot of effort to keep updated in comparison to data collection in a clinical trial. There are various types of registries available, such as disease- or condition specific registries, product registries used in post-marketing surveillance and health services registries. Numerous registries have been established in vascular neurosurgery in particular, aimed at post-marketing surveillance of devices used for aneurysm treatment.

Registries are usually designed as prospective observational studies not bound to a specific research question, therefore they have a high degree of flexibility. Despite their high external validity and ability to collect large cohorts of patients, even for rare conditions or events not amenable to study in RCTs, registries have the weaknesses of observational studies, such as observed and unobserved confounding and limited data quality [51]. There are ways to help control for confounding in this type of observational data, such as propensity score methods or E-value [52, 53]. Standardized outcome measures could help improve the quality of collected data. Registries are efficient in use, though the major drawback in this kind of observational design is confounding by indication.

Registry based RCTs (rRCTs) have emerged in the past years as a way to combine the advantages of randomization and low costs and high external validity of registries [47]. rRCTs are pragmatic by design and often address comparative effectiveness research questions [50]. rRCTs are built on a structure of existing large-scale all-inclusive registries. Therefore, patient enrolment can be more efficient and less selective by using existing registries with an advantage of high generalisability. Furthermore, data collection process is less extensive than in classical RCT with the majority of baseline data already available at enrolment [54]. This study design has been increasingly popular in the past years with several successful trials conducted in Sweden and Denmark, such as TASTE-trial based on SWEDEHEART registry

and SORT OUT trials [55, 56]. Due to the relative novelty of this trial design, clear reporting guidelines and guidelines on quality assessment are unfortunately still lacking.

Clinical Relevance in Medical Trials

Recently, the American Statistical Association (ASA) has posted a statement on the correct use of p-value based on a growing concern about its use, fueling the discussion about clinical relevance of results and the amount of false positive findings in trials [57, 58]. Clinical significance can be expressed in different ways depending on the sort of the outcome, such as minimal clinically important difference (MCID), number needed to treat (NNT) or substantially clinical benefit (SCB). MCID and SCB in particular are considered to be a patient-centered concepts aiming to capture the improvement and the value of such improvement for the patients [59]. As MCID is meant to represent the minimal treatment effect of clinical importance trying to define a threshold of subjective change, SCB is a measurement of clinically important change which reflects the intended benefit of an intervention [60–62]. These measures are particularly relevant in studies focusing on incremental cost-effectiveness. A recent snap review has suggested that most published trials with statistically significant results were less likely to be clinically relevant, as for example MCID was only used for sample size calculation and not for the interpretation of results [63].

As SCB and MCID are considered patient-centered measures, PROMs are frequently used to estimate them. However, a large number of PROMs for different patient populations has produced a great variability in estimation of MCID and SCB, making it extremely complex to compare the data across studies [64, 65]. So, considering the increasing attention to clinical relevance in trials, it is important to create more uniformity in this type of measures. One of the recent initiatives in the field PROMs has been the development of PROMIS, which is a collection of item response theory-based item banks that can be administered as short form of computer adapted testing [66]. Computer adapted testing allows for selection of relevant questions for each patient based on earlier answers, resulting in shorter questionnaires with better measurement properties than "classical" PROMs. The aim of this initiative is to disseminate standardized and validated PROMs which can be used across patient groups and medical conditions and to encourage the use of the outcomes which are most meaningful for patients. Next to PROMIS, PCORI and COMET have defined disease specific PROMs. [67, 68] This development could be a great step in increasing clinical relevance of future trials in neurosurgery.

Shared Decision Making

Due to the lack of high-quality evidence, more than one treatment option might be available to treat a patient. Shared decision-making (SDM) is a process that helps patients to consider and share their preferences regarding the pros and cons of the

treatment options, and also helps physicians explicitly to evoke these preferences and incorporate them into the final treatment decision.

That is, it comprises a process in which decisions are made in a collaborative way, where trustworthy information is provided in accessible formats about a set of option, typically in situations where the concerns, personal circumstances, and contexts of patients and their families play a major role in decisions [69]. Elwyn et al. [69] developed the three-talk model of shared decision making which clinicians can use to support them when using SDM. Step one is team talk where you work together, describe choices, offer support and ask about goals and preferences. The next step is a discussion of alternatives using risk communication principles. Lastly, a decision talk could help to get to informed preferences and make preference-based decisions.

Evidence from trials has shown that engaged patients consume less health care resources [70, 71]; furthermore, when doctors are too focused on EBM, preference misdiagnoses (also known as silent misdiagnoses) can be made, causing the patient to receive an unwanted treatment [72]. However, in some situations patients are too ill to engage in their own decision-making. For example, the (neuro) intensive care units where surrogates (often family members or next-of-kin) are required to make decisions on their behalf. A mixed-methods study of 71 audio-recorded physician-surrogate family meeting discussing life-sustaining treatment decisions for an incapacitated patient near the end of life showed that about a third of conversations did not include discussions about the patient's previously expressed preferences or values. In the same study, there was no conversation about the patient's values regarding autonomy and independence, emotional well-being and relationships, physical function, or cognitive function in close to 90% of conferences [73].

Concluding Remark

Keeping in mind the specific characteristics of diseases amenable for neurosurgical treatment and the innovative attitude within neurosurgery, new methodological designs and initiatives aimed to increase the feasibility of trials and generalisability of trial results will have a prominent role in the near future. Especially in fields with a great amount of rare diseases such as neurosurgery, (inter)national registries, enabling both registry based trials and solid observational studies, could further improve clinical research and encourage collaborative multicenter studies.

Both the authors and the editors hope that this book will further encourage the reader to contribute to evidence-based neurosurgery by means of good scientific research which could hopefully contribute to the second edition of this book.

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