42 Pain Management After Total Knee Arthroplasty

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Keynotes

1. Acute postoperative pain as an important issue in TKA contributes to chronic surgical pain and psychological stress symptoms such as anxiety and helplessness.
2. Postoperative pain therapy after TKA should include different multimodal options and start as early as during surgery.
3. Sufficient pain management is essential for early rehabilitation and patient's satisfaction.
4. Patient-controlled analgesia (PCA) is an effective part of multimodal pain regime.
5. There are several supplemental options like corticosteroids, gabapentin, and pregabalin, which are not evaluated conclusively.
6. There is a tendency of moving from epidural anesthesia to peripheral nerve blocks and local infiltration therapy.
7. At present, no recommendation for a particular PNB (peripheral nerve block) for pain management after TKA can be given.
8. There is not enough evidence for conclusive recommendation regarding PNB or LIA andand/or combined techniques of regional anesthetic after TKA.
9. Multimodal analgesia consists in combinations of analgesics acting via different mechanisms to use additive or synergistic activity while minimizing dose-dependent adverse events.

42.1 Introduction

Pain is a complex and multifactorial experience and involves multiple organ systems. The International Association for the Study of Pain (IASP) defined pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage" [1]. One has to consider that pain is always a subjective feeling [2].

Postoperative pain is still a major issue after total knee arthroplasty (TKA), and some patients may develop severe postoperative pain despite modern analgesic therapy. Severe acute postoperative pain is more frequently in younger, obese female patients and those suffering from central

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pain sensitization. Preoperative pain, in the knee or other areas, predisposes to central pain sensitization [3].

Sufficient postoperative pain management after TKA is of fundamental importance. Postoperative pain influences patients recovery and rehabilitation [1] and overall satisfaction [2].

Furthermore acute postoperative pain is one of the predictors contributing to chronic surgical pain besides preoperative pain at the operated area, preoperative pain elsewhere in the body, capacity overload, psychological stress symptoms such as anxiety and helplessness, and others [4].

Currently multimodal analgesia concepts are implemented for assessing different mechanisms of pain and minimizing narcotic consumption to reduce adverse effects of narcotics as nausea, vomiting, and sedation. The aim is to increase patient's participation in early physical activity and patient's satisfaction to utilize rapid patient rehabilitation in terms of fast track protocols. These therapy strategies are not expected to reduce costs and length of hospital stay only. These also lead to enhance recovery and a decreased intake of analgesic drugs [5, 6].

Multimodal concepts in orthopedic surgery may include pre- and postoperative oral/i.v. opioid and/or nonopioid analgetics supplemented by different regional analgesic techniques [5]. Sufficient pain management starts already during surgery.

Studies on the effectiveness of analgesic therapy options after TKA report on different methods of measuring therapy effects. In general morphine consumption after different therapy strategies is analyzed to describe the analgesic potential of alternative therapy options. Opioids are frequently converted to i.v. morphine equivalents in order to establish comparability between study results [7, 8].

Studies on postoperative pain treatment administer a variety of opioids in different dosage forms like fentanyl i.v./i.m, oxycodone, hydromorphone, sufentanil, and additionally different NSAIDs like ibuprofen, celecoxib, and acetaminophen including gabapentanoids like gabapentin. Frequent administration of pain medications starts preoperatively [9].

In addition, therapy effects are reported in terms of different pain scores, visual analog scale for pain (VAS) 0-10 or 0-100 [10], verbal pain score (VPS) [10], and WOMAC pain scale [11] at rest and at mobilization covering postoperative periods from 0 to 72 h [9].

These differences of pain regimes and measuring therapy effects as well as small study populations complicate the evaluation of various therapy options for postoperative pain management. Therefore, currently a globally recognized gold standard analgesic treatment for TKA has not been established [9, 12].

Side Summary
Sufficient pain management starts already during surgery as a multimodal procedure.

42.2 Preoperative Patient Education

It was hypothesized that the outcome of total hip (THA) and TKA may be optimized through preoperative patient education (PPE).

McDonald (2004) found in their meta-analysis of nine studies involving 782 participants less evidence for an advantage of preoperative education versus standard care to improve postoperative outcomes in patients undergoing hip or knee replacement surgery.

Side Summary
Preoperative education does not improve outcome after TKA.

In particular no general recommendation could be given with respect to pain and function [13]. This statement is underlined by a further meta-analysis on the outcome after THA and TKA [14]. No effect was found, except for a significant reduction in preoperative anxiety, which was confirmed by others [13]. The significance of

this conclusion was limited by a general heterogeneity of the studies.

It was stated that there is a strong need for properly designed randomized and controlled studies that are sufficiently powered to draw general conclusions [14].

42.3 Oral or Parenteral Systemic Analgesia

42.3.1 Postoperative Conventional NSAIDs (Nonsteroidal Anti-inflammatory Drugs, COX-2-Selective Inhibitors and Paracetamol)

Conventional NSAIDs are recommended because of their ability to spare opioids and their analgesic effect. Typical NSAIDs which were evaluated for pain are ketoprofen, piroxicam, tenoxicam, acetaminophen, and diclofenac. They should be administered in combination with strong opioids (e.g., oxycodone, oxymorphone, or buprenorphine).

Currently no recommendation is given for exclusive combination of NSAIDs with regional analgesia.

The use of conventional NSAIDs should consider patient-specific risk profile in particular regarding bleeding disorders, gastroduodenal ulcer history, cardiovascular morbidity, aspirin-sensitive asthma, and renal and hepatic functions [15].

Previous studies have shown that conventional preoperative nonselective NSAIDs increase the bleeding risks [16]. Conventional nonselective NSAIDs reversibly inhibit the cyclooxygenase (COX) and interfere with platelet functions. Selective COX-2 inhibitors have less anti-platelet effects than conventional nonselective NSAIDs [17]. Therefore, selective COX-2 inhibitors could be a better choice for multimodal analgesia. Additionally selective COX-2 inhibitors may be associated with decreased gastrointestinal adverse effects and less cardiovascular risk [18].

There are concerns about disturbance of bone healing processes by COX-2-selective inhibitors. At present, no evidence exists to confirm detrimental effects in knee arthroplasty. Their potential of negative influence on bone healing could be an issue for postoperative treatment of fractures [19].

Paracetamol is recommended in combination with other potent analgesic drugs but not as sole agent for pain management after TKA [15].

42.3.2 Opioids

Strong oral opioids (e.g., oxycodone, oxymorphone, or buprenorphine) but not weak opioids (like tramadol) are regarded as appropriate for postoperative pain therapy after TKA. They should be administered in combination with other nonopioid analgesia in order to reduce opioid consumption and associated adverse effects like sedation, dizziness, nausea, vomiting, and obstipation.

No recommendation is given for i.m. application because of inferior pharmacokinetics, injection-associated pain, and therefore patient discomfort [15].

Orthopedic surgery represents a frequent opioid prescribing specialty, and up to 40% of patients with osteoarthritis are already opioid users before surgery. Because of the side effects of opioids, their potential for drug addiction but also the evidence that preoperative opioid use is associated with higher postoperative morbidity and mortality and worse clinical outcomes in total knee arthroplasty prescription of opioids for analgesia after TKA should follow strict indications. One has to consider that there is a considerable risk for chronic postoperative opioid use in patients who received preoperative pain therapy with opioids [20–22].

This, in particular, underlines the importance of a multimodal regime for analgesia after TKA to reduce the use of opioids.

Currently no time point is defined at which patents are expected to wean off their pain medi-

cations after TKA, although three months are regarded as an appropriate period [23].

Side Summary
There is a considerable risk for chronic postoperative opioid use in patients after TKA, therefore wean off of pain medication and particularly opioids should not exceed three months.

42.3.3 Intravenous Patient-Controlled Analgesia (PCA)

Patient-controlled analgesia (PCA) is recommended in preference to other inflexible analgesic opioid regimes because of its potential of improved pain control and higher patients satisfaction [15].

Despite different approaches of analgesia, PCA is still used frequently as one component of multimodal pain therapy after TKA as reported by many trials [24].

PCA empowers patients to have an important degree of control over their pain which is a benefit to reduce anxiety which will in turn reduce pain experience. One considerable advantage is the immediate effect and patient's independency.

However, it is necessary that patients are able to understand the principle to be compliant.

Preferred opioids for PCA should have a rapid onset of effect, a middle effect duration, and a wide therapeutic margin, such as piritramide or morphine [25].

PCA management is complex, and monitoring of patient's compliance as well as pain monitoring is necessary to define the individual setting for loading dose, bolus dose, and lockout interval and background infusion. The optimal dose is the minimum dose to produce appreciable analgesia consistently without producing objective or subjective side effects [26].

Side Summary
PCA is still used frequently as part of a multimodal pain management.

42.4 Continuous Epidural Analgesia (CEA)

Epidural analgesia is widely used after TKA and can be performed as continuous epidural infusion (CEI), patient-controlled epidural analgesia (PCEA), or intermittent epidural bolus (IEB) [27]. Continuous epidural infusion or patient-controlled epidural analgesia (PCEA) with local anesthetic or local anesthetic-narcotic is one of the standard regimes for postoperative analgesia after TKA [28].

This is reflected by the fact that CEA is frequently used as a control against other regimes to investigate the efficiency of pain management strategies in TKA [29, 30].

Choi et al. (2003) concluded that CEA may be useful for postoperative pain relief following major lower limb joint replacements. They found that benefits may be limited to the early (four to six hours) postoperative period compared to systemic analgesia or long-acting spinal analgesia. From their meta-analysis they deducted that epidural infusion of local anesthetic or local anesthetic-narcotic mixture may be better than epidural narcotic alone.

One of the disadvantages of CEA is the difficult evaluation of potential postoperative neurologic deficits. Therefore, the dose has to be carefully titrated to prevent complete sensible and motoric blockage of lower extremities. Severe complications are more frequently associated with regional spinal anesthesia than with peripheral nerve blocks for which reason the trend goes toward those techniques [25].

The differences between CEA and systemic analgesia in the frequency of nausea and vomiting or depression of breathing seem to be not statistically significant. Sedation occurred less frequently with epidural analgesia, otherwise retention of urine, itching, and low blood pressure were more frequent compared to systemic analgesia. It was pointed out that the frequency of rare complications from epidural analgesia, postoperative morbidity or mortality, functional outcomes, or length of hospital stay is inconclusive [31]. The finding of a higher occurrence of adverse effects like retention of urine, itching, and low blood pressure compared to

peripheral nerve blocks (PNB) was also confirmed by others [32].

Anderson et al. (2010) observed superiority of peri- and intra-articular infiltration analgesia with multimodal drugs for postoperative pain relief and reduction of morphine consumption compared with CEA with ropivacaine combined with intravenous ketorolac after TKA. On the other hand, they noted that the concept of CEA varies. There is no "gold standard" of CEA to which all other treatment regimens can be compared, and therefore the epidural regime chosen for their study may not be optimal [28].

In conclusion, one has to consider that analgesic regime with PNB or local infiltration/intra-articular infiltration is superior [28, 30, 33] or at least similar to CEA [34–36] regarding reduction of pain and consumption of opioids or even knee flexion [30].

Current discussion of pain management options after TKA shows that the trend runs toward PNB and periarticular/intra-articular infiltration techniques to avoid immobilization and specific adverse effects of CEA [25].

Side Summary
Currently, epidural anesthesia seems to be superseded by LIA or PNB.

42.5 Peripheral Nerve Blocks (PNB)

Regional techniques of pain management are particularly appropriate for TKA to gain optimal reduction of pain and spare systemic use of opioids to avoid adverse effects. Central neuraxial blockade (CAN, spinal and epidural analgesia) was proven to provide excellent intraoperative anesthesia and postoperative pain management [37].

However, there are side effects such as retention of urine, itching, and low blood pressure. Recently PNB are regarded as potentially optimal postoperative pain management after TKA because of the more specific effect, reduction of adverse effects, and appropriate anesthesia [32].

Several studies have shown that anesthesia by PNB can be as effective as CNA [35, 37, 38] and are associated with improved rehabilitation, reduced hospital stay, sparring effect for opioids, and even superior postoperative anesthesia 0–24 h compared to PCA [9, 32]. One has to note that meta-analyses showed only a low or moderate grade of evidence for pain, reduced hospital stay, and reduction of morphine consumption (GRADE) [9, 39]. However, there is also evidence that PNB may be inferior regarding pain management compared with CEA [30, 40].

Side Summary
PNB after TKA are associated with improvement in postoperative pain control and reduction of opioids.

Furthermore, a block failure rate of 0–67% depending on particular block, experience, and method of nerve localization has to be considered [37].

A review of regional anesthesia following TKA includes 28 trials from 1990 to 2007 with 1538 patients included in 17 trials reported on the effectiveness of different PNB for pain management (of these: 9× single-injection femoral nerve block (sFNB), 7× continuous catheter-based femoral nerve block (cFNB), 7× CEA, 1× obturator nerve block). These treatment options were compared with PCA (n = 9), i.m. morphine (n = 1), obturator block (n = 1), placebo/sham block (n = 4) or CEA (n = 2), or a combination of these in terms of different study arms. In summary this meta-analysis illustrates very impressive heterogeneity of postoperative pain therapy following TKA [24].

The authors concluded that the level of evidence is rather low due to methodology and small sample sizes. If focusing on prevention of cardiovascular morbidity, hypotension, mortality, DVT, or reduction of blood loss, no conclusion could be made on one analgesic technique that should be preferred. This is reflected by limited study numbers on these issues or not reported outcome parameters in the included studies.

In conclusion, it was stated that regional anesthesia reduced postoperative pain and opioid consumption (21 of included 28 trials), even when no significant differences could be shown in this review [24].

In general, this reflects the difficulties to evaluate different techniques of analgesia regarding their potential of pain and opioid consumption due to heterogeneity of studies, low numbers of patients in therapy arms, or lack of adequate numbers of studied to conclude on techniques like adductor canal block (ACB) and sciatic nerve block (SNB) [9].

There is a controversial discussion about a potential increase of falling induced by PNB after TKA. While some retrospective studies could not prove an increased risk of falling [41], a meta-analysis showed more falls in patients with lower extremity continuous peripheral nerve blocks (cPNB) with ropivacaine [42]. Potential risks of PNB are vascular puncture and bleeding, nerve damage, and local anesthetic systemic toxicity (LAST). PNB placement using ultrasound guidance is associated with a lower risk of vascular puncture [23]. Neurologic complications like tingling, pain, or pins and needles are crucial because they can persist for weeks or months after surgery [43].

Side Summary
There is an ongoing discussion about increased risk of fall events associated with femoral nerve blocks.

PNB for pain management after TKA can typically be applied as FNB, as sFNB or cFNB, ACB, and FNB in combination with SNB [9, 24].

In one meta-analysis FNB in combination with SNB did not reveal conclusive results regarding superiority compared with FNB alone [44]. Sciatic nerve block (SNB) is commonly performed in combination with FNB after TKA [45]. FNB provides analgesia of the anterior and medial part of the knee. Therefore, SNB is regarded as an important and useful supplement for analgesia after TKA. There is evidence that the combination of FNB with SNB may be more effective than FNB alone and is therefore recommended [46, 47]. However, a meta-analysis showed no superiority of combining FNB with SNB compared with FNB alone after TKA [48].

Side Summary
PNB for pain management after TKA can typically be applied as FNB, as sFNB or cFNB, ACB, and FNB in combination with SNB.

The rationale behind the cFNB for pain management after TKA is an extended effect of analgesia. On the other hand, cFNB did not show superiority compared with sFNB in meta-analyses [9, 44]. In addition performance of cFNB is more time consuming an invasive [9].

Because of excellent pain relief and opioid-sparing effect, FNB is regarded as standard PNB after TKA [44]. However, there are concerns regarding negative influence on quadriceps strength which may delay mobilization and increase the risk of falls during the early postoperative period [42].

ACB is regarded as a potential alternative which offers almost selective block of sensory without influencing motor function [49]. Like FNB ACB also is performed as single shot or continuous block. ACB leads to complete sensory loss of the medial, anterior, and lateral region of the knee including an area from the superior pole of the patella to the proximal tibia [50]. Recent meta-analyses provide evidence that ACB has the same potential of analgesia compared with FNB without negative effect on muscle strength and with improved mobilization ability [12, 51].

On the other hand, superior functional recovery was limited to 24–48 h, patient satisfaction did not differ, there was no evidence for prevention postoperative falls with ACB, and length of hospital stay was not reduced [12].

Unfortunately, Koh et al. (2017) could not prove significance for these conclusions or state a specific consensus due to heterogeneity of the analyzed studies regarding drug composition, infiltration techniques, and concomitant pain therapy and outcome variables [12].

PNB after TKA is associated with improvement in postoperative pain control and reduction in the use of opioids [9]. At this point in time no specific recommendation can be given regarding a best option for PNB for analgesic pain management after TKA. However, FNB is widely accepted and seems to be a reliable and effective procedure for multimodal pain management after TKA. Study results suggest that sFNB and cFNB are comparable regarding the effect on pain scores [9, 44]. Furthermore, a combination of FNB with SNC may offer advantages for pain management [47]. ACB appears as alternative option compared to FNB with same potential for pain management after TKA and to avoid negative effect on quadriceps strength [51].

Further studies are required to provide conclusive information which PNB is preferable for pain management following TKA.

Side Summary
In summary, there is no proof for preferable PNB for pain management after TKA.

42.6 Periarticular/Intra-articular Infiltration Analgesia and Continuous Intra-articular Analgesia

Local infiltration analgesia (LIA) has established as an alternative technique for pain management after TKA, was shown to be effective for pain relief, and provides a sparing effect for opioids in combination with low rate of infection and local anesthetic toxicity [52].

LIA is administered as peri- or intra-articular injection. The latter can be performed intra- or postoperatively. In addition, postoperative intra-articular catheter placement for prolonged LIA can be used [52].

Periarticular infiltration commonly covers subcutaneous tissue, the capsule including posterior capsule, periosteum, deep tissues around the medial and lateral collateral ligaments, and the fat pad. LIA is a very heterogeneous technique, and infiltration sites, dosage, and drugs differ considerably among different trials [53].

Seamgleulur et al. (2016) performed a meta-analysis including 38 studies to assess the efficiency of LIA in the early postoperative period after TKA. They analyzed 28 trials which compared LIA against no injection or placebo and 10 studies comparing LIA with no injection or placebo with additional use of systemic or regional anesthetic technique. Of these 28 studies, in 11 intraoperative intra-articular injection and in three postoperative intra-articular injection were used. In 12 studies, intraoperative periarticular injection was performed including four studies which used additionally postoperative intra-articular catheter placement. Several substances and dosages were used for infiltration: ropivacaine 190—400 mg, levobupivacaine 150 mg, bupivacaine 30 mg–150 mg–300 mg or 2 mg/kg body weight, morphine 1—5 mg, ketamine 0.25–0.5 mg/kg body weight, and patients with bilateral and unilateral TKA were included in the meta-analysis. Furthermore, several substances were additionally used for LIA: epinephrine, diclofenac, ketorolac, betamethasone, morphine, ketamine, dexamethasone, and methylprednisolone. A mixture of ropivacaine (2.0 mg/mL)–ketorolac (30 mg)–adrenaline (10 μg/mL) diluted in a total of 150 mL with normal saline is well accepted [54]. LIA was performed with different volumes depending on additional substances and the particular solution in saline [52]. This reflects the considerable heterogeneity of studies and different understanding and administration of LIA—there is no consistent concept.

Especially when considering the usage of different mixtures, surgeons should be aware that the injection of a combination of different drugs

at the same time means that they design a new drug. For legal reason one should discuss the usage of mixtures with the pharmacist of the hospital beforehand.

It could be shown that LIA compared with placebo or no injection LIA provides better pain control associated with better range of motion (ROM) and shorter LOS and reduces adverse effects of systematic opioid use like nausea and vomiting [52].

In this meta-analysis, a significant better pain control was found for periarticular infiltration than for the intra-articular group. In fact, only periarticular injection led to better pain control after 24 h, greater reduction of opioid consumption was found, and ROM after 24 h was better in the periarticular group. This conclusion is supported by the findings of another meta-analysis [55].

Intra-articular infiltration was shown to be very effective in a meta-analysis of 1338 patients compared with a placebo group. Significant lower pain score with rest up to 48 h and less opioid consumption up to 72 h postoperatively [56]. On the other hand, this meta-analysis appears to have methodical limitations as two studies did not meet inclusion criteria, two studies included postoperative intra-articular infusion, and one did not administer LIA intraoperatively [52]. Other meta-analyses missed to pool all included studies for their analyses or did not include all available studies due to their inclusion criteria [52, 57].

However, the reduction in VAS in this meta-analysis for periarticular infiltration after 24 h was small (0.89) and disappeared after 48 h when two studies were excluded which used opioids in only one study group of LIA [55].

Also, no conclusion could be drawn for choice of several substances and different doses and administration sites whereas high-dose local anesthetic use seems to be safe. In three studies the plasma concentration was measured which was less than the toxic level. However, it stays questionable if higher doses are associated with better pain relief.

Side Summary
There is no conclusion regarding several suggested substances and dosages for LIA.

The question, if continuous LIA by catheter placement (CLIA) would have superior effects on pain relief and opioid consumption is still unsolved [52]. In one meta-analysis, only two trials were included which compared conventional LIA with CLIA concluded that CLIA can possibly reduce pain up to 48 h during rest and activity. However, the small number of trials and considerable heterogeneity makes it impossible to draw sufficient conclusions [58].

Infection was reported in four of the included total of 735 patients receiving LIA, three of them had intra-articular catheter placement [52].

One unsolved issue is whether the infiltration of the posterior capsule would provide a benefit for pain relief. No conclusion could be drawn from the abovementioned meta-analysis [52]. Pinsornsak et al. (2017) reported no difference between two groups after TKA of which one was provided with posterior capsule infiltration when performing LIA regarding pain relief and reduction of opioid consumption [53]. They concluded that local anesthetic might infiltrate the posterior capsule by following gravity in supine position. Therefore posterior capsule infiltration seems to have no advantages about LIA of the other commonly infiltrated structures of the knee and is therefore not recommended to avoid possible risks like intravascular application of local anesthetic and nerve injury [53].

Side Summary
Infiltration of the posterior capsule did not show superiority compared with LIA without infiltration of the posterior capsule.

PNBs have been proven to be effective for pain management after TKA. However, it is inconclusive if LIA could be beneficial if addi-

tively performed to PNB. Following the results of the meta-analysis performed by Seangleulur et al. (2016), one can expect little benefit by adding LIA to PNB which is probably due to the high efficiency of regional anesthetic techniques [52].

One meta-analysis comparing LIA or SNB as an adjunct to FNB which included seven clinical trials did not reveal conclusive differences and therefore concluded that LIA may be an alternative to SNB when combined with FNB [59].

In an attempt to increase the duration of local anesthetic action also, liposomal bupivacaine was used for LIA. Liposomal bupivacaine (LB) is an amide local anesthetic and consists of vesicles of bupivacaine loaded in the aqueous chambers using DepoFoam® technology (Pacira Pharmaceuticals Inc, San Diego, CA). The particles are structured like a honeycomb and contain numerous internal aqueous chambers containing encapsulated bupivacaine. This very cost-effective anesthetic is supposed to provide increased duration of analgesia compared to standard local anesthetic solutions [60].

Mont et al. (2017) performed a prospective randomized trial comparing LB with standard bupivacaine (SB) for LIA after TKA and concluded a considerable opioid-sparing effect when LB was administered [61]. Furthermore, there is evidence that the high costs could be compensated by lower opioid consumption and overall hospital costs for USA health care system [62].

However, meta-analyses are unable to conclude about the usage of LB for LIA after TKA [52].

In addition, it was investigated whether LIA in combination with steroids could decrease surgical pain by reduction of prostaglandin production and increased vasodilation. In summary, the current meta-analysis is not conclusive enough regarding the use of steroids for LIA due to a low number of trials and heterogeneous results and outcome parameters [63].

The situation of inconclusive results about several issues of LIA like catheter placement, sites of infiltration and volumes, substances, and dosages is further complicated by different meta-analyses which have different priorities.

In fact, LIA was proven to be effective as part of a multimodal pain management after TKA at least up to 24 h [52] and is regarded as an alternative option among others in particular PNB [52, 55, 57].

Side Summary
LIA is regarded to be effective as a part of pain management.

42.7 Comparison of LIA and PNB and Combining Techniques

The technique for peripheral pain management during the perioperative periode in TKA remains controversial. Concerns regarding the quadricpes muscle function to facilitate early mobilisation favors the usage of LIA alternatively to PNB.

LIA was frequently evaluated against FNB as this regional anesthesia is regarded as one of the standard PNB after TKA. LIA has shown to be at least as effective as sFNB [64–66], but less effective as cFNB [67] which might be comprehensible by the enhanced effect of regional anesthesia in a continuous nerve block.

As expected there are controversial results, and Mei et al. [65] included trials with partially conflicting results in their meta-analysis even though overall quality of FNB and LIA was concluded.

Some studies compared the combination of FNB and LIA with FNB and SNB as this is regarded as useful combination after TKA.

As already stated, no evidence is presented to prove superiority of combining FNB with SNB compared with FNB alone after TKA [49].

The evaluation of analgesic effect of FNB/SCB versus FNB/LIA by meta-analysis showed no difference [59] despite there being single trials with conflicting results [68]. However, the evidence of the prospective study by

Nagafuchi et al. (2015) to evaluate analgesic potential of FNB/SCB vs. FNB/LIA was rather low. Seventeen patients were included. Furthermore in this trial a combination of periarticular and intra-articular infiltration was administered, 70 mL for subcutaneous/periarticular infiltration was used [68], and outcome parameters (pain scores) were assessed for 24 h only.

Currently, there is not enough evidence for conclusive recommendation regarding PNB or LIA and combined techniques of regional anesthetic after TKA.

42.8 Corticosteroids

Steroids are applied for postoperative pain management in TKA as peri-/intra-articular infiltration or systemically (in general intravenously). The use of steroids and its possible advantage was discussed under paragraph 42.5.

The mechanism of modulation by which steroids may influence pain after TLA is not completely understood. It is hypothesized that steroids reduce the nociceptive input into the spinal cord [69]. Furthermore, steroids may act by suppressing CRP, which is involved in the modulation of nociception [70]. It was found that perioperative use of single, low-dose corticosteroids significantly decreased inflammatory markers after TKA [71].

Among several trials with smaller sample sizes, Koh et al. (2013) randomized 269 patients undergoing TKAs and received dexamethasone (10 mg) 1 h before surgery and ramosetron immediately after surgery (n = 135), or ramosetron alone (n = 134). They assessed the incidence of postoperative nausea and vomiting (PONV), pain level, and opioid consumption.

The Dexa-Ramestron group had a lower incidence of PONV during the entire 72-h evaluation period. In addition, lower pain and less consumption of opioids during the 6–24-h period was observed. No differences were found regarding wound healing disturbances or periprosthetic joint infection.

Other studies on efficiency of corticosteroids for reduction of pain after TKA involved only smaller sample sizes of about 25 patients per group and showed considerable heterogeneity regarding type, dosage (dexamethasone single dose 4–25 mg i.v.), and administration protocol of corticosteroids and concomitant pain control regime [72–74]. These differences make it difficult to evaluate beneficial effects of corticosteroid use after TKA.

Also, one has to consider a potential risk for infection associated with the use of corticosteroids during the perioperative period [75].

Side Summary

At present, no recommendation can be given for general use of systemic corticosteroids to supplement analgesic regime after TKA.

42.9 Gabapentinoids

Gabapentin and pregabalin are gabapentinoids and act at the α 2 δ subunit of a calcium channel which is involved in the regulation of neurotransmitter release.

Both are assigned to the group of antiepileptic drugs and are additionally administered for treatment of neuropathic pain and for generalized anxiety disorder. The effects are based on a decrease in neuronal excitability [76, 77].

In addition, gabapentin and pregabalin are administered for conditions of acute postoperative pain and are administered as supplemental analgesic therapy in TKA. Commonly gabapentin is given preoperatively but also may be used pre- and postoperatively [77].

Zhai et al. (2016) included six trials and 769 patients in their meta-analysis about the effect of gabapentin on acute postoperative pain after TKA [78]. They included studies with administered doses of 400–600 mg gabapentin preoperatively and 200–1200 mg postoperatively. Intraoperative pain management was different

and consisted of local infiltration, general and spinal analgesia. Likewise the postoperative analgesia showed differences and included acetaminophen, celecoxib, PCA, NSAIDs, and morphine. VAS at 24 and 48 h rest showed a mean difference of −3.47 at 24 h and −2.25 at 48 h for the gabapentin group. With mobilization, no significant differences were found. The analysis of the cumulative morphine consumption after 24 and 48 h via PCA did not reveal significant superiority of gabapentin treatment.

One limitation of this meta-analysis is the inclusion of one non-RCT [79]. Furthermore, the study population was low in particular in one trial [80], including a therapy group of only 29 and a control group of only 7 patients. The average age of patients in one included trial was 36 years, which is an unusual age for osteoarthritis treated by TKA and may have influenced the results [79].

In contrast Han et al. (2016) who partially included the same trials [80–82] concluded that there was no significant difference in VAS after 12, 24, and 48 h postoperatively. Furthermore, no difference for postoperative knee flexion was found between gabapentin and control groups [77].

Both research groups conclude that the number of studies and included patients is low. They stated that there is no consensus regarding the dosage and duration of gabapentin when administered for postoperative pain management in TKA [77, 78].

There is one meta-analysis on the efficiency of pregabalin for the management of THA and TKA. In this analysis, four trials of TKA were included, which represents a study population of 510 patients. The dosage of pregabalin for TKA patients was 150 or 300 mg preoperatively and daily postoperatively. Only one trial for TKA showed significant difference for morphine consumption between the pregabalin and control groups [83]. Only one study reported superior results for VAS at movement at 24 h [83]. There were only two studies reporting on flexion results among the TKA trials. Flexion results were significantly different at 48 and 72 h, but clinical relevance was low (improvement of 2 and 7 degrees respectively after 72 h) [76].

Side Summary

At present, no recommendation can be given for additional use of gabapentin and pregabalin for supplemental analgesia after TKA.

Take Home Message

Multimodal analgesia refers to the use of combinations of analgesics acting via different mechanisms and thus taking advantage of additive or synergistic activity while minimizing adverse events with larger doses of a single analgesic [3]. Evidence-based multimodal techniques are procedure specific and may include combinations of systemic analgesics (e.g., opioids, acetaminophen, nonsteroidal anti-inflammatory drugs), neuraxial analgesia (spinal, epidural, and combination spinal/epidural), local infiltration, and peripheral nerve blocks [84].

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