European Spine Journal (2023) 32:289–300
https://doi.org/10.1007/s00586-022-07469-4

REVIEW ARTICLE

Opioid versus non-opioid analgesia for spine surgery: a systematic review and meta-analysis of randomized controlled trials

Kamath Sriganesh[1] · Suparna Bharadwaj[1] · Harsha Shanthanna[2] · Ganne S. Umamaheswara Rao[1] · Boris W. Kramer[3] · Talakad N. Sathyaprabha[1,4]

Received: 21 September 2022 / Revised: 28 October 2022 / Accepted: 12 November 2022 / Published online: 28 November 2022

Abstract

Purpose Opioids are the primary analgesics used in patients undergoing spine surgery. Postoperative pain is common despite their liberal use and so are opioid-associated side effects. Non-opioid analgesics are gaining popularity as alternative to opioids in spine surgery.

Methods This systematic review evaluated current evidence regarding opioid and non-opioid intraoperative analgesia and their influence on immediate postoperative pain and adverse events in spine surgery.

Results A total of 10,459 records were obtained by searching Medline, EMBASE and Web of Science databases and six randomized controlled trials were included. Differences in postoperative pain scores between opioid and non-opioid groups were not significant at 1 h: 4 studies, mean difference (MD) = 0.65 units, 95% confidence intervals (CI) [−0.12 to 1.41], $p = 0.10$, but favored non-opioid at 24 h after surgery: 3 studies, MD = 0.75 units, 95%CI [0.03 to 1.46], $p = 0.04$. The time for first postoperative analgesic requirement was shorter (MD = −45.06 min, 95%CI [−72.50 to −17.62], $p = 0.001$), and morphine consumption during first 24 h after surgery was higher in opioid compared to non-opioid group (MD = 4.54 mg, 95%CI [3.26 to 5.82], $p < 0.00001$). Adverse effects of postoperative nausea and vomiting (Relative risk (RR) = 2.15, 95%CI [1.37 to 3.38], $p = 0.0009$) and shivering (RR = 2.52, 95%CI [1.08 to 5.89], $p = 0.03$) were higher and bradycardia was lower (RR = 0.35, 95%CI [0.17 to 0.71], $p = 0.004$) with opioid analgesia.

Conclusion The certainty of evidence on GRADE assessment is low for studied outcomes. Available evidence supports intraoperative non-opioid analgesia for overall postoperative pain outcomes in spine surgery. More research is needed to find the best drug combination and dosing regimen.

Prospero Registration: CRD42020209042.

Keywords Adverse events · Spine surgery · Non-opioid analgesia · Opioids · Postoperative pain · Systematic review

Introduction

Opioids are the primary analgesics used for perioperative pain management both in developed and developing world [1, 2]. However, considering their potential for abuse and undesirable side effects in patients undergoing spine surgery [3], non-opioid analgesics including loco-regional and multimodal analgesia techniques are increasingly utilized to reduce or avoid perioperative opioid administration [4–8]. Many patients undergoing spine surgery have preexisting pain and these patients continue to experience pain in the postoperative period as well [9]. For early ambulation and discharge after spine surgery, pain management strategies should begin before surgery, continue intraoperatively and extend into the postoperative period. Postoperative pain can

Kamath Sriganesh and Boris W Kramer conceptualized the study.

✉ Kamath Sriganesh
drsri23@gmail.com

[1] Department of Neuroanaesthesia and Neurocritical Care, National Institute of Mental Health and Neurosciences, Neurosciences Faculty Block, 3rd Floor, Bengaluru, India

[2] Department of Anesthesia, McMaster University, Hamilton, ON, Canada

[3] Maastricht University Medical Center, The Netherlands, School of Women's and Infants' Health, University of Western Australia, Perth, Australia

[4] Department of Neurophysiology, National Institute of Mental Health and Neurosciences, Bengaluru, India

be minimized to a great extent with good intraoperative analgesia, yet a significant variance and bias in intraoperative pain management is seen [10]. There are limited randomized controlled trials (RCTs) which have directly compared to postoperative pain outcomes in patients undergoing spine surgery receiving intraoperative opioid analgesia versus non-opioid analgesia [11–16]. Moreover, these primary studies had small sample size to instill confidence for change in current practice.

The purpose of this systematic review was to identify RCTs comparing intraoperative administration of opioid with non-opioid analgesia in patients undergoing spine surgery and inform pooled estimates of effect for pain relief and adverse outcomes. We assessed postoperative pain scores at 1 and 24 h after surgery, time to first requirement of rescue analgesia and opioid use in the first 24 h after spine surgery as our primary objectives. Our secondary objectives were to compare adverse events related to opioid and non-opioid analgesia such as postoperative nausea and vomiting (PONV), pruritis, sedation, respiratory depression, shivering, bradycardia and hypotension and recovery characteristics of time to respond to verbal commands, peri-extubation hemodynamics and discharge time from the postanesthesia care unit (PACU).

Methods

This systematic review was registered with the PROSPERO- CRD42020209042 on 14-10-2020 [17]. This manuscript is prepared as per PRISMA guidelines [Appendix S1: PRISMA checklist].

Inclusion and exclusion criteria

We included RCTs that compared opioid with non-opioid as the primary intraoperative analgesia technique in adult patients undergoing spine surgery. Trials were included if both groups had received similar anesthesia and differed only with regard to the primary analgesics used for surgery. Included studies were allowed to use a single dose of short acting opioid for induction in both groups, considered primarily to mitigate stress response during intubation. No language or publication restrictions were applied at initial search stage. Non-RCTs, studies in children, involving non-spine surgery population, comparing postoperative opioid and non-opioid analgesia administration for pain management, where randomization was performed at the end or after the surgery, and which did not report any pain outcome were excluded for this review.

Database sources

We searched the electronic databases of Medline, EMBASE and Web of Science from their inception till March 19, 2022. We considered additional strategies to identify studies including physical reviews of reference lists from articles that fulfilled our inclusion criteria and 'related articles' option in PubMed.

Search strategy

An experienced librarian and the first author performed the literature search using a predefined strategy for all the three databases. The search terms included study population of spine surgery, study interventions and comparators involving any opioid and non-opioid drugs during surgery and any pain outcome. Our search strategy for the databases is available as an appendix [Appendix S2: Search strategy].

Study selection

Two reviewers (KS and SB) independently screened the studies for selection in two stages. A calibration exercise was performed between the reviewers to ensure consistency in screening and selection before the start of screening. Titles and abstracts were screened initially using Rayyan software tool (http://rayyan.qcri.org), following which full-text review was performed. Disagreements were addressed by consensus and if unresolved, settled by a senior author. A quadratic kappa statistic on full-text selection was estimated as a measure of inter-observer agreement [18].

Data extraction

The same pair of reviewers (KS and SB) extracted data from the included studies independently and in duplicate, using Microsoft Excel worksheet. An instruction sheet was provided to help in the data extraction process. Extracted data included study and patient characteristics, interventions and comparators, definitions, scales used and time of assessment of outcomes (continuous or binary measures) and potential Risk of Bias (RoB). We contacted individual study authors to obtain missing data or clarify items related to the study.

Risk of bias assessment

The RoB of individual studies was assessed independently by same reviewers (KS and SB) using Cochrane RoB tool

2 for RCTs. Components of potential bias arising from the randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in measurement of the outcome and bias in selection of the reported result were obtained [19]. The RoB was classified as low, some concerns and high. Any discrepancies were resolved through discussion. Individual study authors were not contacted to clarify RoB items. Bias in selection of the reported result was considered if the results section did not report the outcomes described in the methods.

Outcome assessment

The primary outcome was postoperative pain score. Other outcome measures were postoperative opioid consumption during first 24 h after surgery, time for first requirement of rescue analgesia, adverse events and recovery from anesthesia (time to respond to verbal commands, peri-extubation heart rate [HR] and mean blood pressure [MBP]). Postoperative pain details were extracted as reported in the primary studies (pain score used, description of pain as continuous and categorical outcomes and time points of pain assessment). For meta-analysis, we considered the most commonly used time points of 1 and 24 h after surgery for pain scores. For pain assessment expressed as continuous scores, we transformed outcomes to a 0–10 scale, (0 = no pain, 10 = severe pain), as it is the most commonly used tool and is easy to interpret [20]. Adverse events were evaluated by comparing the risk of commonly reported adverse events—PONV, pruritis, sedation, shivering, respiratory depression, bradycardia and hypotension. When multiple time points were reported, the most commonly reported time points were considered for pooling of the outcome results.

Synthesis of results and summary measures

The extracted data were compiled using Microsoft Excel, and analysis was performed using Review Manager Software (RevMan version 5.4.1) [Computer program] The Cochrane Collaboration, 2020. Meta-analysis was performed only if there were two or more studies for an outcome domain. A random effects model (inverse variance statistical method) was used for analysis. We calculated risk ratio (RR) for dichotomous outcomes and mean differences (MD) for continuous outcomes with their 95% confidence intervals (CI). We used Cochran's Q test to estimate statistical heterogeneity and describe variability in individual effect estimates with I^2 statistic. When trials had more than two interventions, we compared data of only opioid and non-opioid group. The quality of evidence was assessed using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) approach [21], with a summary of findings table.

Additional analysis

A subgroup analysis was planned if sufficient numbers of studies were available to interpret heterogeneity among studies depending on the types of intervention (non-opioid) and comparator (opioid).

Results

Study selection

Our search of the three databases retrieved 10,459 articles which after removal of duplicates resulted in 7929 records. The titles and abstracts were then screened resulting in 332 records for full-text review. Among these, 6 studies were selected after exclusion of 326 reports as noted in PRISMA 2020 flow diagram in Figure 1. A substantial agreement (kappa = 0.76) was observed for full-text assessment between the two reviewers.

Study characteristics

The study characteristics of the included studies such as surgery duration, age, gender, opioid and non-opioid drugs used, primary pain outcome and postoperative follow-up period are shown in Table 1. Three studies used remifentanil, two used fentanyl and one used morphine as the opioid intervention while five studies used dexmedetomidine and one study used ketamine as the non-opioid intervention. One study had three groups, with the third group combining opioid and non-opioid interventions [11]. In all except one study [15], the analgesic drugs were administered as intravenous infusions throughout the surgery.

Risk of bias findings

The potential RoB was high for three studies based on their randomization process and bias due to missing outcome data, some concern for one study for bias due to deviation from intended intervention and low for two studies. Figure 2 informs the potential RoB of included studies for various domains.

Study outcomes and synthesis of results

Of the included studies, three reported pain score, two reported time to first analgesic requirement and one study reported 24-h opioid consumption after surgery as their primary pain outcome. Five studies reported at least

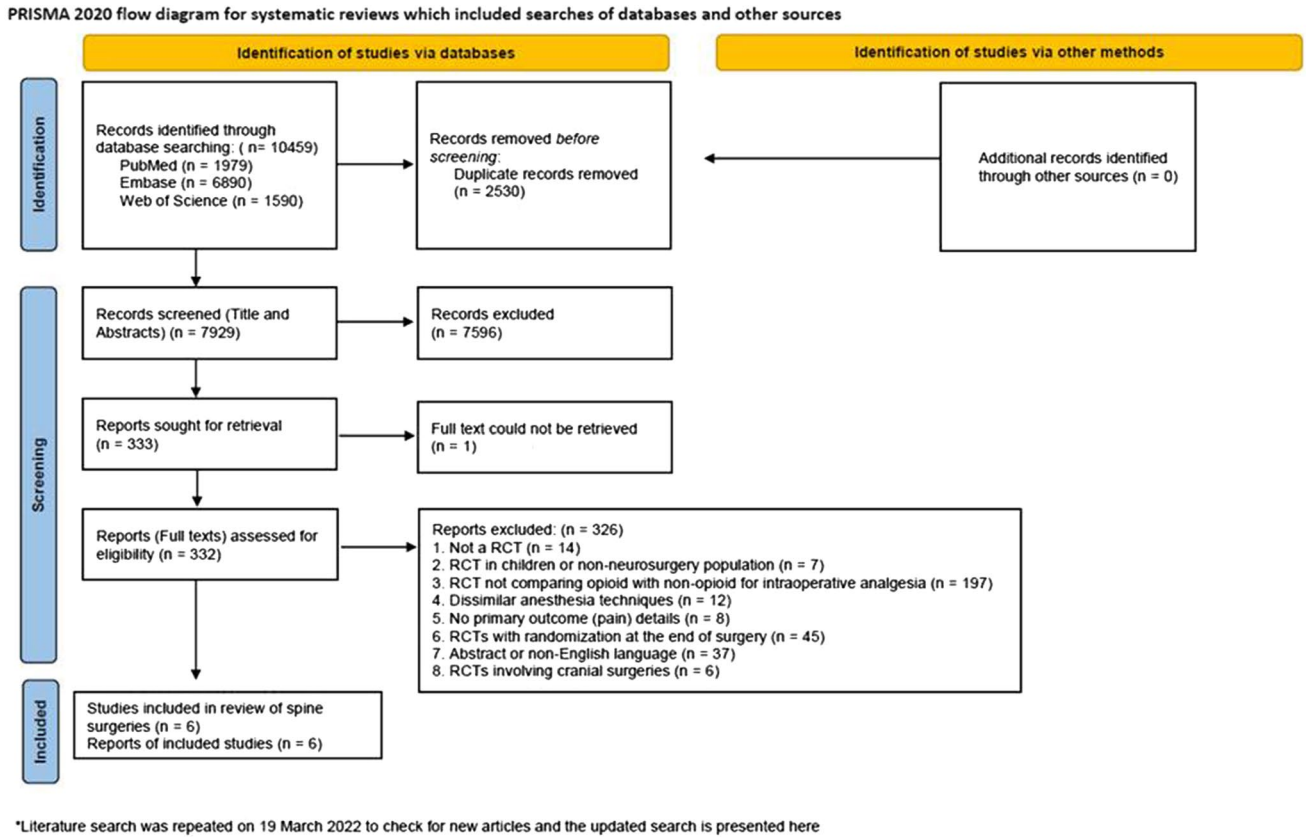

Fig. 1 PRISMA flow diagram informing records obtained after search of databases

one adverse event and four studies at least one recovery characteristic.

The time points of postoperative pain assessment varied from immediately after surgery up to 48 h with most studies reporting pain scores at 1 and 24 h after surgery. Hence, meta-analysis was performed for pain scores at these two time points. All the studies reported pain scores as visual analog scale except one where pain score was not informed. One study reported pain on a 0 to 100 scale [11], which we converted to 0–10 scale for pooling. The time for first analgesic requirement and 24-h opioid consumption after surgery were reported by three studies each.

There was no difference in pain score between opioid ($n=101$) and non-opioid ($n=101$) group at 1 h after surgery: 4 studies, mean difference (MD) = 0.65 units, 95% confidence intervals (CI) [−0.12 to 1.41], $p=0.10$. (Figure 3a) However, a statistically significant but clinically nonsignificant reduction in pain score was observed with non-opioid ($n=71$) compared to opioid ($n=71$) analgesia at 24 h after surgery: 3 studies, MD = 0.75 units, 95%CI [0.03 to 1.46], $p=0.04$. (Figure 3b) The time for first postoperative analgesic requirement was longer in the non-opioid group (MD = 45.06 min, 95%CI [17.62 to 72.50], $p=0.001$) (Figure 3c), and morphine consumption during first 24 h after surgery was higher in the opioid group (MD = 4.54 mg, 95% CI [3.26 to 5.82], $p<0.00001$). (Figure 3d) In one study [13], hydromorphone was used and this was converted to morphine equivalent using a conversion of 1 mg hydromorphone equals to 5 mg of morphine [22].

The adverse events evaluated in the included studies were PONV ($n=5$), shivering ($n=3$) and perioperative bradycardia ($n=2$). The incidence of PONV was significantly higher in the opioid group as compared to non-opioid group (RR = 2.15, 95% CI [1.37 to 3.38], $I^2=1\%$, p = 0.0009). (Figure 4a) The incidence of postoperative shivering was also significantly higher in the opioid group vis-à-vis non-opioid group (RR = 2.52, 95% CI [1.08 to 5.89], $I^2=15\%$, $p=0.03$). (Figure 4b) The incidence of perioperative bradycardia was, however, significantly lower with opioid analgesia as compared to non-opioid analgesia (RR = 0.35, 95%CI [0.17 to 0.71], $I^2=0\%$, $p=0.004$). (Figure 4c) We did not perform a meta-analysis for sedation as the sedation scores used were different in all the studies reporting it (Ramsay Sedation Scale[15], four-point scale[11] and an unnamed scale[14])

Table 1 Characteristics of included studies: Population, intervention, comparator, outcome and study duration

Sl No	Study author, Year, Population	Surgery duration (min)		Age (years) Mean [SD]		Male gender (n/total)		Intervention	Comparator	Primary pain outcome assessed	Follow-up period
		Opioid	Non-opioid	Opioid	Non-opioid	Opioid	Non-opioid	Opioid [Route]	Non-opioid [Route]		
1	Alansary 2019 lumbar disk surgery	103.9 [5.7]	102.6 [5.9]	41.5 [7.4]	43.2 [7.4]	23/40	27/40	Fentanyl [Epidural]	Dexmedetomidine [Epidural]	Time to first analgesic requirement	24 h
2	Aveline 2006 lumbar disk surgery	36.8 [14.8]	40.6 [18.1]	44.4 [11.2]	44.8 [8.4]	10/23	11/22	Morphine [IV]	Ketamine [IV]	24-h morphine consumption	48 h
3	Hwang 2015 posterior lumbar interbody fusion	171.1 [23.2]	177.2 [23.9]	65.1 [5.3]	65.9 [5.8]	8/18	8/19	Remifentanil [IV]	Dexmedetomidine [IV]	Postoperative pain score	48 h
4	Janatmakan 2021 Lumbar discectomy	Not clear	Not clear	45.2 [6.72]	46.7 [6.83]	17/30	16/30	Remifentanil [IV]	Dexmedetomidine [IV]	Postoperative pain score	24 h
5	Rahimzadeh 2015 Posterior spinal fusion	Not clear	Not clear	54 [7.7]	55.6 [9.0]	21/30	18/30	Remifentanil [IV]	Dexmedetomidine [IV]	Postoperative pain score	6 h
6	Turgut 2008 lumbar laminectomy	85	84	42.6 [9.0]	36.5 [10.3]	9/25	8/25	Fentanyl [IV]	Dexmedetomidine [IV]	Time to first analgesic requirement	Not clear

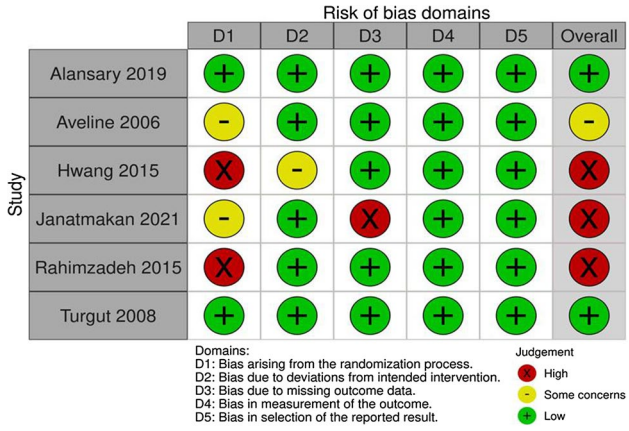

Fig. 2 Potential RoB of included studies for various domains

and at different time points (at extubation, in the PACU and overall during the 48-h study period). No study reported respiratory depression while only one study reported pruritis (15% versus 0% in opioid and non-opioid group)[15].

The recovery characteristics between opioid and non-opioid groups were reported in the included studies as time to respond to verbal commands ($n=2$), PACU discharge time ($n=3$), and peri-extubation HR ($n=2$) and MBP ($n=2$). The time to respond to verbal commands was significantly shorter with opioid analgesia than with non-opioid analgesia (MD = −14.25 min, 95% CI [−20.86 to −7.64], $I^2=82\%$, $p<0.0001$). (Figure 5a) The peri-extubation HR was significantly higher in opioid group than non-opioid group (MD = 12.81 beats per minutes, 95% CI [8.06 to 17.55], $I^2=74\%$, $p<0.0001$). (Figure 5b) The peri-extubation MBP was also higher in opioid group as compared to non-opioid group (MD = 10.99 mmHg, 95% CI [1.55 to 20.43], $I^2=93\%$, $p=0.02$). (Figure 5c) The discharge time from the PACU was similar for patients receiving opioid and non-opioid analgesia during surgery (MD = −4.88 min, 95% CI [−16.86 to 7.10], $I^2=97\%$, $p=0.42$) (Figure 5d).

Our planned subgroup analysis for individual opioid and non-opioid drugs was not possible due to an insufficient number of studies for analysis of our primary outcome. The GRADE quality of evidence was assessed using GRADEpro GDT software [23] and is presented in Table 2. The certainty of evidence on GRADE assessment was low to very low for pain score at 1 and 24 h after surgery, moderate to low for adverse events (PONV and shivering) and low to very low for recovery outcomes (awakening time and PACU discharge). Most were rated low due to RoB and inconsistency, imprecision or indirectness for outcome measures.

Publication bias

Publication bias was checked for primary outcome using funnel plots and Egger's test. We did not find publication bias, as evidenced by symmetric funnel plot [Appendix S3A and B: Funnel plot for postoperative pain scores at 1 and 24 h, respectively] and statistically insignificant Egger's test ($P=0.092$ and 0.088 for 1 and 24 h pain scores).

Discussion

Summary of findings

In this systematic review and meta-analysis of patients undergoing spine surgery, postoperative pain scores were similar at 1 h but lower at 24 h after surgery with intraoperative use of non-opioid as compared to opioid analgesia. Also, the time for the first analgesic requirement was longer and morphine consumption during the first 24 h after spine surgery was lesser in the non-opioid analgesia group vis-à-vis opioid group. Opioid-related adverse effects of PONV and shivering were higher and perioperative bradycardia was lower with opioid analgesia. Although the response time to verbal commands was faster with opioids, the PACU discharge time was similar between opioid and non-opioid groups. However, peri-extubation HR and MBP were lower with non-opioid analgesia as compared to opioid analgesia group.

Review of literature

More than 50% of patients report pain during the first 24 h after spine surgery [24]. This high incidence of pain is despite opioids being the most common analgesics used during the intraoperative period. Moreover, opioid adverse effects are common. To overcome these limitations, opioid alternatives are studied. However, very few RCTs have directly compared intraoperative opioids with non-opioid analgesics with regard to postoperative pain in patients undergoing spine surgery [11–16]. Most of the included studies reported using remifentanil and dexmedetomidine as the opioid and non-opioid analgesic drugs, respectively, during the intraoperative period. Remifentanil is an ultra-short acting analgesic while dexmedetomidine has a significant residual analgesic effect after discontinuation of the infusion [13, 25]. The difference in postoperative pain scores in this review between opioid and non-opioid groups at 24 h but not at 1 h after spine surgery could reflect these differential drug effects or remifentanil-associated hyperalgesia [26]. The overall pain scores in the non-opioid group were 0.65 units and 0.75 units lower than the opioid group at 1 h

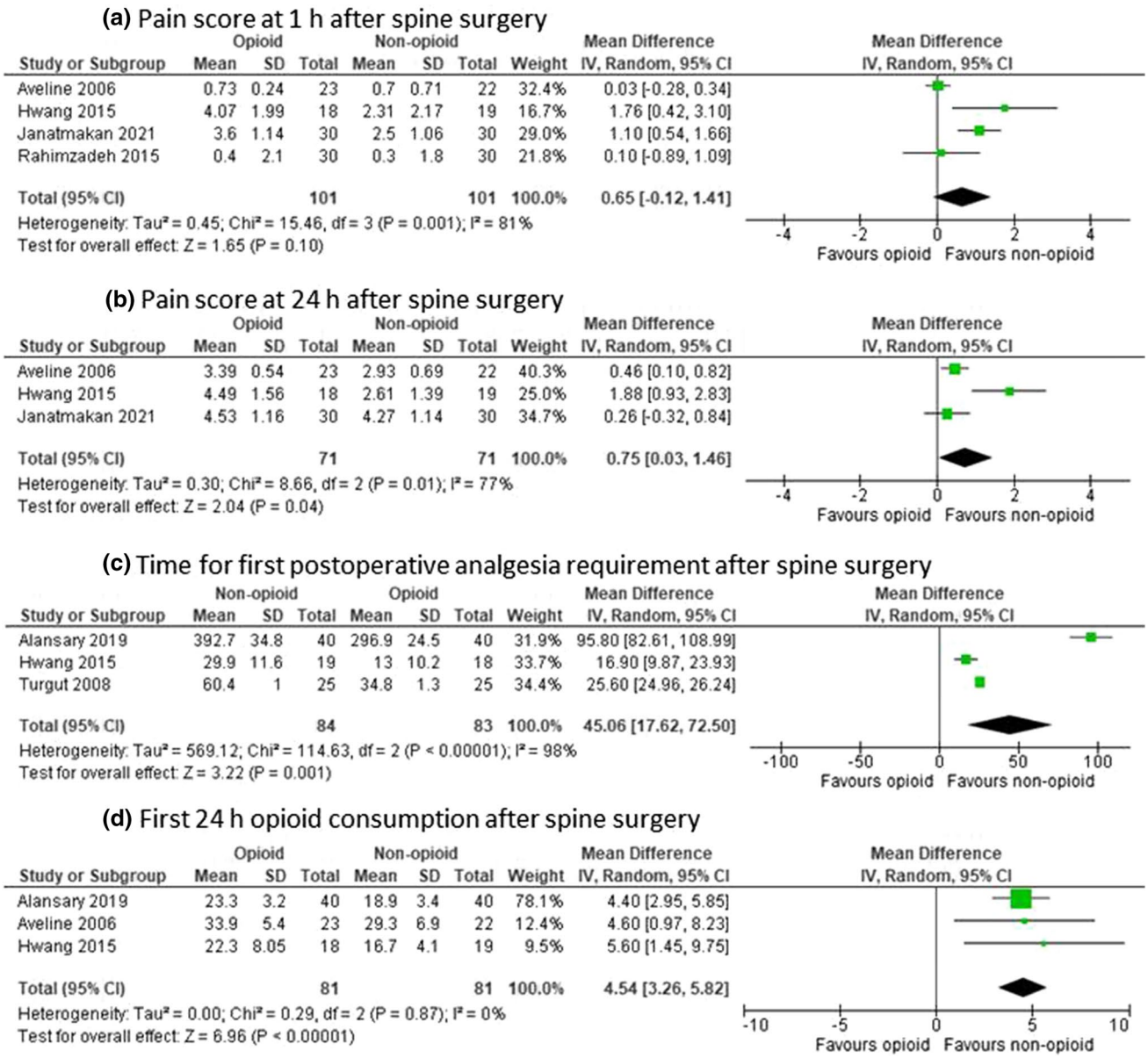

Fig. 3 **a** Postoperative pain score at 1 h after surgery. **b** Postoperative pain score at 24 h after surgery. **c** Time for first postoperative analgesia requirement. **d** First 24 h opioid consumption after surgery

and 24 h, respectively. A previous systematic review noted that the minimum clinically important difference ranged between 0.8 and 4 cm on a 0–10 cm scale for acute pain [27]. Considering this finding, our observation of smaller difference in pain scores can be considered as not important [28]. However, we observed meaningful differences in the time to first rescue analgesia and morphine requirements in the first 24 h after surgery. In addition, we observed reduced risks of adverse events (PONV and shivering) in the non-opioid group. These findings of better pain-related effects and lower drug-related adverse events with non-opioids are likely to influence anesthesiologist's clinical decisions regarding choice of intraoperative analgesics for postoperative pain management.

Fear of opioid side effects has often led to under treatment of pain. However, several non-opioid analgesia options are available and effective for pain relief in patients undergoing spine surgery. Non-opioid multimodal intraoperative analgesia including loco-regional technique such as erector spinae plane block [5, 8], and systemic drug infusions of dexmedetomidine [29], ketamine [30], lignocaine [31] and gabapentinoids [32], and drugs such as NSAIDs, cyclooxygenase-2 inhibitor and paracetamol [33] have shown to provide better analgesia and reduce opioid consumption

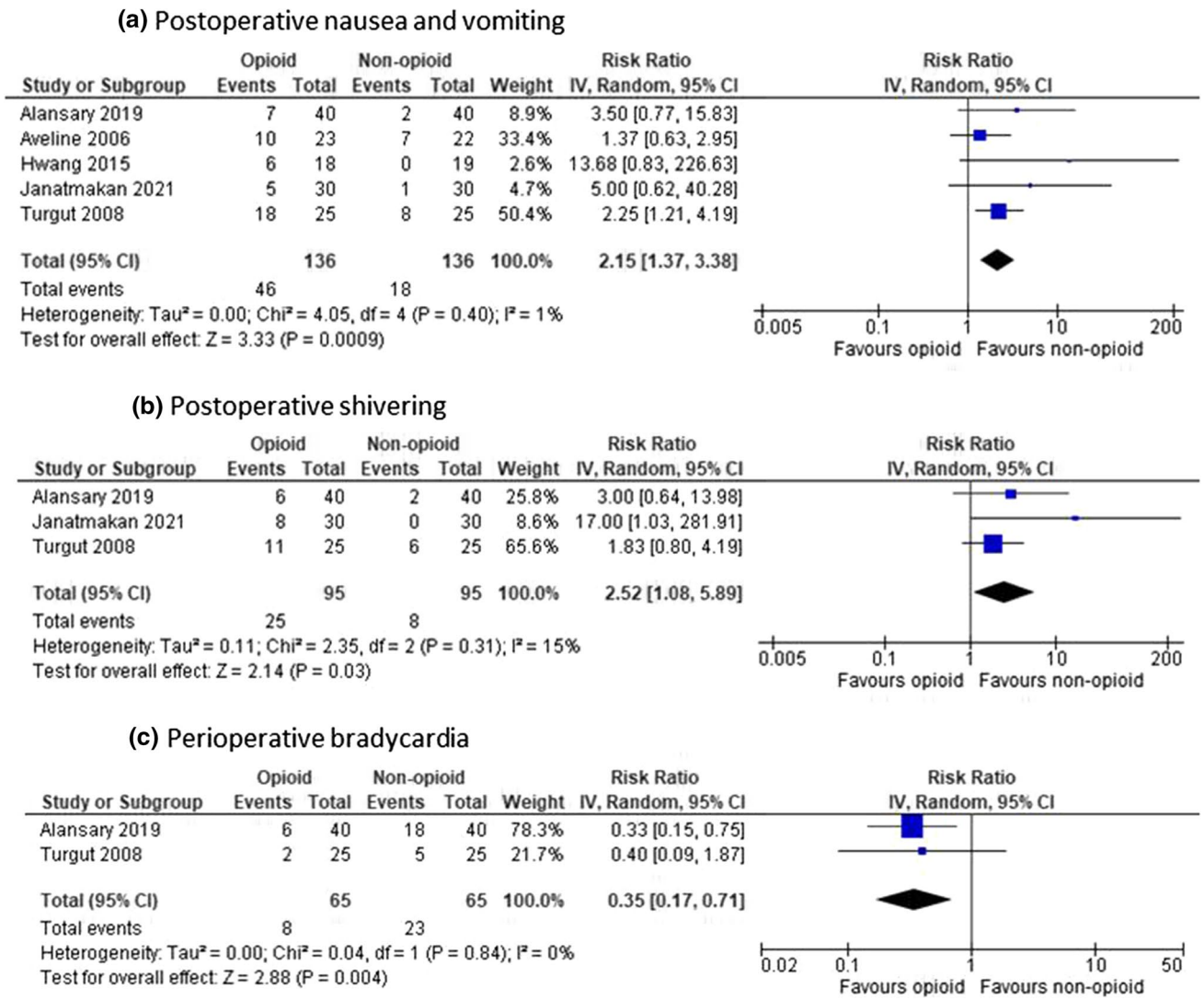

Fig. 4 **a** Comparison of postoperative nausea and vomiting. **b** Comparison of postoperative shivering. **c** Comparison of perioperative bradycardia

(consequently, reduce adverse effects) in patients undergoing spine surgery as compared to opioids alone [4]. Most of these non-opioid analgesics are used in combination and not as the sole analgesic. In our review too, most of the included studies reported using less potent non-opioid analgesics such as paracetamol or NSAIDs during or at the end of surgery in both opioid and non-opioid groups. Ideally, loco-regional and multimodal analgesia must be maximally employed for pain relief as non-opioid interventions and compared with opioids. Consequently, for such comparisons, the effect size is likely to be different.

Strengths and limitations

This is the only review to our knowledge that compared opioid and non-opioid intraoperative analgesia for postoperative pain in patients undergoing spine surgery. Previous reviews reported mainly on postoperative analgesia comparisons with regard to pain outcome. Our findings will help anesthesiologists make informed evidence-based decisions on the choice of intraoperative analgesia for spine surgery. However, our review has certain limitations. We observed a lack of uniformity in reporting pain outcomes such as time of assessments and type of opioid and non-opioid analgesics used in the included studies. Two studies reported using bolus fentanyl (opioid) in both the groups at anesthetic induction to ablate nociceptive response to laryngoscopy and intubation before randomization to study interventions. The residual effect of fentanyl at induction could influence postoperative pain, though this is unlikely as the duration of action of fentanyl is between 30 and 60 min [34]. We could not perform

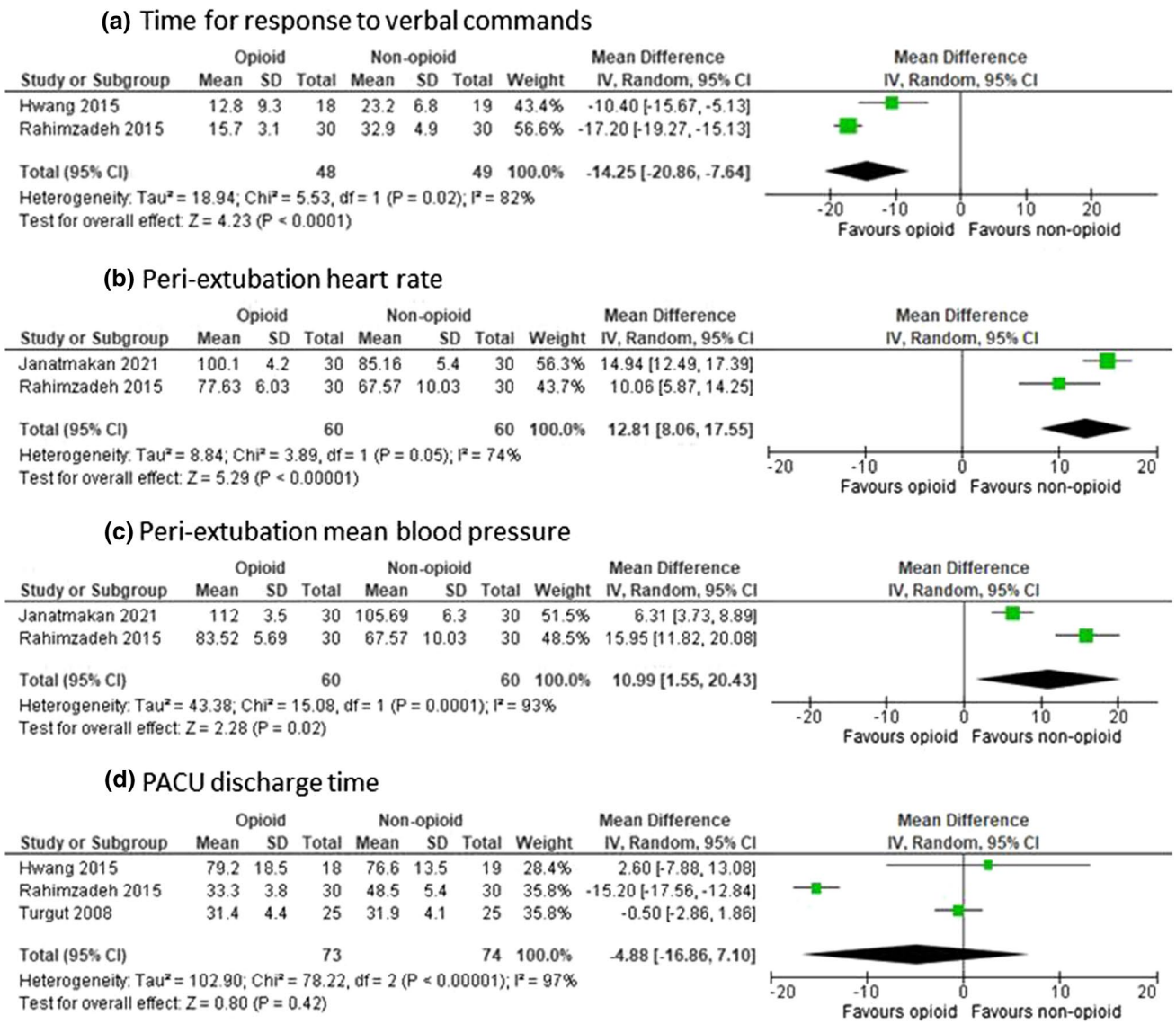

Fig. 5 **a** Time to respond to verbal commands. **b** Comparison of peri-extubation heart rate. **c** Comparison of peri-extubation mean blood pressure. **d** Comparison of discharge time from the post-anesthesia care unit

a meta-analysis for postoperative sedation as the scores used, time of assessment and method of reporting central tendency and variance were different in different studies. We also could not perform analysis for intraoperative hemodynamics as the time point of assessment after the initiation of study interventions could not be agreed upon. However, we performed a meta-analysis for important pain and adverse effects outcomes that matter to the clinicians and patients. Significant heterogeneity was observed for some of the outcomes studied which could have been due to the small sample size or few events in the RCTs. Lastly, this review is limited by the quality of included studies. The limitation emphasizes the need for more research with good quality RCTs having large samples and similar opioid and non-opioid interventions in order to find the best drug combination and dosing regimen.

Conclusions

Intraoperative use of non-opioid analgesia in patients undergoing spine surgery probably reduces postoperative pain at 24 h, delays time to rescue analgesia and reduces opioid consumption in the first 24 h after surgery with fewer adverse events of PONV and shivering. However, the high RoB and heterogeneity resulted in low to very low certainty of

Table 2 GRADE certainty of evidence for study outcomes

Opioid compared to non-opioid for perioperative pain management in spine neurosurgery

Patient or population: perioperative pain management in spine neurosurgery
Setting: perioperative period
Intervention: opioid
Comparison: non-opioid

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with non-opioid	Risk difference with opioid
Pain score at 1 h after surgery assessed with: VAS Scale from: 0 to 10 follow-up: mean 1 hour	202 (4 RCTs)	⨁◯◯◯ Very low[a,b,c]	-		MD **0.65 higher** (0.12 lower to 1.41 higher)
Pain score at 24 h after surgery assessed with: VAS Scale from: 0 to 10 follow-up: mean 24 hours	142 (3 RCTs)	⨁⨁◯◯ Low[a,b]	-		MD **0.75 higher** (0.03 higher to 1.46 higher)
Adverse event: Postoperative Nausea Vomiting (PONV) assessed with: presence or absence	272 (5 RCTs)	⨁⨁◯◯ Low[a,d]	**RR 2.15** (1.37 to 3.38)	132 per 1,000	**152 more per 1,000** (49 more to 315 more)
Adverse event: Shivering assessed with: presence or absence	190 (3 RCTs)	⨁⨁⨁◯ Moderate[a]	**RR 2.52** (1.08 to 5.89)	84 per 1,000	**128 more per 1,000** (7 more to 412 more)
Time to respond to verbal commands (Awakening time) assessed with: observed minutes	97 (2 RCTs)	⨁⨁◯◯ Low[b,e]	-		MD **14.25 lower** (20.86 lower to 7.64 lower)
PACU discharge time assessed with: observed minutes	147 (3 RCTs)	⨁◯◯◯ Very low[a,b,c]	-		MD **4.88 lower** (16.86 lower to 7.1 higher)

*__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; **MD:** mean difference; **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.

Explanations

a. Risk of Bias arising from randomization process, missing outcome data, measurement of outcome and selection of reported result
b. Inconsistency- variation in effect, heterogeneity
c. Imprecision - confidence interval crosses the clinical decision threshold
d. Indirectness- nausea and/or vomiting reported
e. Indirectness - Outcomes tested included time to eye opening or obeying commands

evidence on GRADE assessment for the outcomes studied. Considering the minimal difference in postoperative pain scores, the available evidence does not support intraoperative use of non-opioid over opioid analgesia in patients undergoing spine surgery. More research with good quality primary studies is needed before change in analgesia practice is contemplated.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00586-022-07469-4.

Acknowledgements We thank Dr. Eduardo Villamor, Maastricht University, Netherlands, for his guidance and support during the conceptual phase of the review. We acknowledge Mr. George Franssen, Maastricht University, Netherlands, for his guidance in performing literature search for this review. We also thank the National Institute of Mental Health and Neurosciences, Bengaluru, India and the Maastricht University, Netherlands, for their administrative support.

Author contributions KS, BWK and H.S. were involved in the study design. Title and Abstract and full-text screening, and data extraction were performed by KS and S.B. Manuscript preparation was done by K.S., S.B., H.S., G.S.U.M., B.W.K., T.N.S. reviewed the manuscript and approved the final draft before submission.

Funding Non-funded research.

Declarations

Conflict of interest Authors have nothing to declare with regards to competing interests.

References

1. Rajan S, Devarajan J, Krishnaney A et al (2022) Opioid alternatives in spine surgery: a narrative review. J Neurosurg Anesthesiol 34:3–13. https://doi.org/10.1097/ANA.0000000000000708
2. Sriganesh K, Bidkar PU, Krishnakumar M et al (2021) Perioperative Analgesia in Neurosurgery (PAIN): A national survey of pain assessment and management among neuroanesthesiologists of India. Int J Clin Pract 75:e13718. https://doi.org/10.1111/ijcp.13718
3. Yerneni K, Nichols N, Abecassis ZA et al (2020) Preoperative opioid use and clinical outcomes in spine surgery: a systematic review. Neurosurgery 86:E490–E507. https://doi.org/10.1093/NEUROS/NYAA050
4. Dunn LK, Durieux ME, Nemergut EC (2016) Non-opioid analgesics: novel approaches to perioperative analgesia for major spine surgery. Best Pract Res Clin Anaesthesiol 30:79–89. https://doi.org/10.1016/J.BPA.2015.11.002
5. Goyal A, Kalgudi P, Sriganesh K (2021) Ultrasound-guided erector spinae plane block for perioperative analgesia in cervical and thoracic spine surgeries - a case series. Neurol India 69:487–489. https://doi.org/10.4103/0028-3886.314568
6. Waelkens P, Alsabbagh E, Sauter A et al (2021) Pain management after complex spine surgery: a systematic review and procedure-specific postoperative pain management recommendations. Eur J Anaesthesiol 38:985–994. https://doi.org/10.1097/EJA.0000000000001448
7. Garg N, Panda NB, Gandhi KA et al (2016) Comparison of small dose ketamine and dexmedetomidine infusion for postoperative analgesia in spine surgery - a prospective randomized double-blind placebo controlled study. J Neurosurg Anesthesiol 28:27–31. https://doi.org/10.1097/ANA.0000000000000193
8. Ma J, Bi Y, Zhang Y et al (2021) Erector spinae plane block for postoperative analgesia in spine surgery: a systematic review and meta-analysis. Eur Spine J 30:3137–3149. https://doi.org/10.1007/S00586-021-06853-W
9. Corley JA, Charalambous LT, Mehta VA et al (2022) Perioperative pain management for elective spine surgery: opioid use and multimodal strategies. World Neurosurg 162:118-125.e1. https://doi.org/10.1016/J.WNEU.2022.03.084
10. Ward S, Guest C, Goodall I, Bantel C (2018) Practice and bias in intraoperative pain management: results of a cross-sectional patient study and a survey of anesthesiologists. J Pain Res 11:561–570. https://doi.org/10.2147/JPR.S153857
11. Aveline C, Le HH, Vautier P et al (2006) Peroperative ketamine and morphine for postoperative pain control after lumbar disk surgery. Eur J Pain 10:653. https://doi.org/10.1016/j.ejpain.2005.10.005
12. Turgut N, Turkmen A, Gökkaya S et al (2008) Dexmedetomidine-based versus fentanyl-based total intravenous anesthesia for lumbar laminectomy. Minerva Anestesiol 74:469–474
13. Hwang W, Lee J, Park J, Joo J (2015) Dexmedetomidine versus remifentanil in postoperative pain control after spinal surgery: a randomized controlled study. BMC Anesthesiol. https://doi.org/10.1186/S12871-015-0004-1
14. Rahimzadeh P, Faiz SHR, Alimian M, Mohammadian Erdi A (2015) Remifentanil versus dexmedtomidine for posterior spinal fusion surgery. Med J Islam Repub Iran 29:215
15. Alansary AM, Elbeialy MAK (2019) Dexmedetomidine versus fentanyl added to bupivacaine for epidural analgesia in combination with general anesthesia for elective lumbar disc operations: A prospective, randomized double-blinded study. Saudi J Anaesth 13:119–125. https://doi.org/10.4103/SJA.SJA_600_18
16. Jannatmakan F, Nassajian N, Jarirahmadi S et al (2021) Comparison of the effect of dexmedetomidine and remifentanil on pain control after spinal surgery: a double-blind. Randomized Clin Trial Anesthesiol pain Med. https://doi.org/10.5812/AAPM.111533
17. Sriganesh K, Boris K, GS Umamaheswara R, et al (2022) Non-opioid intraoperative analgesia for perioperative pain management in neurosurgical patients: A systematic review and meta-analysis of randomized clinical trials. PROSPERO 2020 CRD42020209042
18. McHugh ML (2012) Interrater reliability: The kappa statistic. Biochem Medica 22:276–282. https://doi.org/10.11613/bm.2012.031
19. Sterne JAC, Savović J, Page MJ et al (2019) RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ 366:14898. https://doi.org/10.1136/bmj.l4898
20. Williamson A, Hoggart B (2005) Pain: a review of three commonly used pain rating scales. J Clin Nurs 14:798–804. https://doi.org/10.1111/j.1365-2702.2005.01121.x
21. Schünemann H, Brożek J, Guyatt G, Oxman A E (2013) GRADE handbook for grading quality of evidence and strength of recommendations. Updated October 2013. The GRADE Working Group, 2013. Available from guidelinedevelopment.org/handbook
22. UNC Health Care Guideline Analgesic equivalent chart. In: https://www.med.unc.edu/aging/wp-content/uploads/sites/753/2018/06/Analgesic-Equivalent-Chart.pdf. https://www.med.unc.edu/aging/wp-content/uploads/sites/753/2018/06/Analgesic-Equivalent-Chart.pdf. Accessed 30 Apr 2022
23. GRADEpro GDT: GRADEpro Guideline Development Tool [Software]. McMaster University and Evidence Prime, 2022. Available from. gradepro.org
24. Yang MMH, Riva-Cambrin J, Cunningham J et al (2020) Development and validation of a clinical prediction score for poor postoperative pain control following elective spine surgery. J Neurosurg Spine 34:3–12. https://doi.org/10.3171/2020.5.SPINE20347
25. Grape S, Kirkham KR, Frauenknecht J, Albrecht E (2019) Intraoperative analgesia with remifentanil vs. dexmedetomidine: a systematic review and meta-analysis with trial sequential analysis. Anaesthesia 74:793–800. https://doi.org/10.1111/ANAE.14657
26. Rivosecchi RM, Rice MJ, Smithburger PL et al (2014) An evidence based systematic review of remifentanil associated opioid-induced hyperalgesia. Expert Opin Drug Saf 13:587–603. https://doi.org/10.1517/14740338.2014.902931
27. Olsen MF, Bjerre E, Hansen MD et al (2017) Pain relief that matters to patients: systematic review of empirical studies assessing the minimum clinically important difference in acute pain. BMC Med. https://doi.org/10.1186/S12916-016-0775-3
28. Kelly AM (2001) The minimum clinically significant difference in visual analogue scale pain score does not differ with severity of pain. Emerg Med J 18:205–207. https://doi.org/10.1136/EMJ.18.3.205
29. Tsaousi GG, Pourzitaki C, Aloisio S, Bilotta F (2018) Dexmedetomidine as a sedative and analgesic adjuvant in spine surgery: a systematic review and meta-analysis of randomized controlled trials. Eur J Clin Pharmacol 74:1377–1389. https://doi.org/10.1007/S00228-018-2520-7

30. Zhou L, Yang H, Hai Y, Cheng Y (2022) perioperative low-dose ketamine for postoperative pain management in spine surgery: a systematic review and meta-analysis of randomized controlled trials. Pain Res Manag 2022:1–20. https://doi.org/10.1155/2022/1507097
31. Licina A, Silvers A (2022) Perioperative intravenous lidocaine infusion for postoperative analgesia in patients undergoing surgery of the spine: systematic review and meta-analysis. Pain Med 23:45–56. https://doi.org/10.1093/PM/PNAB210
32. Yu L, Ran B, Li M, Shi Z (2013) Gabapentin and pregabalin in the management of postoperative pain after lumbar spinal surgery: a systematic review and meta-analysis. Spine (Phila Pa 1976) 38:1947–1952. https://doi.org/10.1097/BRS.0B013E3182A69B90
33. Peene L, Le Cacheux P, Sauter AR et al (2021) Pain management after laminectomy: a systematic review and procedure-specific post-operative pain management (prospect) recommendations. Eur Spine J 30:2925–2935. https://doi.org/10.1007/S00586-020-06661-8
34. Vahedi HSM, Hajebi H, Vahidi E et al (2019) Comparison between intravenous morphine versus fentanyl in acute pain relief in drug abusers with acute limb traumatic injury. World J Emerg Med 10:27. https://doi.org/10.5847/wjem.j.1920-8642.2019.01.004