Postoperative pain treatment after spinal fusion surgery: a systematic review with meta-analyses and trial sequential analyses

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Abstract
Patients undergoing spinal surgery are at high risk of acute and persistent postoperative pain. Therefore, adequate pain relief is crucial. This systematic review aimed to provide answers about best-proven postoperative analgesic treatment for patients undergoing lumbar 1- or 2-level fusions for degenerative spine diseases. We performed a search in PubMed, Embase, and The Cochrane Library for randomized controlled trials. The primary outcome was opioid consumption after 24 hours postoperatively. We performed meta-analyses, trial sequential analyses, and Grading of Recommendations assessment to accommodate systematic errors. Forty-four randomized controlled trials were included with 2983 participants. Five subgroups emerged: nonsteroidal anti-inflammatory drugs (NSAIDs), epidural, ketamine, local infiltration analgesia, and intrathecal morphine. The results showed a significant reduction in opioid consumption for treatment with NSAID \((P < 0.0008)\) and epidural \((P < 0.0006)\) (predefined minimal clinical relevance of 10 mg). Concerning secondary outcomes, significant reductions in pain scores were detected after 6 hours at rest (NSAID \(P < 0.0001\)) and intrathecal morphine \((P < 0.0001)\), 6 hours during mobilization (intrathecal morphine \(P = 0.003)\), 24 hours at rest (epidural \(P < 0.00001\)) and ketamine \(P < 0.00001)\), and 24 hours during mobilization (intrathecal morphine \(P = 0.03\)). The effect of wound infiltration was nonsignificant. The quality of evidence was low to very low for most trials. The results from this systematic review showed that some analgesic interventions have the capability to reduce opioid consumption compared with control groups. However, because of the high risk of bias and low evidence, it was impossible to recommend a "gold standard" for the analgesic treatment after 1- or 2-level spinal fusion surgery.

Keywords: Spinal fusion, Pain, Analgesics, Pain treatment

1. Introduction
Multimodal or balanced analgesia continues to be the leading treatment principle for managing postoperative pain.\(^{31}\) The main concern is to achieve better pain treatment through additive or synergistic effects of several nonopioids, thereby reducing the need for postoperative opioid treatment and opioid-related adverse events such as nausea and vomiting.\(^{34,35}\)

Postoperative pain management remains a significant clinical challenge mirroring the lack of knowledge and documentation regarding the effects of most combinations of analgesics.\(^{10,17}\)

A commonly performed orthopedic procedure, with increasing rates worldwide (increase of 118% in the United States between 1998 and 2014), is 1- or 2-level spinal fusion surgery.\(^{58}\) Patients undergoing this procedure are at a high risk of acute and persistent postoperative pain, development of postoperative hyperalgesia, and possibly opioid tolerance followed by excessive and continuous use of opioids.\(^{4,51}\)

Furthermore, postoperative pain often negatively influences the patients' mobility, resulting in delayed recovery and rehabilitation. These patients often receive preoperative opioid treatment, making postoperative pain treatment difficult to manage.\(^{36}\)

Adequate postoperative pain relief improves patient satisfaction and patients' perception of the quality of their hospital stay, and it facilitates early mobilization and optimal rehabilitation.\(^{9,35,36}\) However, there is a lack of consensus regarding the "gold standard" of the postoperative pain treatment strategy in patients undergoing 1- or 2-level lumbar spinal fusion procedures.\(^{46,47}\)
Therefore, this systematic review aims to investigate whether the existing literature contains evidence concerning procedure-specific, medication-based interventions for 1- or 2-level spinal fusion surgery.

2. Methods

This review follows the methodology recommended by the Cochrane Collaboration. We performed this systematic review according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses guidelines.49 Before performing the literature search, we registered the protocol at PROSPERO, the international prospective register of systematic reviews on July 26, 2020, registration number: CRD42020192899. We designed a broad search string, including MeSH and All fields terms, in collaboration with a professional search co-ordinator to avoid overlooking relevant trials (Appendix 1, available at http://links.lww.com/PR9/A157). Because there was a change in MESH terms after 1988, we only included trials published after 1988. We searched the following databases: PubMed, Embase, and The Cochrane Library (Appendix 1, available at http://links.lww.com/PR9/A157). The last search was on January 18, 2021. We searched published systematic reviews and articles by hand for eligible trials and screened The PROSPECT Database8 and reference lists from relevant reviews.

We included RCTs comparing the postoperative effect of a peripерioperative analgesic intervention for 1- or 2-level spinal fusion surgery against a control group. The analgesic intervention had to be initiated in the immediate perioperative period, and trials had to report at least one of the predefined endpoints. Exclusion criteria were abstracts, unpublished observations, quasi-randomized and observational studies, trials not written in English, trials not dealing with spinal fusion surgery, fusions performed on scoliosis, tumors or trauma and more than 2 levels, age <18 years, trials published before 1988, as well as editorials, letters, protocol articles, and comments.

Two authors screened titles and abstracts for eligibility using the predefined inclusion and exclusion criteria.

The primary endpoint was the opioid-sparing effect of the active interventions within 0 to 24 hours postoperatively. Secondary endpoints were pain at rest and during mobilization at 6 and 24 hours postoperatively, opioid-related adverse effects, serious adverse events (SAEs), and length of stay (LOS).

Six authors extracted the data, assessed the full texts independently, and compared their findings afterward. We managed and compared risk of bias using Covidence (Covidence systematic review software; Veritas Health Innovation, Melbourne, Australia). We resolved disagreements by consensus.

We contacted the corresponding author for the trial by email to confirm or obtain data if data were missing, or we classified bias evaluation as unclear in one or more domains. We contacted the authors again after 2 weeks if they had not responded to our initial contact. We used open questions to prevent false confirmation of suggested measures in the answers.

We converted opioid consumption to intravenous (i.v.) morphine equivalents (Appendix 2, available at http://links.lww.com/PR9/A157) and pain scores, such as visual analog scale (VAS) 0 to 10 and numerical rating scale (NRS) 0 to 10, to a 0 to 100 VAS scale. For trials with several treatment arms, we combined mean values and SDs in the intervention groups.

Furthermore, we converted median and interquartile range values to mean and SDs using the method described by Hozo et al.28 We calculated the risk ratio (RR) with a 95% confidence interval (CI) for dichotomous data.

Two authors performed bias assessment by using Cochrane’s 7-step risk of bias tool.29

2.1. Statistical analyses

We performed meta-analyses and sensitivity analyses using Review Manager provided by Cochrane (RevMan version 5.4.1) whenever 3 or more trials reported the preplanned outcomes for continuous data regarding opioid consumption, postoperative nausea and vomiting (PONV), or continuous data regarding pain reporting. For the overall assessment of overall significance, we used the procedure suggested by Jakobsen et al.30 We applied the trial sequential analysis (TSA) (computer program) version 0.9.5.10 Beta (Copenhagen Trial Unit, Center for Clinical Intervention Research, Rigshospitalet, Copenhagen, Denmark).70

We assessed the heterogeneity between trials by $I^2$, which quantifies the observed differences and $D^2$ for information size adjustments in the trial sequential analyses.70 Additionally, we inspected the forest plots visually for statistical heterogeneity.

We used sensitivity analyses to explore whether the choice of summary statistics and choices made through the review process, such as selection of event category, were critical for the conclusions of the meta-analysis. To control for random errors, we performed TSA for the primary and secondary outcomes dealing with pain intensity, and we calculated and visualized the diversity-adjusted required information size (DARIS) and the cumulative Z-curve. It was not possible to perform TSA if the accrued information size was $<$5% or the data were insufficient. We calculated RR for dichotomous data in the presence of interventions of 3 or more trials, with a 95% CI. We considered in both dichotomous and continuous data that, $P$ $<$0.05 was statistically significant. We performed funnel plots if 10 or more trials were included in the meta-analysis and assessed the presence of heterogeneity by using the magnitude by $I^2$ and forest plots.27

To detect a minimal clinical relevant effect, we chose to detect even a small beneficial effect. Therefore, a mean difference was set to 10 mg morphine i.v. equivalents per 24 hours for opioid consumption and 10 mm on a VAS (0–100 mm) scale for pain scores at 6 and 24 hours.42,50

We used Grading of Recommendations, Assessment, Development, and Evaluation (GRADEpro GDT) to assess the certainty of evidence.23

3. Results

From the literature search, we identified 25,001 trials. First, Covidence removed 4239 duplicates, and after the abstract and full-text screening, we removed 20,080 trials. Furthermore, we excluded trials dealing with spine surgery not related to spinal fusion, 409 trials were full-text screened, ending up with a total exclusion of 364 trials. Hence, 44 trials remained for the final data extraction randomizing 2983 participants ($n = 1–3,9–11,15,18,19,21,22,24,25,29,32,33,38–41,43,44,45,53,54–57,59–62,64–66,68,69,71–74$ (Fig. 1).

For subgroup analyses, we identified 5 groups, which included 3 or more trials: nonsteroidal anti-inflammatory drugs (NSAIDs), $n = 3,5,5,6,2,7$, epidural analgesia, $n = 2,7,21,23,60$, ketamine infusion, $n = 1,5,24,41,50,64,66$, local infiltration analgesia, $n = 6,22,44,61$, and intrathecal (i.t.) morphine, $n = 12,14,88,74$.

The remaining studies, $n = 11,13,15,18,19,25,29,33,38–40,43,52,60,67,68,70,72,73$ reported 12 different interventions, including 4 studies that reported on pregabalin but did not have comparable outcomes. For baseline variables, see Table 1.
Of the included 44 trials, 38 contained one or more unclear domains, which we addressed by emailing the corresponding authors twice. However, in 6 trials, the corresponding author had left no email address, and 7 email addresses were out of order. Finally, 3 authors answered our questions.

The summarized bias was high in 11, unclear in 26, and low in 7 trials (Fig. 2). Regarding the trial sample size, 32 trials implicated moderate risk of bias and 13 trials implicated high risk of bias.

We changed the original plan to use the most conservative effect estimate regarding random or fixed effect when performing TSA when inspecting the data because considerable heterogeneity was detected between the studies. Therefore, we chose random-effects models to accommodate that.

3.1. Supplemental analgesics

Fifteen trials reported that patients postoperatively were provided with patient-controlled analgesia with morphine, and in 6 cases, the morphine was solely administrated as i.v. or s.c. In 22 cases, patients had a patient-controlled analgesia device with hydro-morphone, oxycodone, meperidine, piritramide, sufentanil, piritramide, or fentanyl. In one study, the patients had flurbiprofen at request. Thirty-five trials reported total opioid consumption but not all after 24 hours postoperatively.

Regarding the primary analgesic treatment provided for the patients postoperatively, 14 trials administrated acetaminophen as i.v. or orally, 8 trials administrated different kinds of NSAIDs, 4 studies administrated pregabalin or gabapentin, 3 trials used other analgesics. In 7 trials, they combined analgesics, eg, acetaminophen and ketorolac or pregabalin.

3.2. Pain ratings

The majority of the included studies used NRS (0–10, 0 is no pain, and 10 is worst imaginable pain) or VAS (0–10 cm, or 0–100 mm, where 0 is no pain and 10/100 is the worst imaginable pain. Thirty-one trials reported pain at rest at 6±2 hours ranging from VAS 14–63 mm, mean 33 mm for intervention groups, and VAS 15–69 mm, mean 45 mm for control groups. Thirty-eight trials reported pain at rest after 24±4 hours ranging from VAS 6–53 mm, mean 31 mm for intervention groups and 14–57 mm, mean 39 mm for control groups. For pain during mobilization at 6 hours, 8 studies reported on VAS outcomes ranging from 17 to 71 mm, mean 46 mm for interventions and VAS 32–79 mm, mean 57 mm for control groups. Pain during mobilization was reported after 24 hours postoperatively by 12 studies, with VAS ranging from 12 to 69 mm, mean 42 mm for intervention groups and 15 to 80 mm, mean 46 mm for control groups (Table 1).

3.3. Adverse events and other outcomes

Twenty-nine trials included patients with chronic pain and daily opioid consumption, 13 trials accepted pain but excluded preoperatively opioid consumption, 2 trials did not mention preoperatively pain or opioid consumption.

Twelve trials reported on LOS, PONV were reported in 20 trials, also separately as nausea (16 trials) and vomiting (7 trials). Dizziness, sedation, and pruritus were reported in 10, 9, and 11 trials, respectively. Furthermore, headache, shivering, paresthesia, hematomata, infection, hallucinations, visual disturbance, confusion, urine retention, and constipation were reported. None of the studies reported SAE.

3.4. Subgroup analysis

3.4.1. Nonsteroidal anti-inflammatory drugs

Eight trials reported on NSAIDs as an intervention,3,38,40,55,57,59,62,71 3 studies in combination with other analgesics.38,40,57 The risk of bias for all trials was low in one trial, unclear in 5 trials, and high in 2 trials (Fig. 2).

3.4.2. Opioid consumption 0 to 24 hours

Three trials reported 0- to 24-hour opioid consumption3,59,62 (Fig. 3). The meta-analysis reported a significant reduction in opioid consumption of 35.7 mg i.v. (95% CI: 15–57 mg/24 hours), with large heterogeneity (I² = 92%). Trial sequential analysis showed that neither the required information size nor the DARIS was crossed or reached (Appendix 3, available at http://links.lww.com/PR9/A157). The quality of evidence (GRADE) was very low (Table 2).

3.4.3. Pain at rest after 6 hours

Four trials reported on NSAIDs and postoperative pain at rest after 6 ± 2 hours.3,59,62,71 The meta-analysis found a significant reduction of 12 mm in mean VAS score (95% CI: –6.5–17.5), Heterogeneity was moderate I² = 65% (Appendix 4, available at http://links.lww.com/PR9/A157). Trial sequential analysis showed that neither the required information size nor the DARIS line was crossed or reached (Appendix 3, available at http://links.lww.com/PR9/A157). The quality of evidence (GRADE) was very low (Table 2).

3.4.4. Pain at rest after 24 hours

Three trials reported on NSAIDs and postoperative pain at rest after 24 ± 4 hours.59,62,71 The meta-analysis found a
### Table 1

**Study information.**

| Author                  | Basic analgesic regimen all groups | Type of supplemental analgesics | Analgesics in intervention and control groups |
|-------------------------|----------------------------------|---------------------------------|-----------------------------------------------|
| Abrishamkar, 2012       | Routine analgesic protocol        | Morphine s.c. VAS > 4           | 1: (n = 22) ketamine 0.5 mg/kg/h i.v. Control: (n = 23) morphine s.c. |
| Aglio, 2018             | None                             | Hydromorphone i.v.              | 1: (n = 33) hydromorphone 0.5 mg; epidural preoperatively 2: (n = 34) bupivacaine 31.25 mg and hydromorphone 0.5 mg; epidural preoperatively Control: (n = 32) saline 10 mL; epidural preoperatively |
| Aubrun, 2000            | Propacetamol 2 g p.o. every 6 hours. | Morphine i.v.                   | 1: (n = 25) ketoprofen 100 mg i.v. at the end of surgical procedure Control: (n = 25) dextrose |
| Brinck, 2020            | i.v. paracetamol                  | PCA oxycodone                   | 1: (n = 65) ketamine bolus pre-incisional (0.5 mg/kg), followed by S-ketamine infusion of 0.12 mg/kg/h 2: (n = 62) ketamine bolus pre-incisional (0.5 mg/kg), followed by S-ketamine infusion of 0.6 mg/kg/h Control: (n = 62) matching saline pre-incisional |
| Brown, 2018             | None                             | Hydromorphone i.v.              | 1: (n = 24) liposomal bupivacaine 266 mg, 60 mL before wound closure; local anaesthetic Control: (n = 26) saline 60 mL before wound closure; local anaesthetic |
| Choi, 2014              | Premedicated with acetaminophen 1,000 mg and gabapentin 600 mg PO After surgery, acetaminophen 1,000 mg every 6 hours and oral gabapentin 200 mg every 8 hours. | PCA hydromorphone              | 1: (n = 20) hydromorphone + bupivacaine 0.6 mg bolus (hydromorphone) Bupi + hydromorphone 15 μg 6 mL/h 0.1%; epidural at PACU Control: (n = 18) matching saline; epidural at PACU |
| Detkordy, 2020          | Paracetamol 1 gr                  | PCA morphine per demand meperidine 50 mg rescue agent | 1: (n = 40) magnesium i.v. 50 mg/kg bolus followed by a continuous 15 mg/kg/h infusion. Before induction + during surgery Control: (n = 40) matching saline |
| Dhaliwal, 2019          | Acetaminophen, oxycodone, codein, morphine i.v. | PCA morphine                   | 1: (n = 74) morphine 0.2 mg, 0.4 mL saline before wound closure; spinal Control: (n = 76) matching saline |
| Firouzian, 2018         | None                             | PCA morphine                    | 1: (n = 40) naloxone 20 μg + morphine 0.2 mg I.T.; end of surgery Control: (n = 37) morphine 0.2 mg I.T.; end of surgery |
| France, 1997            | None                             | PCA opioids                     | 1: (n = 42) duramorph injection 0.011 mg/kg; 30 minutes before surgery Control: (n = 26) matching saline |
| Fujita, 2016            | Indomethacin sup. (50 mg, first choice) pentazocine hydrochloride (15 mg IM, second choice) | PCA morphine                    | 1: (n = 30) pregabalin 75 mg, 2 hours Prior to surgery 2: (n = 30) pregabalin 150 mg, 2 hours before surgery Control: (n = 29) diazepam 5 mg, 2 hours before surgery |
| Ghabach, 2019           | Paracetamol 1 g every 8 hours and ketoprofen 50 mg every 12 hours i.v. | Sufentanil i.v. 5 mg to reach a VAS score <4 Meperidine 50 mg IM (VAS score 4) | 1: (n = 14) ropivacaine 0.5% 10 mL before wound closure; sponge Control: (n = 16) saline 10 mL before wound closure sponge |
| Ghamry, 2019            | Paracetamol i.v. 1 g per 6 hours, Ketorolac 30 mg loading dose then 15 mg per 8 hours. | Morphine 0.1 mg/kg i.v. (VAS >30) | 1: (n = 30) bupivacaine 0.25%, 20 mL erector spinae block Control: (n = 30) none |
| Gottschalk, 2004        | None                             | PCA pimididine                  | 1: (n = 13) ropivacaine 0.1% 12 mL/hr during surgery; epidural postoperatively Control: (n = 13) matching saline; epidural postoperatively |
| Greze, 2017             | Acetaminophen (1 g x 4 daily), ketoprofen (100 mg x 2 daily) nefopam (20 mg x 4 daily) | PCA morphine                    | 1: (n = 19) ropivacaine 10 mL bolus + 8 mL/h for 48 hours; end of surgery; wound infiltration Control: matching saline; wound infiltration |
| Hadi, 2010              | None                             | PCA morphine                    | 1: (n = 15) ketamine i.v. 1 μg/Kg/min; during surgery Control: (n = 15) none |
| Martí/Hernandez-Palazón, 2001 | None                             | PCA morphine                    | 1: (n = 21) propacetamol 2 g i.v. every 6 hours; during a period of 72 hours. Control: (n = 21) matching saline |
| Ibrahim, 2018           | Ketorolac 30 mg i.v. and paracetamol 1 g injection for 8 hours | Morphine i.v. VAS was ≥4, or by request | 1: (n = 20) lidocaine i.v. loading before incision then 3 mg/kg/h; during surgery Control: (n = 20) matching saline |

(continued on next page)
| Author       | Basic analgesic regimen all groups | Type of supplemental analgesics | Analgesics in intervention and control groups Type, dose, volume, time points, and type of administration |
|--------------|------------------------------------|---------------------------------|--------------------------------------------------------------------------------|
| Kang, 2013   | None                               | PCA fentanyl                    | 1: (n = 32) ropivacaine 0.1% 10 mL 20 minutes; before skin incision; epidural Control: (n = 34) matching saline |
| Kawamata, 2005 | Pre-med: 3 mg i.m. midazolam. Post-med: 200 μg i.v. buprenorphine at 1 mL/h rate s.c. | Flurbiprofen 50 mg i.v.         | 1: (n = 16) buprenorphine 1.2 + 1 mg droperidol, total 48 mL, 1 mL/h for 48 hours after surgery; continuous s.c. infusion Control: (n = 17) buprenorphine 0.6 mg + droperidol 1 mg, total 48 mL, 1 mL/h for 48 hours after surgery continuous s.c. infusion |
| Kien, 2019   | None                               | Morphine 2 mg every 3 minutes   | 1: (n = 30) pregabalin 150 mg P.O., celecoxib 200 mg P.O., 2 hours before surgery Control: (n = 30) placebo |
| Kim, 2011    | None                               | PCA fentanyl                    | 1: (n = 18) pregabalin 75 mg P.O. 1 hour before surgery 2: (n = 17) pregabalin 75 mg P.O. 1 hour before surgery Control: (n = 17) placebo |
| Kim, 2013    | Ketorolac 30 mg i.v. 10 minutes before skin closure | i.v. morphine                   | 1: (n = 32) ketamine i.v. infusion of 1 μg/kg/min after bolus 0.5 mg/kg, before skin incision + continued 48 hours postoperatively 2: (n = 32) ketamine 2 μg/kg/min after bolus 0.5 mg/kg before skin incision + continued 48 hours postoperatively Control: (n = 32) matching saline |
| Kim, 2016    | None                               | PCA morphine                    | 1: (n = 40) celecoxib 200 mg, pregabalin 75 mg, acetaminophen 500 mg, extended-release oxycodone 10 mg 1 hour preop + twice daily Control: (n = 40) morphine i.v. |
| Levaux, 2003 | Piritramide just before wound closure | PCA piritramide 1 mg piritramide bolus until pain free in emergence | 1: (n = 12) magnesium 50 mg/kg i.v. preoperatively Control: (n = 12) saline i.v. preoperatively |
| Li, 2019     | Ropivacaine 0.5% 20 mL 5 minutes Before incision | PCA morphine                    | 1: (n = 29) dexametomidine 20 mL, 0.5% ropivacaine 1 μg/kg dexametomidine 5 minutes before incision Control: (n = 28) 20 mL 0.5% ropivacaine 5 minutes before incision |
| Oh, 2019     | None                               | PCA fentanyl                    | 1: (n = 43) rocuronium 2 mg/mL diluted in 0.9% isotonic saline and started at 15 mL/hr Control: (n = 43) none |
| Pinar, 2017  | Lyrica 150 mg Preop PCM 1 g i.v. per 6 hours | PCA morphine                    | 1: (n = 21) pregabalin 150 mg 1 hour preop and Ibuprofen 300 mg 30 minutes preoperatively Control: (n = 21) pregabalin 150 mg 1 hour preoperatively |
| Quinlan, 2017 | None                                | Hydromorphone i.v.              | 1: (n = 74) 1 L of crushed ice every 4 hours postoperatively applied to the lower back for 20 minutes Control: (n = 74) none |
| Raja, 2019   | Paracetamol 1 g i.v., dexamethasone 8 mg i.v. after skin incision; postop: paracetamol 1 g i.v. every 6 hours, ketorolac 30 mg every 8 hours, pregabalin P.O. 75 mg | PCA morphine                    | 1: Paracetamol 1 g, ketorolac 20 mg, pregabalin 75 mg P.O. 4 hours before surgery Control: (n = 50) none |
| Reuben, 2006 | None                               | PCA, morphine                   | 1: (n = 20) celecoxib 400 mg + placebo capsule, 1 hour before induction; celecoxib 200 mg + placebo capsules, 12 hours after surgery. 2: (n = 20) pregabalin 150 mg + placebo capsules, 1 hour before induction; pregabalin 150 mg + placebo capsules, 12 hours after surgery 3: (n = 20) celecoxib 400 mg + pregabalin 150 mg 1 hour before induction; celecoxib 200 mg + pregabalin 150 mg, 12 hours after surgery Control: (n = 20) matching placebo capsule |
| Šervic-kuchler, 2014 | Metamizole 2.5 g per 12 hours | PCA piritramide 3 mg i.v., VAS >4 | 1: (n = 25) levobupivacaine 0.125% 0.1 mL/kg/h after wound closure; epidural postoperatively Control: (n = 25) matching saline postoperatively |
nonsignificant reduction of 7.5 mm in VAS score (95% CI: 10–25). The heterogeneity was large, $I^2 = 91\%$ (Fig. 4). Trial sequential analysis showed that neither was the required information size reached nor was the DARIS line crossed or reached (Appendix 3, available at http://links.lww.com/PR9/A157). The quality of evidence (GRADE) was very low (Table 2).
3.4.5. Adverse events

Three trials reported on PONV. The meta-analysis found no significant difference between groups, RR 0.79 (95% CI: 0.54–1.17) with moderate heterogeneity $I^2 = 58\%$ (Appendix 5, available at http://links.lww.com/PR9/A157). Quality of evidence (GRADE) was moderate. Two trials reported on sedation, 2 on dizziness, 59,62 and 1 on pruritus.62

3.5. Epidural

Five trials reported on epidural as an intervention. Two trials reported on bupivacaine with hydromorphone, one trial on ropivacaine, 21 and 2 trials on levobupivacaine.60 The risk of bias for all trials was unclear in 3 trials, and 2 trials had high risk of bias (Fig. 2).

3.5.1. Opioid consumption 0–24 hours

Three trials reported opioid consumption. The meta-analysis reported a mean reduction of 17 mg i.v. (95% CI: 7–27 mg per 24 hours), with large heterogeneity $I^2 = 92\%$ (Fig. 3). Trial sequential analysis was not possible to perform. The quality of evidence (GRADE) was very low (Table 2).

3.5.2. Pain at rest after 24 hours

Three trials reported on epidural and postoperative pain at rest after 24 hours. The meta-analysis found a significant reduction of −17.2 mm in mean VAS (95% CI: −25 to 10) with moderate heterogeneity $I^2 = 74\%$ (Fig. 4). Trial sequential analysis showed that the required information size was not reached, but the DARIS line was crossed (Appendix 4, available at http://links.lww.com/PR9/A157). The quality of evidence (GRADE) was low (Table 2).

No trials reported on pain after 6 hours during rest or mobilization, and no studies were detected dealing with pain during mobilization after 24 hours.

3.5.3. Adverse events

Four trials reported on PONV. The meta-analysis found no significant difference between groups, RR 0.70 (95% CI: 0.42–1.14), with moderate heterogeneity $I^2 = 60\%$ (Appendix 5).

When performing sensitivity analyses, we found a significant difference, $P = 0.02$ (only in 2 trials). Quality of evidence (GRADE) was moderate (Table 2). One trial reported on pruritus.68

3.6. Ketamine

Seven trials reported on ketamine as an intervention. The risk of bias for all trials was low in 2 trials, unclear in 2 trials, and high in 3 trials (Fig. 2).

3.6.1. Opioid consumption 0–24 hours

Four trials reported opioid consumption. The meta-analysis reported no significant reduction in opioid consumption 3 mg i.v. for 24 hours (95% CI: 1.5–8) with moderate heterogeneity $I^2 = 43\%$ (Fig. 3). Trial sequential analysis showed that the required information size was not reached, and the DARIS line was not crossed (Appendix 7, available at http://links.lww.com/PR9/A157). The quality of evidence (GRADE) was low (Table 2).
3.6.2. Pain at rest after 6 hours

Five trials reported on ketamine and postoperative pain at rest after 6 ± 2 hours.\textsuperscript{1,7,44,59,73} The meta-analysis showed no significant difference in overall effect in mean VAS 3 mm (95% CI: −24 to 31). The heterogeneity was high, $I^2 = 99\%$ (Fig. 4). Trial sequential analysis showed that neither was the required information size reached nor was the DARIS line crossed or reached (Appendix 7, available at http://links.lww.com/PR9/A157). Quality of evidence (GRADE) was low (Table 2).

3.6.3. Pain during mobilization after 6 hours

Three trials reported on ketamine and postoperative pain at mobilization 6 ± 2 hours.\textsuperscript{44,59,73} The meta-analysis showed no significant difference in mean VAS 4 mm (95% CI: 4−12), heterogeneity $I^2 = 0\%$ (Appendix 8, available at http://links.lww.com/PR9/A157). Trial sequential analysis showed neither was the required information size reached nor was the DARIS line crossed or reached (Appendix 7, available at http://links.lww.com/PR9/A157). Quality of evidence (GRADE) was moderate (Table 2).

3.6.4. Pain at rest after 24 hours

Six trials reported on ketamine and postoperative pain at rest after 24 hours.\textsuperscript{1,5,41,53,64,66} The meta-analysis showed a significant difference between trials in favor of the experimental group of 13 mm in mean VAS (95% CI: 10−17). When performing sensitivity analyses, the meta-analysis was nonsignificant. We found large heterogeneity $I^2 = 90\%$ (Fig. 4). The TSA showed that
### Table 2

Summarized outcomes in Grading of Recommendations Assessment, Development, and Evaluation (GRADE) (mean difference and 95% confidence interval are provided together with quality of evidence).

**NSAID compared with placebo for pain after spinal fusion surgery?**

**Patient or population:** pain after spinal fusion  
**Setting:** the immediate postoperative period  
**Intervention:** NSAID  
**Comparison:** placebo

| Outcomes | Anticipated absolute effects* (95% CI) | Relative effect (95% CI) | No. of participants (studies) | Certainty of the evidence (GRADE) |
|----------|--------------------------------------|-------------------------|-----------------------------|----------------------------------|
| PONV assessed with: numbers of events | 455 per 1.000 | 350 per 1.000 (255–477) | RR 0.77 (0.56–1.05) | 226 (3 RCTs)  
**Morphine consumption assessed with 0–24 hours postoperatively assessed with: mg** | The mean morphine consumption was 9.05 lower (80.63 lower–62.53 higher) | — | 296 (4 RCTs)  
**Pain score 4–8 hours postoperatively assessed with: VAS 0–100 mm** | The mean pain score was 11.29 lower (15.48 lower–7.1 lower) | — | 292 (5 RCTs)  
**Sedation assessed with: number of events** | 511 per 1.000 | 502 per 1.000 (194–465) | RR 0.59 (0.38–0.91) | 130 (2 RCTs)  
**Pain score 20–24 hours postoperatively assessed with: VAS 0–100 mm** | The mean pain score was 7.24 lower (17.15 lower–2.66 higher) | — | 242 (4 RCTs)  
**Dizziness assessed with: number of events** | 212 per 1.000 | 186 per 1.000 (99–351) | RR 0.88 (0.47–1.66) | 176 (2 RCTs)  
**Pruritus** | 167 per 1.000 | 180 per 1.000 (93–345) | RR 1.08 (0.56–2.07) | 166 (2 RCTs) |

**EPI compared with control for pain after spinal fusion surgery?**

**Patient or population:** pain after spinal fusion  
**Setting:** the immediate postoperative period  
**Intervention:** EPI  
**Comparison:** placebo

| Outcomes | Anticipated absolute effects* (95% CI) | Relative effect (95% CI) | No. of participants (studies) | Certainty of the evidence (GRADE) |
|----------|--------------------------------------|-------------------------|-----------------------------|----------------------------------|
| Opioid consumption | The mean opioid consumption was 0 | MD 17.06 lower (26.82 lower–7.3 lower) | — | 205 (3 RCTs)  
| PONV | 296 per 1.000 | 207 per 1.000 (124–337) | RR 0.70 (0.42–1.14) | 198 (4 RCTs)  
| 24 hours pain at rest | The mean 24 hours pain at rest was 0 | MD 17.19 lower (24.55 lower–9.82 lower) | — | 160 (3 RCTs)  
| Pruritus | 667 per 1.000 | 0 per 1.000 (0–0) | Not estimable | 38 (1 RCT) |

**Ketamine compared with placebo for pain after spinal fusion surgery?**

**Patient or population:** pain after spinal fusion  
**Setting:** the immediate postoperative period  
**Intervention:** Ketamine  
**Comparison:** placebo

| Outcomes | Anticipated absolute effects* (95% CI) | Relative effect (95% CI) | No. of participants (studies) | Certainty of the evidence (GRADE) |
|----------|--------------------------------------|-------------------------|-----------------------------|----------------------------------|
| Opioid consumption | The mean opioid consumption was 0 | MD 3.39 lower (8.3 lower–1.52 higher) | — | 155 (4 RCTs)  
| 6 hours pain at rest | The mean 6 hours pain at rest was 0 | MD 3.19 higher (24.37 lower–30.75 higher) | — | 365 (5 RCTs)  
| 6 hours pain during mob | The mean 6 hours pain during mob was 0 | MD 3.99 lower (11.58 lower–3.6 higher) | — | 131 (3 RCTs)  
| 24 hours pain at rest | The mean 24 hours pain at rest was 0 | MD 13.32 lower (17.02 lower–9.62 lower) | — | 389 (6 RCTs)  
| 24 pain during mob | The mean 24 pain during mob was 0 | MD 5.16 lower (14.31 lower–3.99 higher) | — | 103 (3 RCTs) |

(continued on next page)
the required information size was not reached, but the DARIS line was crossed (Appendix 7, available at http://links.lww.com/PR9/A157). The quality of evidence (GRADE) was very low (Table 2).

### 3.6.6. Adverse events

Six trials reported on PONV. The meta-analysis found no significant difference between groups, RR 0.99 (95% CI: 0.76–1.28) with low heterogeneity $I^2 = 12\%$ (Appendix 5, available at http://links.lww.com/PR9/A157). The quality of evidence (GRADE) was very low (Table 2). Three trials reported on dizziness.

### Table 2 (continued)

| Outcomes | Risk with placebo | Anticipated absolute effects$^*$ (95% CI) | Relative effect (95% CI) | No. of participants (studies) | Certainty of the evidence (GRADE) |
|----------|-------------------|----------------------------------------|------------------------|-----------------------------|----------------------------------|
| Opioid consumption | The mean opioid consumption was 0 | MD 2.13 higher (5.34 lower–9.61 higher) | — | 226 (4 RCTs) | Low |
| PONV | 338 per 1.000 | 0 per 1.000 (0–0) | Not estimable | 137 (2 RCTs) | |
| Pruritus | 0 per 1.000 | 0 per 1.000 (0–0) | Not estimable | 57 (1 RCT) | |
| 24 hours pain at rest | The mean 24 hours pain at rest was 0 | MD 2.84 higher (5.25 lower–10.93 higher) | — | 146 (3 RCTs) | Low |

**Ketamine compared with placebo for pain after spinal fusion surgery?**

**Wound infiltration compared with placebo for pain after spinal fusion surgery?**

**Morphine compared with placebo for pain after spinal fusion surgery?**

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The quality of evidence (GRADE) was low (Table 2).

### 3.6.5. Pain during mobilization after 24 hours

Three trials reported on pain during mobilization after 24 hours. The meta-analysis showed no significant difference between groups in mean VAS $-6$ mm (95% CI: $-21$ to $8$), moderate heterogeneity $I^2 = 54\%$ (Fig. 5). The TSA showed that the required information size was not reached, but the DARIS line was crossed (Appendix 7, available at http://links.lww.com/PR9/A157). The quality of evidence (GRADE) was very low (Table 2).
NSAID or COX-2-inhibitors

Epidural

Ketamine

Wound infiltration

IT Morphine

Figure 4. Meta-analyses for 24 hours pain rest.
3.7. Wound infiltration

Four trials reported on local infiltration/wound analgesia and opioid consumption.6,22,44,61 The risk of bias for all trials was low in 2 trials, unclear in 1 trial, and high in 1 trial (Fig. 2).

3.7.1. Opioid consumption 0 to 24 hours

Four trials reported on local infiltration/wound analgesia and 24-hour opioid consumption.6,22,44,61 The meta-analysis favored the control group and reported no significant reduction in opioid consumption 2 mg i.v. per 24 hours (95% CI: 2.5 to 10) with large heterogeneity $I^2 = 98\%$ (Fig. 3). The TSA showed that the required information size was not reached, but the DARIS line was crossed (Appendix 9, available at http://links.lww.com/PR9/A157). The quality of evidence (GRADE) was low (Table 2).

3.7.2. Pain at rest after 24 hours

Three studies reported on this outcome.6,22,44 The meta-analysis favored the control group and showed no significant difference in the overall effect of 3 mm in mean VAS (95% CI: −5 to 11). The heterogeneity was moderate, $I^2 = 79\%$ (Fig. 4). The TSA showed that the required information size was not reached, but the DARIS line was crossed (Appendix 9, available at http://links.lww.com/PR9/A157). The quality of evidence (GRADE) was low (Table 2).

3.7.3. Adverse events

Two studies reported on PONV44,61 and one on pruritus.50

3.8. Intrathecal morphine

Four studies reported on i.t. morphine.12,14,68,74 The risk of bias for all trials was low in one trial, unclear in 2 trials, and high in one trial (Fig. 2).

3.8.1. Pain at rest after 6 hours

Three studies reported on this outcome.12,68,74 The meta-analysis favored the experimental group and showed a significant difference of 12 mm in overall effect mean VAS (95% CI: 6–17). The heterogeneity was moderate, $I^2 = 52\%$ (Appendix 4, available at http://links.lww.com/PR9/A157). The TSA showed that the required information size was not reached, but the DARIS line was crossed (Appendix 10, available at http://links.lww.com/PR9/A157). The quality of evidence (GRADE) was high (Table 2).

3.8.2. Pain during mobilization after 6 hours

Three studies reported on this outcome.12,68,74 The meta-analysis favored the experimental group and showed a significant difference in the overall effect of 9 mm in mean VAS (95% CI: 3–15). The heterogeneity was moderate, $I^2 = 55\%$ (Appendix 8, available at http://links.lww.com/PR9/A157). The TSA showed that the required information size was not reached, but the DARIS line was crossed (Appendix 10, available at http://links.lww.com/PR9/A157). The quality of evidence (GRADE) was moderate (Table 2).

3.8.3. Pain at rest after 24 hours

Three studies reported on this outcome.12,68,74 The meta-analysis favored the experimental group and showed a significant difference in the overall effect of 10 mm in mean VAS (95% CI: 0.04–19). The heterogeneity was large, $I^2 = 88\%$ (Fig. 4). The TSA showed that the required information size was not reached, but the DARIS line was crossed (Appendix 10, available at http://links.lww.com/PR9/A157). The quality of evidence (GRADE) was moderate (Table 2).

3.8.4. Pain during mobilization after 24 hours

Three studies reported on this outcome.12,68,74 The meta-analysis favored the experimental group and showed a significant difference...
in the overall effect of 9 mm in mean VAS (95% CI: 0.75–18). The heterogeneity was large, $I^2 = 85\%$. The TSA showed that the required information size was not reached, but the DARIS line crossed (Appendix 10, available at http://links.lww.com/PR9/A157). The quality of evidence (GRADE) was moderate (Table 2).

### 3.8.5. Adverse events

Three studies reported on PONV. The meta-analysis favored the experimental group and showed no significant difference in the overall effect RR $-0.03$ (95% CI: $-0.13$ to 0.06). The heterogeneity was moderate, $I^2 = 45\%$ (Appendix 5, available at http://links.lww.com/PR9/A157). The quality of evidence (GRADE) was high (Table 2). Four studies reported on pruritus.

### 3.9. Qualitative analyses

Fifteen trials investigated other interventions: buprenorphine s.c., bupivacaine block, cold therapy, dezocine, lidocaine infusion, magnesium, nalaxone, pregabalin, propacetamol, rocuronium, and ropivacaine. Three trials investigated different analgesic combinations. The risk of bias was low in one trial, unclear in 15 trials, and high in 3 trials. From those, 10 trials demonstrated a significant effect on opioid consumption/supplemental analgesics and 12 studies on pain scores. Four trials demonstrated a significant reduction in opioid-related adverse events.

### 4. Discussion

In this systematic review of pain management after 1- or 2-level spinal fusion surgery, we identified 5 significant subgroups dealing with the following analgesic treatment: NSAIDS, epidural, ketamine, wound infiltration, and i.t. morphine.

When applying meta-analyses and TSA, in summary, we found a significant reduction in opioid consumption for NSAIDs and epidural, and both groups achieved the minimal clinical important difference (MCID) of 10 mg. For 6 hours of pain at rest, we found a significant reduction in VAS for NSAID and i.t. morphine. Both groups achieved the MCID of 10 mm. Furthermore, we detected a significant reduction in VAS scores for pain at rest after 24 hours in the following groups: NSAID, epidural, ketamine and wound infiltration. The epidural and ketamine groups achieved MCID. We detected a significant reduction in VAS after 24 hours in pain during mobilization for i.t. morphine. No groups obtained MCID.

For adverse events, it was only possible to perform meta-analysis on PONV because very few studies reported on other types of adverse events, and no trials reported SAEs. Furthermore, it was impossible because of sparse data to report a reduced LOS regarding any analgesic treatment.

Former systematic reviews on postoperative pain and analgesics seem to focus on rare spinal procedures such as complex and major spine surgery, combining different surgery types. Our systematic review is, in our knowledge, the first to investigate the procedure-specific pain treatment for 1- or 2-level spinal fusion, a frequently performed surgical procedure.

Consequently, it was not possible to compare our findings to similar reviews. Reviews of pain treatment in mixed or complex spine surgery indicate that use of paracetamol, NSAIDs, i.v. ketamine infusion, epidural analgesia, and i.t. morphine decrease postoperative pain, similar to our findings. Unfortunately, they do not investigate opioid consumption. Our results indicate that wound infiltration seemed to favor the control groups for pain levels. That seemed not to be the case in a newer systematic review, which investigates all kinds of lumbar spine surgery. The authors found that the demand for opioids significantly reduced in patients who received wound infiltration. Therefore, to further elucidate whether the meta-analyses are relevant for 1- or 2-level spinal fusion patients, several large RCTs are needed.

Our review has several strengths. We performed a broad systematic and stringent search minimizing the risk of missing suitable trials. We published the protocol at PROSPERO in advance. We performed TSAs to reduce type 1 and 2 errors. We assessed all trials for risk of bias and used GRADE to evaluate the certainty of evidence.

This review also has limitations. The majority of the authors we contacted by email to account for the quality assessment did not answer. As a result, we could have rated some of the studies too hard hereby, affecting the GRADE evaluation. Because pain data often per se is nonparametric, it was necessary to perform the meta-analysis by converting median (interquartile range) to mean (SD) values, which could have affected the data. We found considerable heterogeneity between the included studies in sample size and within the analgesic groups such as NSAIDs (including COX-1 and COX-2) and the epidural group (with and without hydromorphone). However, it mirrors the pragmatism in the clinical field. For some regularly used analgesic groups (such as paracetamol), enough studies could not be identified, making it challenging to clarify the evidence on that particular area. According to GRADE, the certainty of evidence was very low or low for the majority of the eligible trials, and bias in most trials was unclear or high, keeping us from recommending any “golden” analgesic treatment.

The principles of multimodal analgesics used for postoperative pain have been the leading principle for years. Unfortunately, it is unclear which patients can benefit from which kind of analgesic combination. Before designating that, studies need to focus on decreasing patients’ pain procedure-specific instead of performing RCTs, which primarily aims to demonstrate an effect of an analgesic intervention by using a patient population. Moreover, studies not only need to focus on average pain in groups but also on the individual patient’s pain.

Effective pain treatment aims to ensure a fast recovery for the patients and to provide an acceptable quality of life, the ability of ambulation, few adverse events from the analgesic treatment, and sufficient sleep. Therefore, future RCTs of postoperative pain treatment should measure pain at rest and during mobilization, measure the quality of sleep, the quality of life, and the opioid-related and intervention-specific adverse events.

### 5. Conclusion

The present systematic review of analgesic treatments for patients undergoing lumbar 1- or 2-level fusion surgery demonstrated that NSAIDs significantly reduce opioid consumption and pain at rest after 6 hours, epidural significantly reduces opioid consumption and pain at rest after 24 hours, i.t. morphine significantly reduces pain levels at 6 and 24 hours during rest and mobilization, and ketamine significantly reduces pain at rest after 24 hours. However, most of the included studies represent an unclear or high risk of bias and low or very low quality of evidence. Therefore, based on the current literature, it is not possible to identify any best-proven analgesic treatment for patients undergoing 1- or 2-level spinal fusion. We suggest that future studies should include large-scale RCTs combined with individual responder analyses to examine relevant clinical analgesic effectiveness.
Disclosures
The authors have no conflicts of interest to declare.

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Appendix A. Supplemental digital content
Supplemental digital content associated with this article can be found online at http://links.lww.com/PR9/A157.

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