Systematic Review and Meta-Analysis

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Is preemptive analgesia a good choice for postoperative pain relief in lumbar spine surgeries?

A meta-analysis of randomized controlled trials

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Abstract

Background: Lumbar spine surgery is associated with moderate-to-severe postoperative pain. Adequate pain management during the postoperative period facilitates rehabilitation. Recently, preemptive analgesia has been considered among the important analgesic methods for reducing postoperative pain. However, its efficacy in postoperative pain relief after lumbar spine surgery remains unclear. This study aimed to evaluate the effects of preemptive analgesia on lumbar spine surgery.

Methods: We searched for randomized controlled trials in PubMed (1996 to May 2020), Embase (1980 to May 2020), and Cochrane Library (CENTRAL, May 2020). We included seven studies that evaluated the preemptive analgesic efficacy in lumbar spine surgeries.

Results: Seven studies, including 509 patients, met the inclusion criteria. Pooled data revealed that preemptive analgesia is effective for lumbar spine surgeries with respect to the visual analog scale score ($P < .05$), total morphine equivalent consumption ($P < .05$), and length of stay ($P < .05$), without increasing complications ($P = .73$).

Conclusions: Our findings indicate that preemptive analgesia is safe and effective for lumbar spine surgery.

Abbreviations: CIs = confidence intervals, LOS = length of hospital stay, MD = mean difference, OR = odd ratio, PRISMA = preferred reporting items for systematic review and meta-analyses, RCT = randomized controlled trial, VAS = visual analog scale.

Keywords: analgesia, lumbar spine surgery, morphine consumption, preemptive, visual analog scale

1. Introduction

Spine surgeries have become more frequent with the aging population[1]; however, postoperative pain is a common complication that can impede patient recovery. Approximately 80% of patients experience postoperative pain; among them, 86% present moderate-to-severe pain.[2]

Inadequate pain management after spine surgery can cause patient dissatisfaction and delayed functional recovery. Adequate postoperative pain management facilitates early ambulation, reduction of hospital stay, and improved satisfaction.[3–6] Various analgesic methods, including nonsteroidal anti-inflammatory drugs, patient-controlled analgesia, paracetamol, and local infiltrations, have been used.[7–10]

Pre-emptive analgesia, which involves preoperative analgesia administration, has recently been used in lumbar spine surgery and has shown great promise.[8,11–13] We hypothesized that preemptive analgesia is effective for postoperative analgesia. This study aimed to evaluate the effects of preemptive analgesia on lumbar spine surgery.

2. Method and materials

The study was approved by the ethics committee of Xiaoshan Traditional Chinese Medical Hospital. We employed the PRISMA guidelines and Cochrane Handbook to ensure that our results are reliable and actual.[14]

2.1. Search strategy

We systematically searched PubMed (1996 to May 2020), Embase (1980 to May 2020), and Cochrane Library (CENTRAL, May 2020). Further, we searched Google Scholar and

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LKZ and QL contributed equally to this work.

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The authors report no conflicts of interest.

The datasets generated during and/or analyzed during the current study are publicly available.

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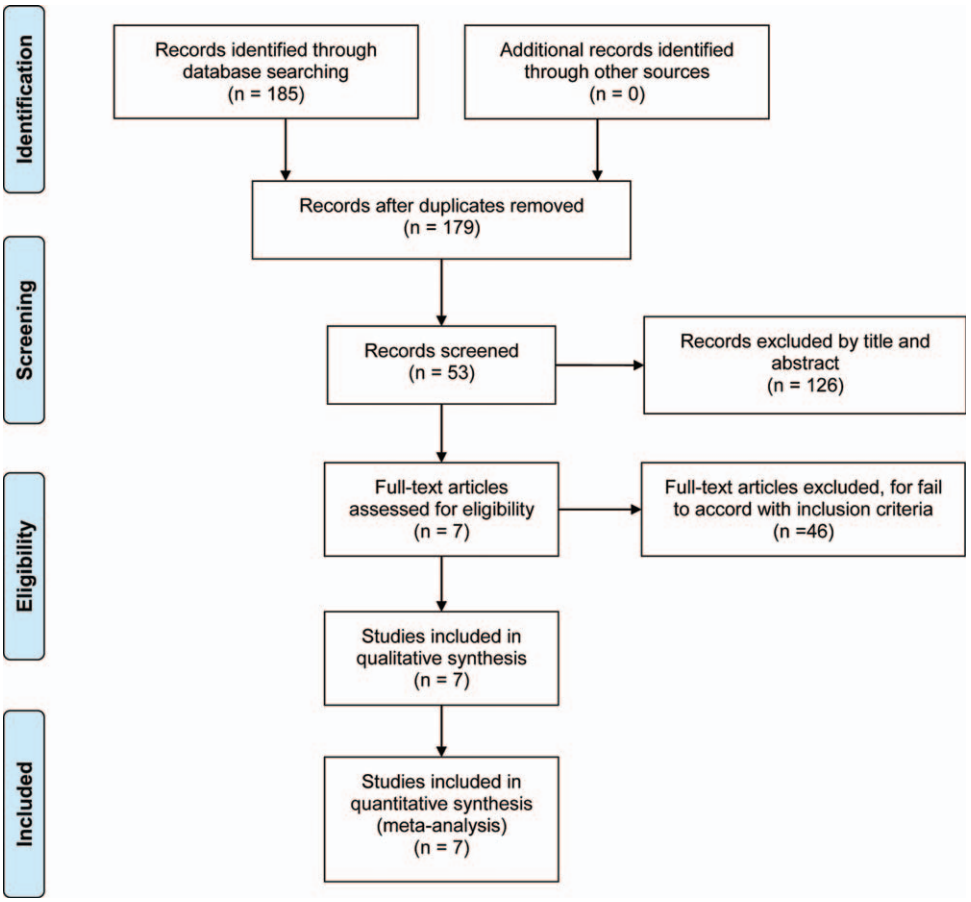

Figure 1. The search results and selection procedure.

identified related references. We only included randomized controlled trials (RCTs). "Spine surgery," "Analgesia," and "Preemptive" were the keywords used with Boolean operators "AND" or "OR." Figure 1 shows the search results.

2.2. Inclusion criteria

We included trials based on the PICOS (i.e., patients, intervention, comparator, outcome, study design) criteria as follows: patients: patients who underwent their first lumbar spine surgery; intervention: patients who received preoperative analgesics (anesthetics, non-steroidal anti-inflammatory drugs, and opioids) through intravenous push, intravenous, epidural, or oral administration; comparator: the comparator was a placebo; outcomes: these included the visual analog scale (VAS) score, equivalent morphine consumption, complications, and length of hospital stay (LOS); study design: RCTs.

2.3. Data extraction and bias risk assessment

Two reviewers independently collected available data, with disagreements being resolved through consultation with a third reviewer. Basic characteristics included the patients' age, sex, body mass index, reference type, analgesic types, and analgesic dosages. Our primary outcome was the VAS score, which comprised 11 pain levels, with 0 and 10 indicating no and worst pain, respectively. Secondary outcomes included equivalent morphine consumption, complications, and LOS. To allow comparison of opioid consumption, we converted all opioids to the equivalent morphine consumption dosage based on the standard formula (Table 1). The Cochrane Handbook for Systematic Review of Interventions (Review Manager 5.3) was used to evaluate the bias risk of the included RCTs.

2.4. Statistical analysis

Statistical analyses were performed using Review Manager Software (version 5.3; Cochrane Collaboration, Copenhagen: The Nordic Cochrane Center). Regarding continuous variables, the mean difference (MD) with 95% confidence intervals (CIs) were applied to weigh the effect interval. For discontinuous data,

Table 1

Conversion of analgesics use into equivalent morphine dosage.

Analgesics	Dosage of Morphine Equivalents (mg)
Morphine (subcutaneous or intramuscular)	10
Hydromorphone (subcutaneous or intramuscular/oral)	1.5/7.5
Codeine (subcutaneous or intramuscular/oral)	120/200
Oxycodone (oral)	20
Demerol (subcutaneous or intramuscular/oral)	80/300

Table 2

The characteristics of included studies.

Studies (yr)	Pre-analgesia Group/Control Group				Analgesics and Dosages	Reference Type
	Patients (n)	Ages (yr)	Female Gender (%)	BMI		
Kien et al 2019	30/30	45/48	40/60	21.8/22	150 mg pregabalin and 200 mg celecoxib	RCT
Raja et al 2018	47/50	49.7/51.6	78/74	26.4/25.8	1 gram paracetamol, 20 mg ketorolac, and 75 mg pregabalin	RCT
Aglio et al 2018	34/32	59.5/60	52/41	N/A	31.25 mg bupivacaine and 0.5 mg hydromorphone	RCT
Kumar et al 2017	30/30	44.3/45.3	N/A	24.4/23.6	20 mL of 0.2% ropivacaine	RCT
Kim et al 2016	40/40	67.9/66.3	N/A	N/A	200 mg celecoxib, 75 mg pregabalin, 500 mg acetaminophen, and 10 mg extended-release oxycodone	RCT
Siribumrungwong et al 2015	32/32	58/55.6	65.6/59.4	26/26	40 mg parecoxib	RCT
Sekar et al 2004	42/40	N/A	38/40	N/A	15 ml 0.5% bupivacaine and 1 ml tramadol hydrochloride	RCT

BMI = body mass index, N/A = not applicable, RCT = randomized controlled trial.

we used the odds risk (OR) and risk difference with 95% CIs to determine the effect interval. We used the P and I^2 values to assess the among-study heterogeneity. When $I^2 < 50\%$ and $P > .1$, we applied a fixed-effects model; otherwise, we applied a random-effects model.

3. Results

3.1. Search results

Based on the search strategy, we retrieved 185 studies; among them, we excluded 6 duplicated papers using Endnote software and 126 studies by reading the title and abstract. After a full-text review, we removed 46 references. Finally, we included seven RCTs[8,15–20] in our meta-analysis. Table 2 summarizes the basic characteristics and interventions.

3.2. Risk of bias of assessment

Figures 2 and 3 present the risk of bias in the RCT assessment. Among the seven RCTs, six RCTs[15–20] described the methods for generating random sequences. Three studies employed a double-blind method.[15,16,18] Publication bias was assessed using a funnel plot diagram (Fig. 4). The symmetrical funnel plot diagram revealed no significant risks of VAS, morphine equivalent consumption, and complications. We could not determine the risk of publication bias due to the two studies on LOS.

3.3. Results of meta-analysis

3.3.1. VAS. Three studies,[8,15,16] on 226 patients reported the VAS score at 8 postoperative hours, with no significant difference between the pre-analgesia and control groups (MD = −1.32; 95% CI, [−2.89, 0.25]; $P = .1$). Fig. 5). Four studies[8,15,16,20] on 323 patients reported the VAS score at 24 postoperative hours, with the preanalgesia group showing a lower score than the control group, (MD = -1.5; 95% CI, [-2.46, -0.54]; $P < .05$). Fig. 5). Similar findings were observed at 48 postoperative hours (MD = −1.5; 95% CI, [−2.46, −0.54]; $P < .05$). Fig. 5)[20] and for combined data (MD = −1.38; 95% CI, [−1.93, −0.82]; $P < .05$. Fig. 5).

3.3.2. Morphine equivalent consumption. Three studies[16,18,19] on 189 patients reported the morphine equivalent consumption at 24 postoperative hours, with the pre-analgesia group showing lower consumption than the control group (MD = −1.69; 95% CI, [−3.36, −0.02]; $P < .05$. Fig. 6). Similar results were reported at 48 hours[18,19] (MD = −8.25; 95% CI, [−12.94, −3.57]; $P < .05$). Fig. 6). One study reported total

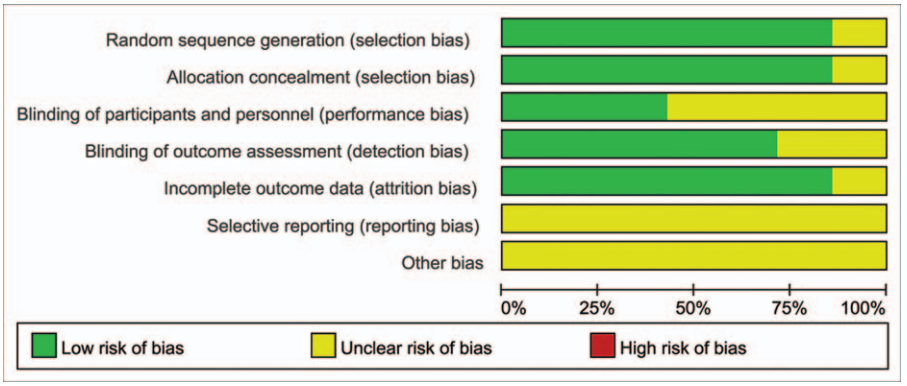

Figure 2. The risk of bias summary: review authors' judgment of each risk of bias items for each included studies.

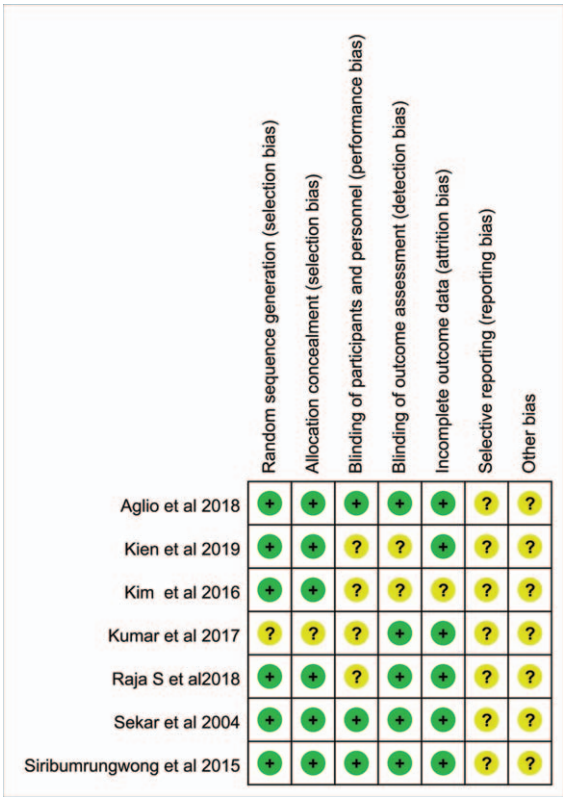

Figure 3. The risk of bias graph of the included studies.

morphine equivalent consumption, with no significant between-group differences (MD = −0.10; 95% CI, [−4.37, 4.17]; $P > .05$. Fig. 6).

3.3.3. Complications. Four studies reported nausea and vomiting, with no significant between-group differences (OR = 0.86; 95% CI, [0.47, 1.57]; $P = .63$; Fig. 7).[16,17,19,20] Two studies on 197 patients reported urinary retention.[17,20] Pooled data revealed no significant between-group differences (OR = 0.94; 95% CI, 0.44. 2.00; $P = .86$). Fig. 7). Siribumrungwong et al.[16] reported dizziness complications, with no significant between-group differences (OR = 1.25; 95% CI, [0.34, 4.59]; $P = .74$). Fig. 7).

3.3.4. Length of stay. Two studies on 162 patients reported the LOS,[18,20] with pooled data revealing that the pre-analgesia group had a reduced LOS than the control group (MD = −0.45; 95% CI, [-0.89, −0.01]; $P < .05$) Fig. 8).

4. Discussion

We observed that preemptive analgesia is effective for patients who have undergone spinal surgery. Approximately 80% of patients who undergo lumbar spine surgery present moderate-to-severe pain, which may delay rehabilitation and functional exercise. In 2016, preemptive multimodal analgesia has been recommended by the American Pain Society. Further, preemptive analgesia is an effective method for reducing postoperative pain in lumbar spine surgery.[21] Preemptive analgesia involves the preoperative application of various analgesic drugs to prevent postoperative pain and complications. Pooled data in this meta-

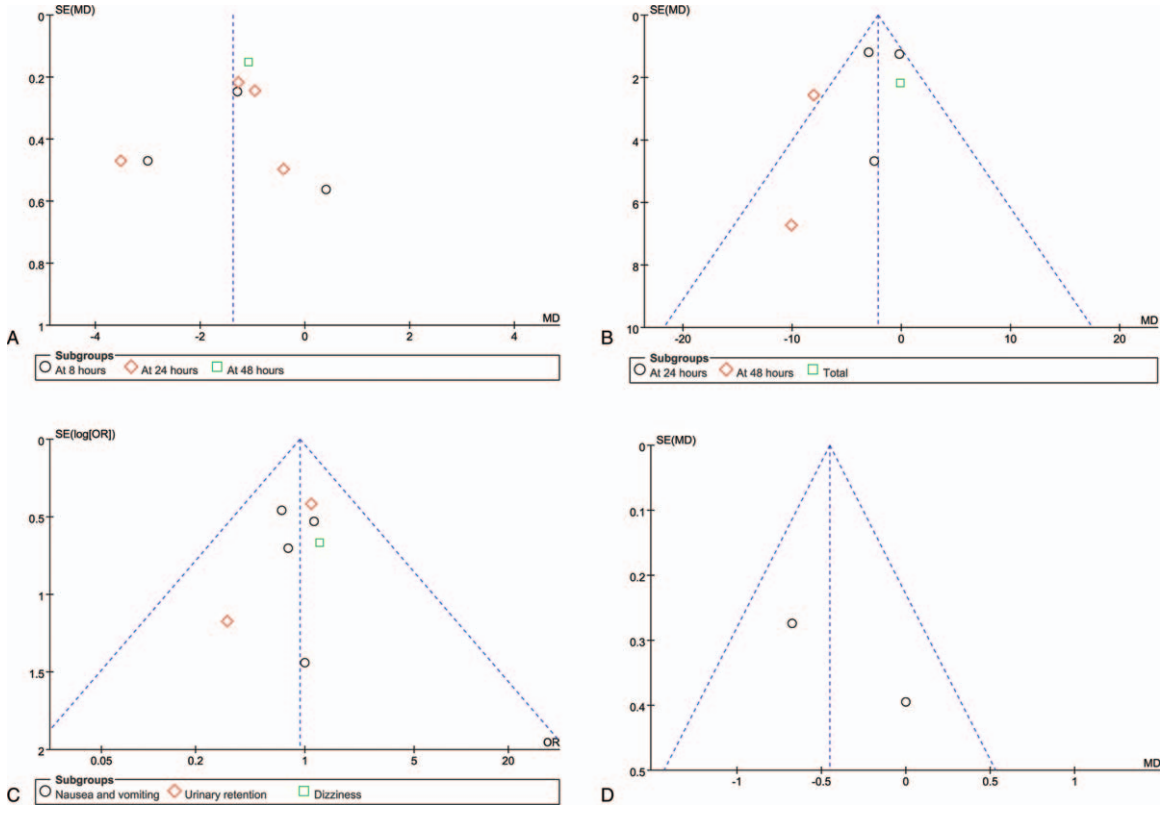

Figure 4. (A) A funnel plot of visual analog scale (VAS); (B) A funnel plot of Morphine equivalent consumption; (C) A funnel plot of Complications; (D) A funnel plot of Length of stay.

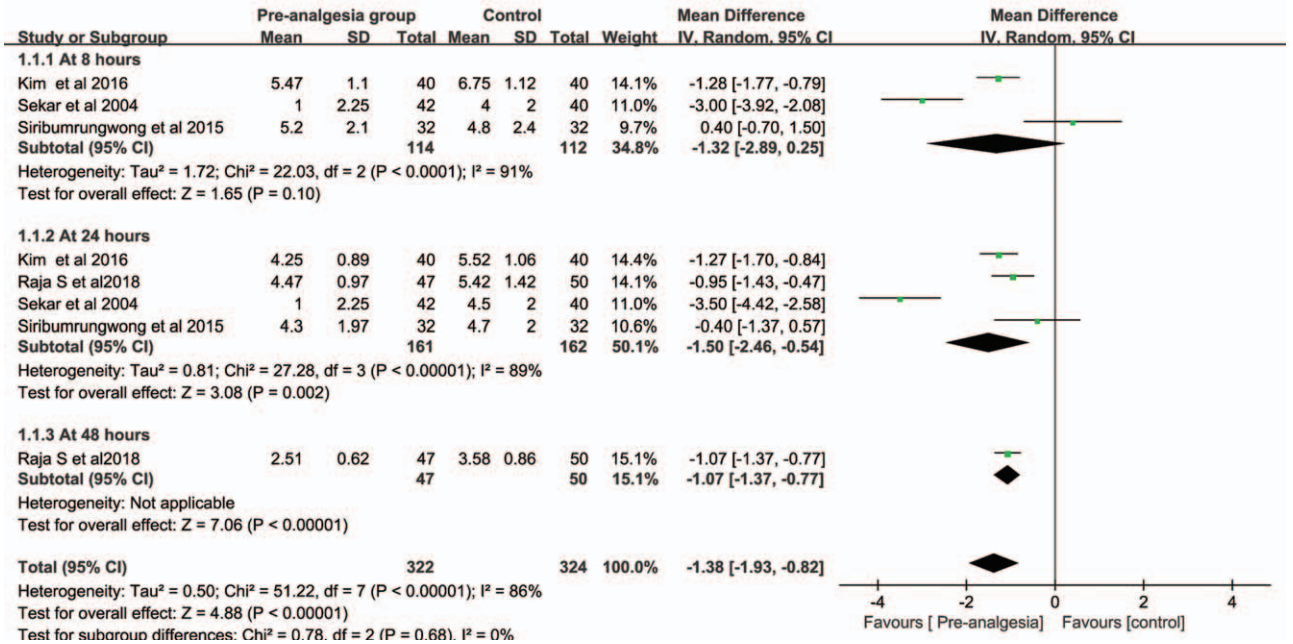

Figure 5. A forest plot diagram showing the visual analog scale (VAS).

analysis revealed that compared with the control group, preemptive analgesia (anesthetics, non-steroidal anti-inflammatory drugs, and opioids) showed lower VAS scores and total equivalent morphine consumption in patients undergoing lumbar spine surgery.

Regarding spine surgery, improved postoperative pain is associated with better clinical outcomes. The increasing importance of postoperative pain management in surgeons could be attributed to pain being among the important indicators for evaluating the surgery quality. Studies included in this meta-analysis evaluated postoperative pain using VAS. Compared with the control group, the pre-analgesia group showed lower VAS scores within the first 48 postoperative hours. Regarding the morphine-equivalent consumption, Kien et al[19] reported that morphine consumption was significantly lower in the pre-analgesia group than in the control group at 48 postoperative

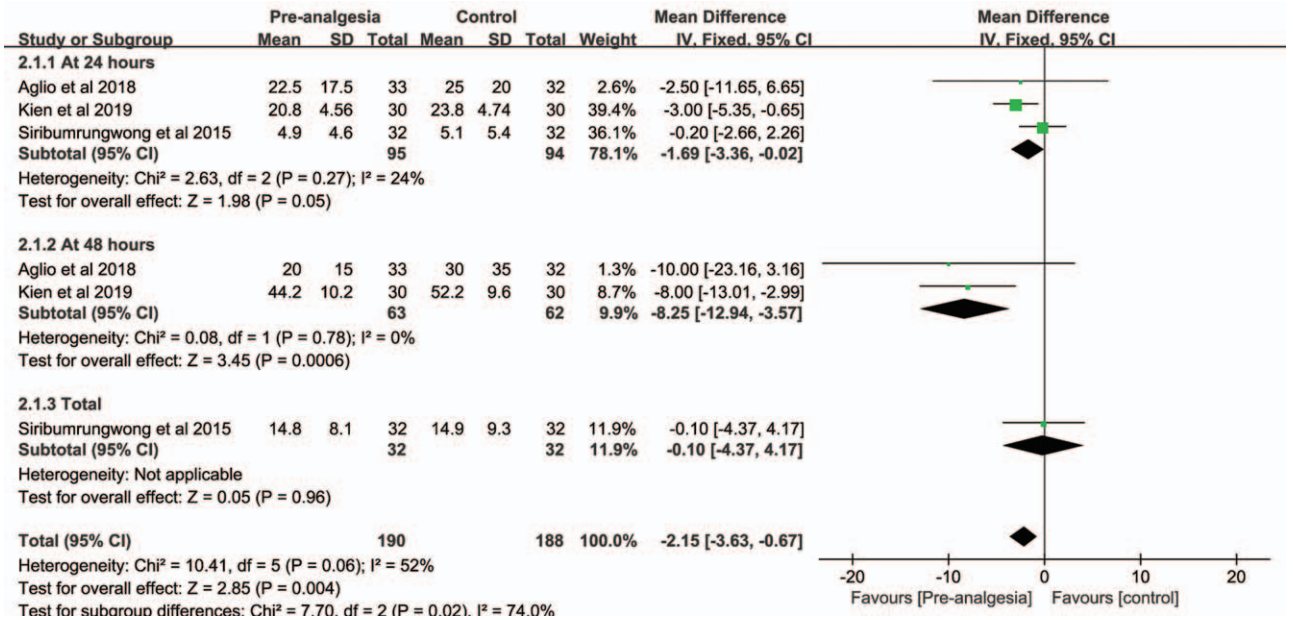

Figure 6. A forest plot diagram showing the Morphine equivalent consumption.

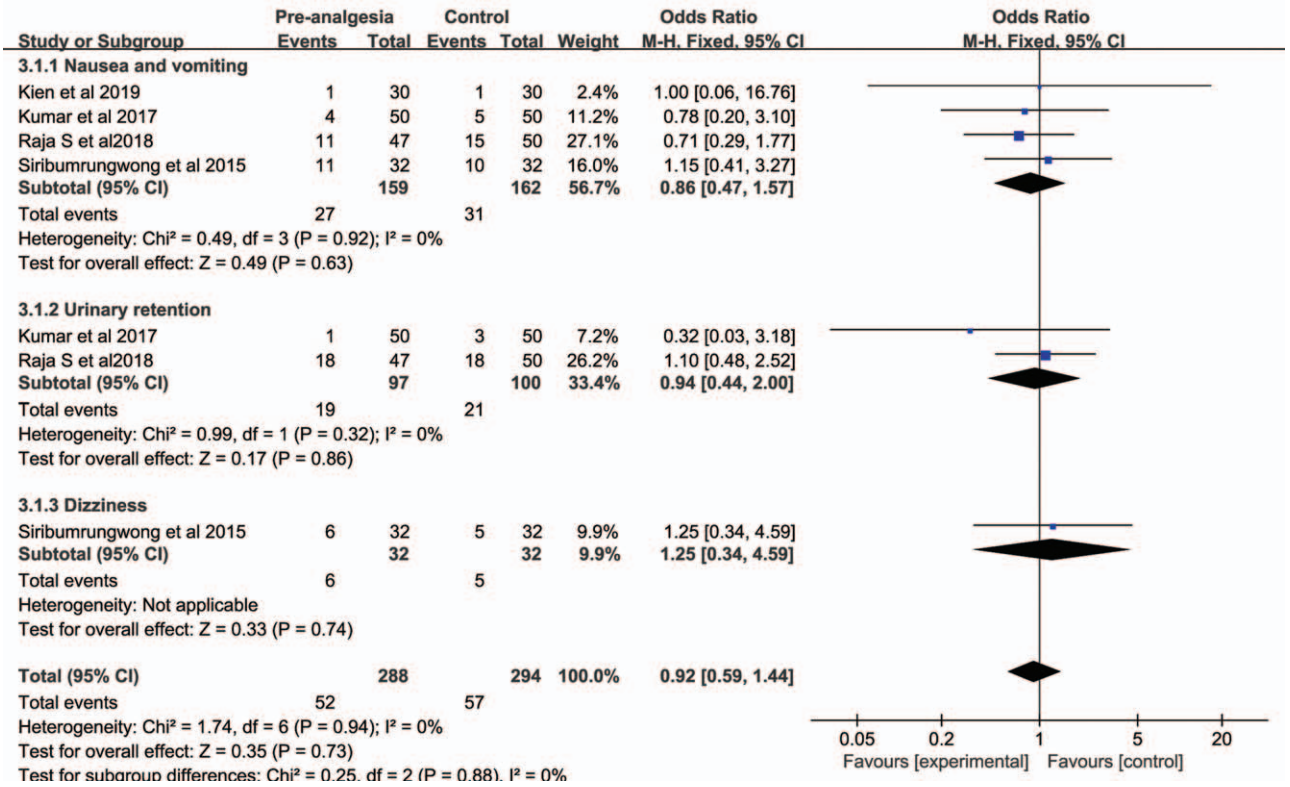

Figure 7. A forest plot diagram showing the Complications.

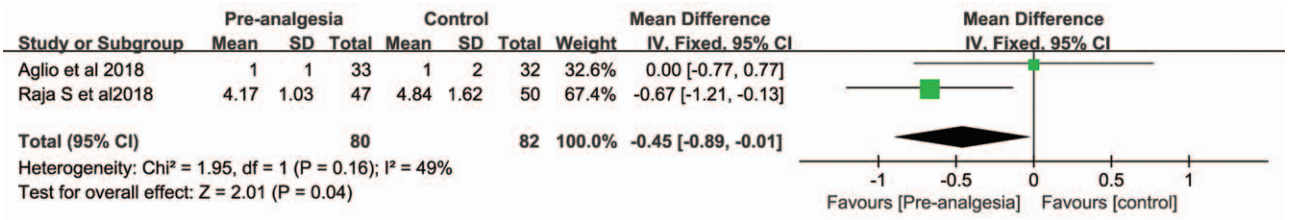

Figure 8. A forest plot diagram showing the Length of stay. Credit: All figures can be printed by the *Medicine*.

hours. We observed no significant between-group difference in morphine consumption, which further supports the use of preoperative analgesics. Further, we analyzed complications, including nausea and vomiting, urinary retention, and dizziness. Pooled data revealed no significant between-group difference in the incidence of complications. Regarding the LOS, the pre-analgesia group showed a shorter hospital stay than the control group.

This meta-analysis had several limitations. First, we only included 7 RCTs and stronger results could have been yielded by including high-quality RCTs. Second, variations in analgesics may result in potential bias. Third, regarding the VAS heterogeneity at 24 postoperative hours, we attempted to determine the heterogeneity source. After removing the RCT by Sekar et al,[15] there was a significant reduction in the heterogeneity of the morphine-equivalent consumption at 24 and 48 postoperative hours. Consequently, we considered the study by Sekar et al[15] as the heterogeneity source. Sekar et al[15] employed two analgesic drugs (15 mL 0.5% bupivacaine and 1 mL tramadol hydrochloride) in the preemptive analgesia group. Other studies applied a combination of ≥ three analgesics. Therefore, the analgesic combination may have resulted in heterogeneity. Fourth, we did not analyze outcomes, including the Oswestry Disability Index, functional scores, and surgery duration due to insufficient data.

5. Conclusion

In conclusion, compared with the control group, the preemptive analgesia group was superior with respect to the VAS scores at 24 and 48 postoperative hours, as well as the morphine-equivalent consumption, without increasing the complication risk. Therefore, we recommend preemptive analgesia as an available method for patients undergoing lumbar spine surgery.

Author contributions

Conceptualization: Lu-kai Zhang.
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Formal analysis: Lu-kai Zhang.
Funding acquisition: Qiang Li.
Investigation: Qiang Li.
Methodology: Qiang Li.
Project administration: Qiang Li.
Resources: Ren-fu Quan.
Software: Ren-fu Quan.
Supervision: Ren-fu Quan.
Validation: Ren-fu Quan.
Visualization: Ren-fu Quan.
Writing – original draft: Ren-fu Quan.
Writing – review & editing: Jun-sheng Liu.

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