

Effect of perioperative intravenous lidocaine for patients undergoing spine surgery

A meta-analysis and systematic review

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Abstract

Background: Perioperative intravenous lidocaine has been reported to have analgesic and opioid-sparing effects in many kinds of surgery. Several studies have evaluated its use in the settings of spine surgery. The aim of the study is to examine the effect of intravenous lidocaine in patients undergoing spine surgery.

Methods: We performed a quantitative systematic review. Databases of PubMed, Medline, Embase database and Cochrane library were investigated for eligible literatures from their establishments to June, 2019. Articles of randomized controlled trials that compared intravenous lidocaine to a control group in patients undergoing spine surgery were included. The primary outcome was postoperative pain intensity. Secondary outcomes included postoperative opioid consumption and the length of hospital stay.

Result: Four randomized controlled trials with 275 patients were included in the study. postoperative pain compared with control was reduced at 6 hours after surgery (WMD -0.50 , 95%CI, -0.76 to -0.25 , $P < .001$), at 24 hours after surgery (WMD -0.50 , 95% CI, -0.70 to -0.29 , $P < .001$) and at 48 hours after surgery (WMD -0.57 , 95%CI, -0.96 to -0.17 , $P = .005$). The effect of intravenous lidocaine on postoperative opioid consumption compared with control revealed a significant effect (WMD -15.36 , 95% CI, -21.40 to -9.33 mg intravenous morphine equivalents, $P < .001$).

Conclusion: This quantitative analysis of randomized controlled trials demonstrated that the perioperative intravenous lidocaine was effective for reducing postoperative opioid consumption and pain in patients undergoing spine surgery. The intravenous lidocaine should be considered as an effective adjunct to improve analgesic outcomes in patients undergoing spine surgery. However, the quantity of the studies was very low, more research is needed.

Abbreviations: HS = hospital stay, IV = intravenous, NRS = numerical rating scales, PACU = postanesthesia care unit, PCA = patient controlled analgesia, PONV = postoperative nausea and vomiting, SD = standard deviation, SE = standard error, VAS = visual analog scales, WMDs = weight mean differences.

Keywords: intravenous lidocaine, multi-model analgesia, spine surgery

1. Introduction

Spine surgery is known to be extremely painful, and postoperative pain is usually hard to control.^[1] The uncontrolled postoperative pain is associated with worsened functional

recovery, delayed early ambulation, and prolonged hospital stay,^[2,3] it may also develop into chronic pain in the long term.^[3] Opioids are fundamental for the postoperative analgesia,^[1,4] however, their administration may cause adverse effects, such as nausea, vomiting, respiratory depression, and pruritus,^[1,4] so multi-model analgesia has been recommended to reduce the consumption of opioid.^[3] Lidocaine was developed in 1948 as a local anesthetic,^[5] systematic administration of lidocaine has the analgesic and anti-inflammatory effect and has been proved to be effective as an adjuvant in postoperative pain management of major abdominal surgery.^[5] Several studies have reported its use in the settings of spine surgery,^[1,6] but their conclusions seem to be contradictory and need to be analyzed. In this study, we conducted a meta-analysis to explore the role of lidocaine in reducing the pain and opioid consumption after spine surgery.

2. Method

2.1. Search strategy and selection criteria

We searched PubMed, Medline, Embase database and Cochrane library (between January 1985 and June 2019) using the following terms: “spine”, “surgery” and “lidocaine”, No language restriction was applied. Randomized controlled studies of any size that compared lidocaine with placebo for patients undergoing spine surgery and took the pain or morphine

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All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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consumption as a primary or secondary outcome, and were published in full in peer-reviewed journals, were included. We excluded studies if they

- 1) were not RCTs,
- 2) did not compare lidocaine and placebo
- 3) did not mention the perioperative use of lidocaine to prevent postoperative pain
- 4) did not include patients undergoing spine surgery
- 5) had not been published or only the abstracts were presented in a conference.

2.2. Method of review

Each article was reviewed by 2 independent researchers who used the double-extraction method for meeting our inclusion criteria. A consensus procedure was conducted for study inclusion through discussion. If the consensus was not reached, a third reviewer would make a judgement before the final analysis. Two researchers were in charge of the data extraction work. The following information was recorded: the first author, the publication time, study design, study name, participant characteristics, outcome measures, surgical procedure, time of follow-up, pain score [time, mean, and standard deviation (SD)], lidocaine administration characteristics, postoperative analgesic administration and endpoints of each study. Groups (≤ 6 hours, 24 hours, and 48 hours after the surgery) were divided according to the contents of included studies. Numerical rating scale of pain or visual analog scale was adapted to an 11-point numeric rating scale (0 = no pain, 10 = extreme pain). Postoperative opioids were transformed to the equianalgesic dose of intravenous morphine assuming no cross-tolerance. When the same outcomes were reported more than once, the most conservative value was used. The quality of the RCTs was assessed with the use of the Cochrane Collaboration's recommended tool by 2 reviewers.

The primary outcome was patients' self-reported level of pain intensity on 0–10 pain scales such as visual analog scales (VAS), numerical rating scales (NRS), and other validated pain scales. The secondary endpoints were defined as the opioid-sparing effect of perioperative use of lidocaine and the length of hospital stay.

2.3. Statistical analysis

Continuous data were analyzed using weight mean differences (WMDs) and their 95% CIs for combining various scales. Data provided as mean and standard deviation were extracted. Data provided as standard error were transformed to standard deviation through the formula: $SD = SE \text{ (standard error)} \times \sqrt{n}$ (n = sample size). Data provided as 25% and 75% percentiles or 95% CI were transformed to standard deviation through the formula described by Hazo et al.^[7] For dichotomous data, RR with 95% CI were estimated. The heterogeneity among these included studies was evaluated by I² statistics, random effect model was applied when there was high heterogeneity ($I^2 > 50\%$) across the studies, whereas significant heterogeneity was not observed across the studies ($I^2 \leq 50\%$), fixed effect model was applied. Publication bias was examined by Egger test. All statistical was executed by stata15.1. Statistical significance was represented by $P < .05$.

2.4. Ethics approval and consent to participate

No patients or members of public were involved in the present study. No patients were asked to advise on the interpretation or

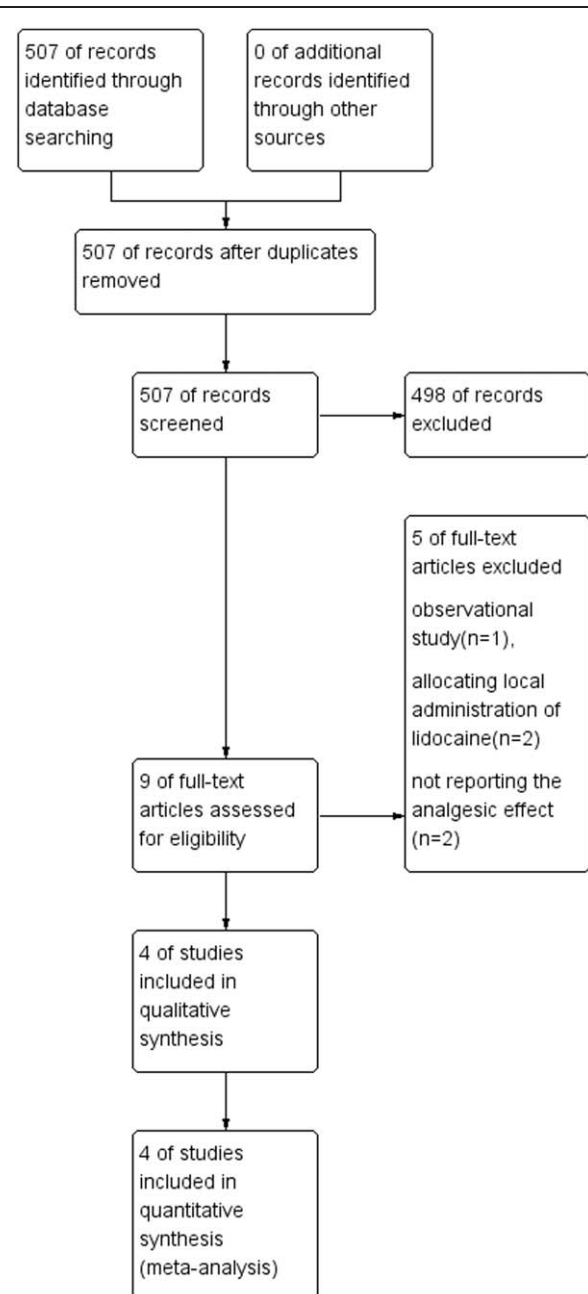


Figure 1. Article selection flow chart.

writing up of results. The results of the present research will be communicated to the relevant patient community.

3. Result

We identified 507 studies in the initial literature research. Based on the inclusion criteria, 498 studies were excluded, with a selection of 9 studies for a more detailed review. 5 studies were subsequently excluded, including 1 observational study, leaving 4 randomized controlled trials (Fig. 1). Finally, 4 randomized controlled trials were included for meta-analysis.^[1,6,8,9] There were 137 patients in the lidocaine group and 138 patients in the control group. Characteristics of each study are presented in Table 1. Their methodological quality is presented in the Figures 2 and 3.

Table 1

Characteristics of included study.

Author	Country	Year	Study Type	n	Time of Administration	Time of Observation	Primary outcome	Secondary outcome	Key message
Farag et al	The United States	2013	RCT	115	Intravenous lidocaine (2 mg/kg-1 h-1) with maximum of 200 mg/h starting at induction of anesthesia and continuing until discharge from the postanesthesia care unit (PACU) or a maximum of 8 h	Pain was evaluated with verbal response scores (0 = no pain and 10 = worst pain) at 30-min intervals while in the postanesthesia care unit, and every 4–6 h, thereafter.	Verbal response scores during the first 24h postoperatively	Opioid consumption, quality of life	Lidocaine administration to patients undergoing complex spine operations reduced pain but not opioid requirements early in the postoperative period
Dewinter et al	Belgium	2017	RCT	69	Patients in the lidocaine-group were given an IV bolus injection of lidocaine 1.5 mg/kg-1 at induction of anesthesia and then a continuous infusion of 1.5 mg -kg-1-h-1 which was continued until 6 h after arrival at the PACU	Postoperative pain as evaluated with the numeric rating scale (NRS) at rest and coughing, assessed each 15 min the first two hours postoperatively at the PACU, every h during the following 22 hours, and once daily on day 2 and 3	Morphine requirements during the first 24h postoperatively	Postoperative pain, PONV, inflammatory response, time to recovery of bowel function, length of hospital stay, quality of life	Systemic lidocaine had no analgesic benefits in posterior arthrodesis when added to an opioid based anesthetic regimen.
Ibrahim et al	Egypt	2018	RCT	40	Lidocaine group patients received a loading dose of IV lidocaine 2mg/kg slowly just before induction of anesthesia, then the lidocaine infusion started at a rate of 3mg/kg/h	Postoperative pain evaluation during rest was assessed by VAS (visual analogue scale). The score was recorded at the following times: immediately at 1 hour, 6hours, 12 hours, 24 hours, at discharge time, 1 month, 2 months, and 3 months after surgery.	Visual analogue scale	The total dose of rescue analgesia (morphine)	Intra-operative lidocaine, when given intravenously as a bolus followed by an infusion, significantly decreased long term postoperative back pain intensity in patients undergoing spinal fusion surgery
Kim et al	South Korea	2013	RCT	51	Patients assigned to Group Lidocaine received an IV bolus injection of 1.5 mg/kg lidocaine followed by a continuous infusion of 2 mg/kg/h	Postoperative pain evaluation during rest was assessed by VAS (visual analogue scale). The score was recorded at the following times: at 2, 4, 8, 12, 24, and 48 hours after surgery	The VAS (0–100 mm) pain score at 4 hours after surgery	The VAS pain score at 2, 8, 12, 24, and 48 hours after surgery, the frequency that patients pushed the button (FPB) of the PCA system, and the fentanyl consumption at 2, 4, 8, 12, 24, and 48 hours after surgery	Intraoperative systemic infusion of lidocaine decreases pain perception during microdiscectomy, thus reducing the consumption of opioid and the severity of postoperative pain. This effect contributes to reduce the length of HS.

HS = hospital stay, IV = intravenous, NRS = numeric rating scale, PACU = postanesthesia care unit, PCA = patient controlled analgesia, PONV = postoperative nausea and vomiting, RCT = randomized controlled study, VAS = visual analogue scale.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Dewinter 2017	+	+	+	+	+	?	?
Farag 2013	?	?	+	+	+	+	?
Ibrahim 2018	+	+	+	+	+	+	?
Kim 2014	+	+	+	+	+	+	?

Figure 2. Risk of bias summary.

3.1. Postoperative pain ≤ 6 hours after surgery

There was moderate heterogeneity among the trials ($I^2 = 34.4\%$, $P = .206$). The pooled data from 4 studies investigating the effect of perioperative lidocaine on the postoperative pain at 6 hours

after the surgery showed a statistically significant effect in fixed-effect models (WMD -0.50 , 95%CI, -0.76 to -0.25 , $z = 3.84$, $P < .001$, Fig. 4). Result of the Egger test for the postoperative pain at 6 hours after surgery ($P = .68$) suggested that any publication bias across included studies was unlikely.

3.2. Postoperative pain at 24 hours after surgery

There was no significant heterogeneity among the trials ($I^2 = 24.7\%$, $P = .263$). The pooled data from 4 studies investigating the effect of perioperative lidocaine on the postoperative pain at 24 hours after surgery showed a statistically significant effect in fixed-effect models (WMD -0.50 , 95%CI, -0.70 to -0.29 , $z = 4.65$, $P < .001$, Fig. 5). Result of the Egger test for the postoperative pain at 24 hours after surgery ($P = .20$) suggested that any publication bias across included studies was unlikely.

3.3. Postoperative pain at 48 hours after surgery

There was statistically high heterogeneity among the trials ($I^2 = 74.2\%$, $P = .009$). The pooled data from 4 studies investigating the effect of perioperative lidocaine on the postoperative pain at 48 hours after surgery showed a statistically significant effect in random-effect models (WMD -0.57 , 95%CI, -0.96 to -0.17 , $z = 2.85$, $P = .005$, Fig. 6). Result of the Egger test for the postoperative pain at 48 hours after surgery ($P = .15$) suggested that any publication bias across included studies was unlikely. Sensitivity analysis by removing individual studies did not reduce the heterogeneity substantially.

3.4. Opioid-sparing effect

Four studies investigated the opioid-sparing effect of perioperative lidocaine, 2 studies reported the opioid consumption during the first 24 hours after surgery,^[6,8] 2 studies reported the opioid consumption during the first 48 hours after surgery.^[1,9] There was high heterogeneity among the trials ($I^2 = 67.2\%$, $P = 0.027$), heterogeneity existed in the 24-hour group ($I^2 = 79.6\%$, $P = .027$). In random-effect models, the pooled data showed perioperative lidocaine had statistically significant effect on reducing the postoperative opioid consumption (WMD -15.36 , 95%CI,

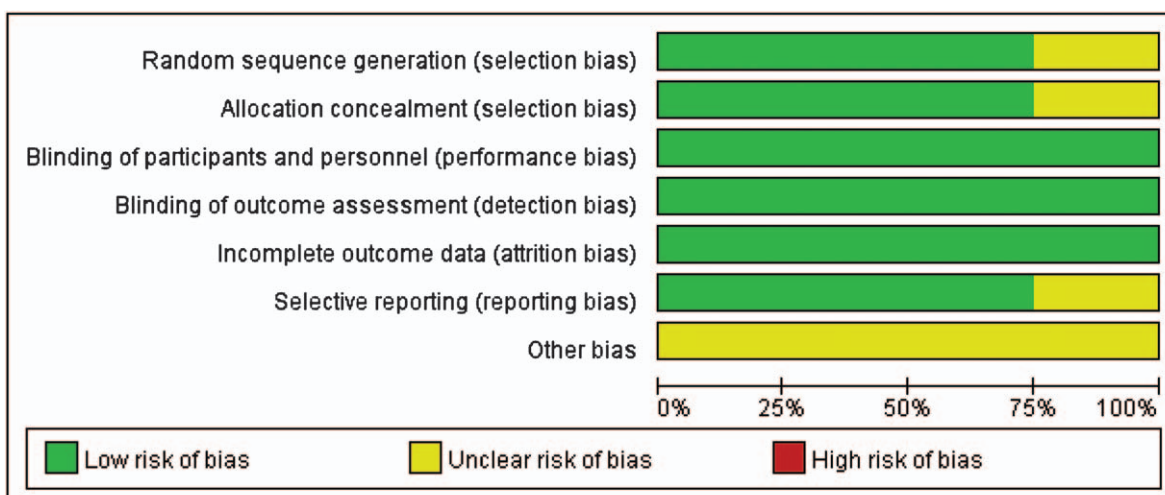


Figure 3. Risk of bias graph.

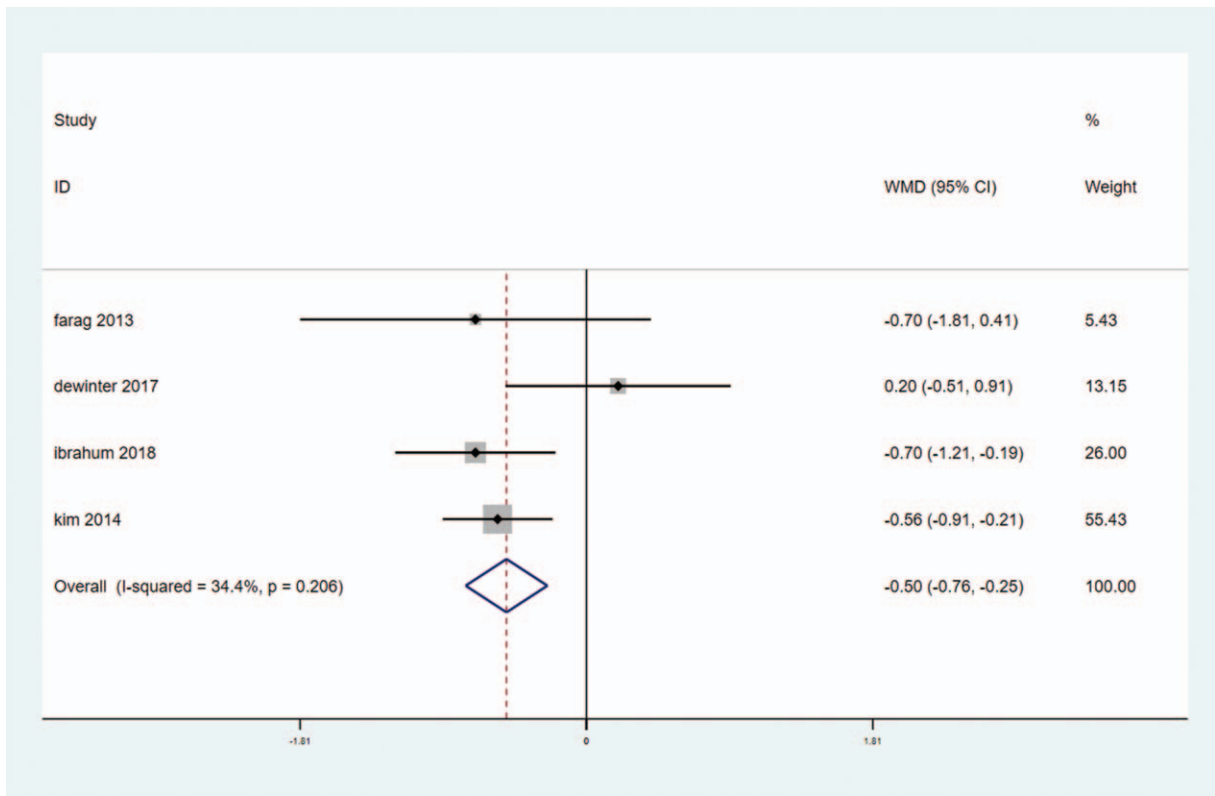


Figure 4. Forest plot of pain scores in 0 to 6 hours after surgery.

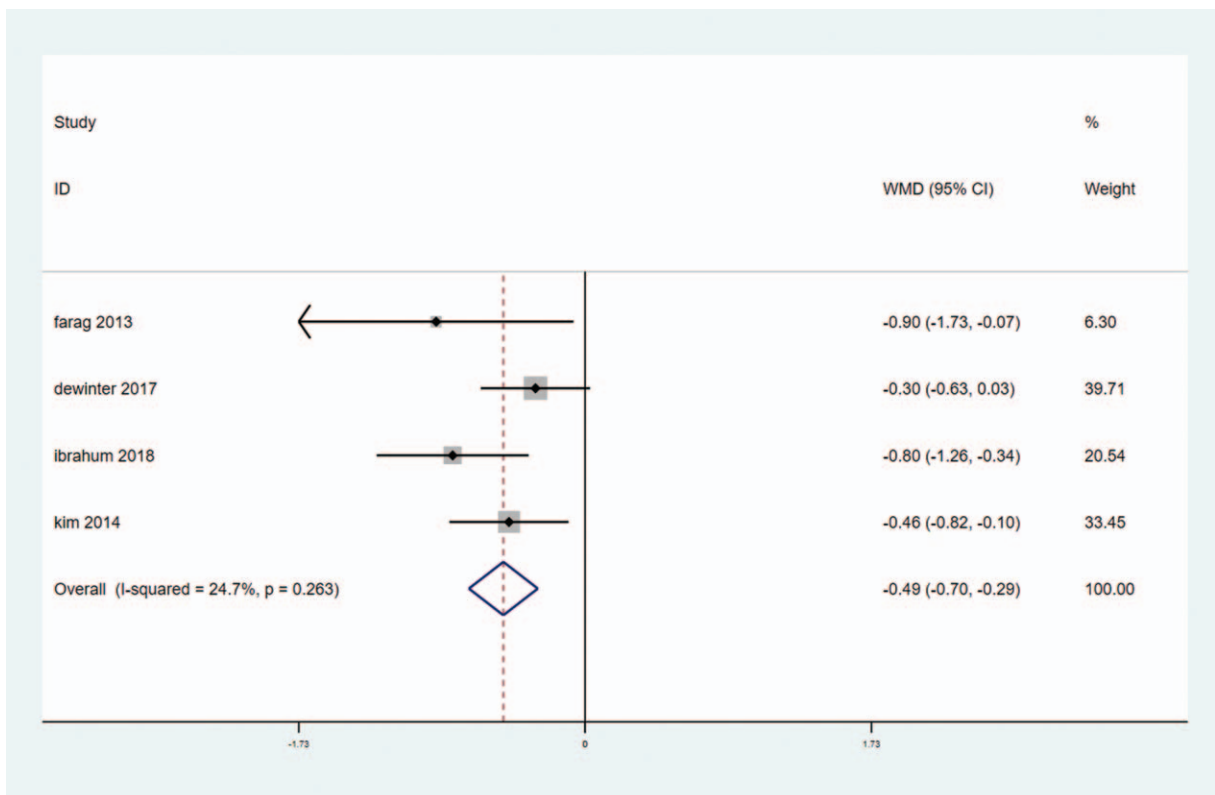


Figure 5. Forest plot of pain scores at 24 hours after surgery.

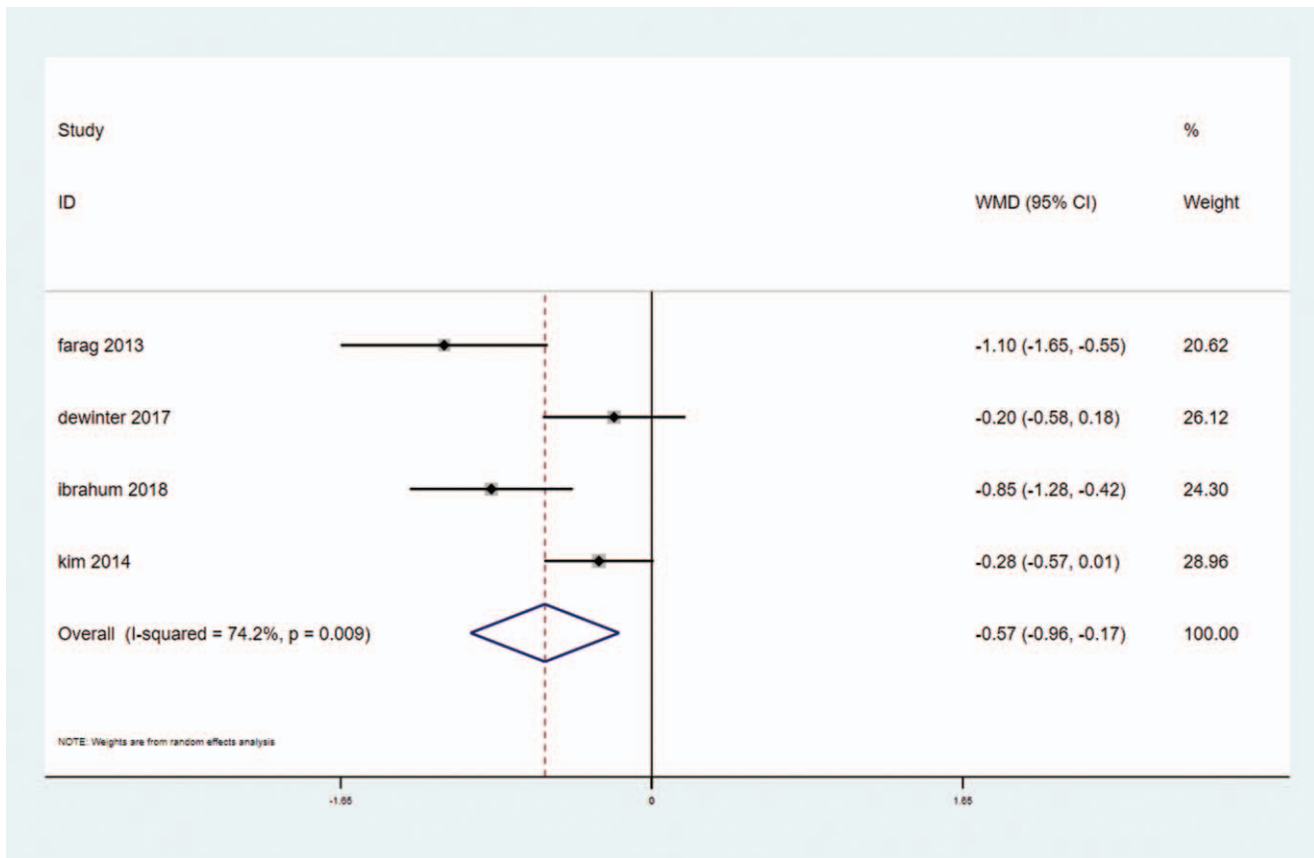


Figure 6. Forest plot of pain scores at 48 hours after surgery.

-21.40 to -9.33, $z=4.99$, $P<.001$; Fig. 7). Result of the Egger test for the opioid consumption after surgery ($P=.69$) suggested that any publication bias across included studies was unlikely. The sensitivity analysis suggested that the heterogeneity was reduced significantly by removing Dewinter et al study ($I^2=0\%$, $P=.41$).

3.5. Length of hospital stay

The hospital stay was collected from 4 studies. There was high heterogeneity among the trails ($I^2=71.8\%$, $P=.014$). In random-effect models, no significant difference was observed between the lidocaine and the control group (WMD -0.53, 95%CI, -1.30 to 0.23, $z=1.37$, $P=.172$, Fig. 8). Result of the Egger test for the length of hospital stay ($P=.65$) suggested that any publication bias across included studies was unlikely.

4. Discussion

As far as we know, this is the first meta-analysis and systematic review focusing on the effect of perioperative intravenous lidocaine in spine surgery. Our pooled data showed that perioperative intravenous lidocaine attenuated the pain intensity at 6, 24, and 48 hours after the surgery and reduced opioid consumption. Our finding suggested that perioperative intravenous lidocaine could be an effective multi-modal analgesia adjunct for acute pain management in patients undergoing spine surgery.

Our findings are of clinical importance, because the pain after the spine surgery is usually difficult to control, and massive use of opioid is associated with adverse clinical event. Besides, the poor management of acute postoperative pain could promote the development of persistent chronic postsurgical pain.^[10] As the pooled data showed, lidocaine infusion helped to reduce not only the pain intensity but also the opioid consumption. However, unlike major abdominal surgery,^[3,11] these benefits did not decrease the length of hospital stay. The reduction of length of hospital stay is probably mediated by the prevention of bowel obstruction in the setting of major abdominal surgery,^[12,13] and the disruption of bowel function in spine surgery is much lower than that in major abdominal surgery.

Perioperative lidocaine infusion may also provide benefit for patients undergoing spine surgery in the long-term, it is reported that patients receiving lidocaine had much less postsurgical chronic back pain intensity and better quality of life compared to the placebo group in 3 months after the spine surgery.^[1,14] Besides, perioperative intravenous lidocaine was reported to be associated with less occurrence of postoperative cognitive dysfunction for patients undergoing spine surgery.^[8] However, the result was doubted by Dewinter et al study showing no positive long-term effect of lidocaine infusion.^[15] Further studies with larger samples and longer follow-up time are still needed to draw a stronger conclusion.

The injection and infusion half-life of intravenous lidocaine is around 1.5 and 12 hours respectively,^[6] however, the analgesic effect of lidocaine persists at 48 hours after the surgery. The

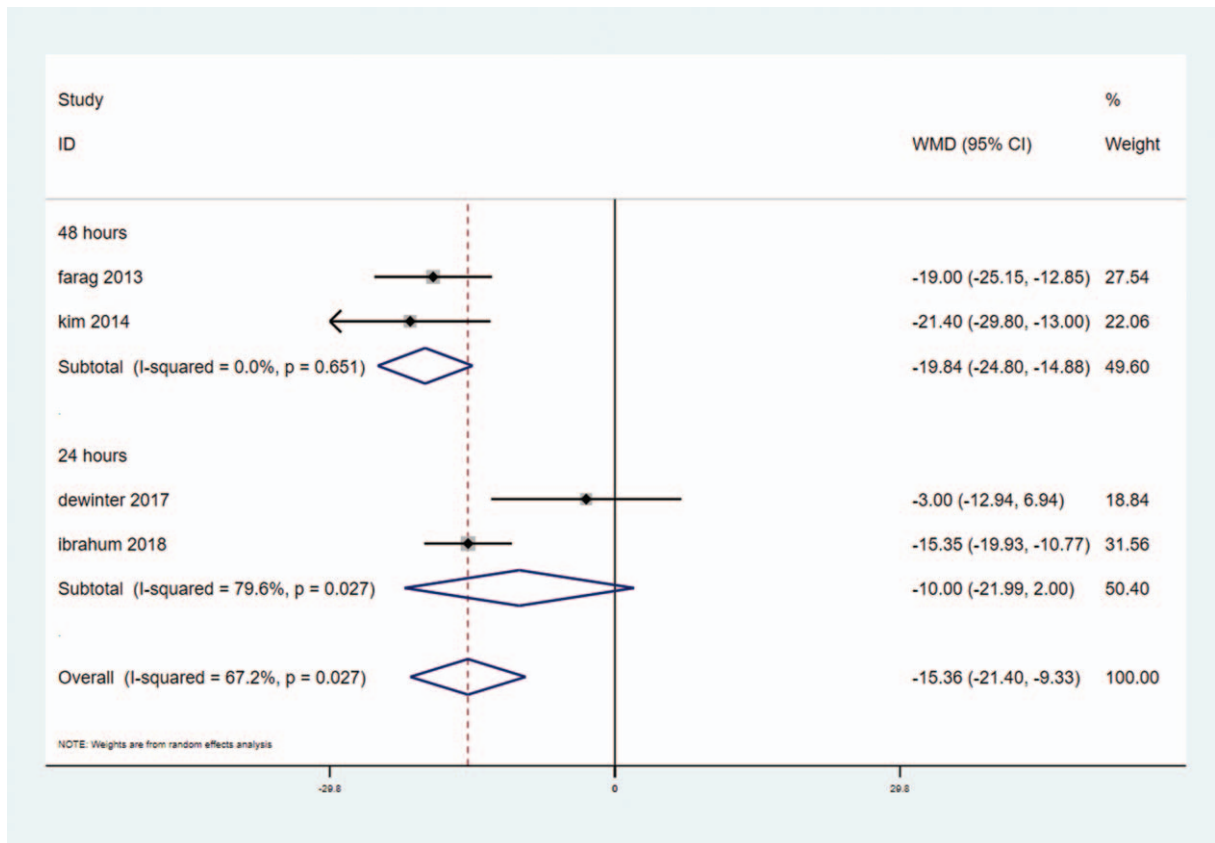


Figure 7. Forest plot of opioid consumption.

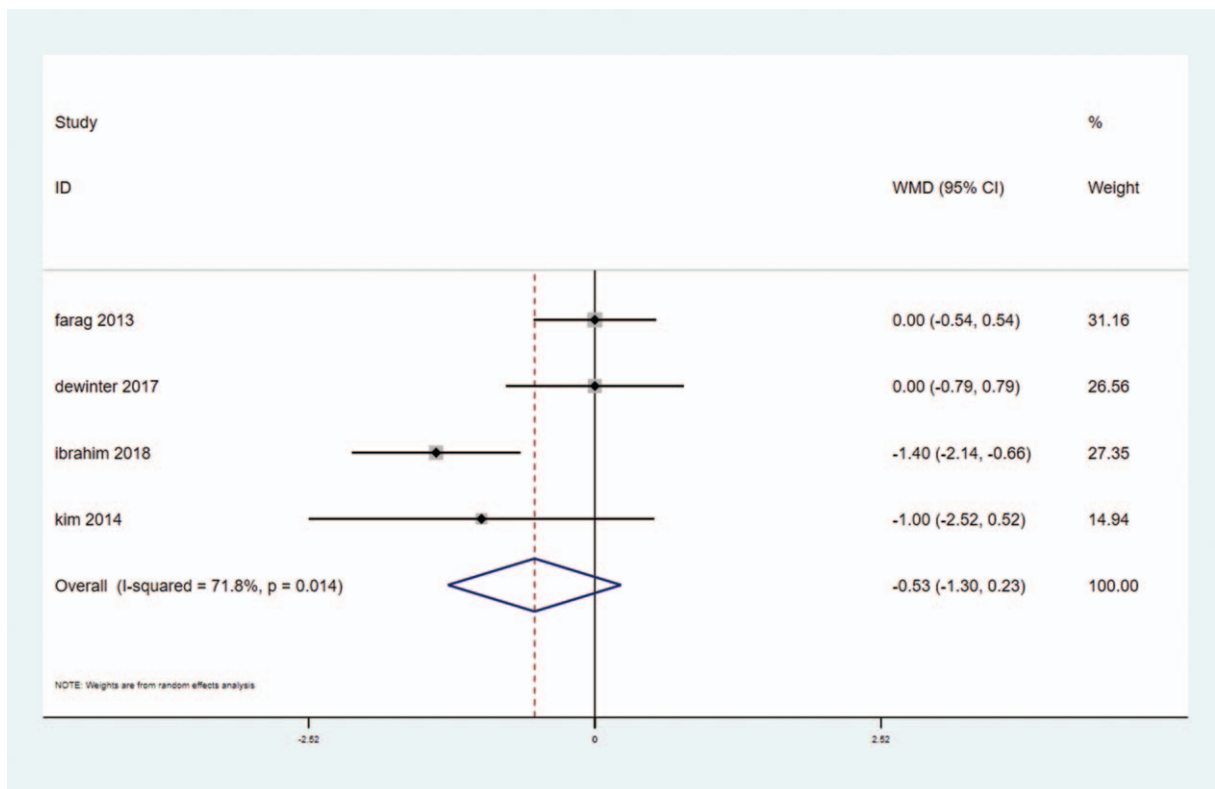


Figure 8. Forest plot of length of hospital stay.

prolonged analgesic effect might be due to the molecular anti-inflammation property of lidocaine.^[16] The inflammation suppressing effect of lidocaine is mediated by the inhibition of N-methyl-d-aspartate receptors and leukocyte activation.^[1,17] Besides, the plasma concentration of pro-inflammatory cytokines like interleukin-6 and C-reaction protein was reported to be significantly lower in lidocaine group than those in control group,^[9,18] those pro-inflammatory cytokines are associated with the postoperative pain intensity.^[19] Another possible mechanism might be the inhibition of glycine transporter 1. Glycine transporter 1 was reported to take part in the development of pain and cognitive dysfunction in an animal model of chronic pain.^[20]

Systematic use of lidocaine has been reported to have the early analgesic effect in different kinds of surgery, including major abdominal surgery,^[13,21,22] inguinal herniorrhaphy,^[23] and outpatient laparoscopy.^[24] However, intravenous lidocaine has also failed to improve postoperative pain management in many kinds of surgery, such as breast surgery,^[25] total hip arthroplasty.^[26] The effect of lidocaine infusion varies by the different surgery and anesthesia procedure.^[27] The mechanism behind the difference remains unclear, future study should further investigate the overlap and distinction of the effect of intravenous lidocaine in different settings.

The high heterogeneity in opioid consumption was reduced by removing the Dewinter et al study. The main difference between Dewinter et al study and others was the infusion dosage of lidocaine, patients in Dewinter et al study received a continuous lidocaine infusion of $1.5 \text{ mg} \cdot \text{h}^{-1} \cdot \text{kg}^{-1}$, yet the infusion rates of lidocaine in other studies were no less than $2 \text{ mg} \cdot \text{h}^{-1} \cdot \text{kg}^{-1}$. A previous meta-analysis suggested that the clinical benefit like reduced pain intensity and opioid consumption was significant only when the rates of lidocaine infusion was greater or equal to $2 \text{ mg} \cdot \text{h}^{-1} \cdot \text{kg}^{-1}$, no positive effect of perioperative intravenous lidocaine was observed at the rates less than $2 \text{ mg} \cdot \text{h}^{-1} \cdot \text{kg}^{-1}$.^[28] Future studies should focus on the ideal dosage and rate of intravenous lidocaine administration to reach a better and safer clinical outcome.

Our study is also inevitable in shortage. First, the sample size was small (<300 patients), this may raise the possibility of false-positive, further study are needed to draw a firmer conclusion. Second, we did not examine the dose-response effect of lidocaine due to the insufficient number of studies. Third, we could not perform meta-regression to find out the factors resulting in the significant heterogeneity in postoperative pain at 48 hours after the surgery and length of hospital stay. Fourth, we could not analyze the long-term effect of lidocaine due to the diversity in time and measurement of assessment.

5. Conclusion

Perioperative use of intravenous lidocaine attenuates the postoperative pain intensity and reduces the postoperative opioid consumption for patients undergoing spine surgery, although the effect is not associated with the reduction in length of hospital stay. Systematic use of lidocaine could be an effective analgesia adjunct for patients undergoing spine surgery. However, the quantity of the studies was very low, more studies are needed to draw a firmer conclusion.

Author contributions

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