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Systematic Reviews/Meta-analyses

Intravenous lidocaine in spine surgery: A meta-analysis of randomized controlled trials

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ABSTRACT

Background: This study aimed to evaluate the role of intravenous lidocaine as a supplemental pain control modality in patients undergoing spine surgery.

Methods: We conducted a meta-analysis of randomized controlled trials (RCTs) involving the use of supplemental intravenous lidocaine in spine surgery. We developed a comprehensive search strategy to adequately screen for randomized controlled trials involving intravenous lidocaine in spine surgery. Continuous outcomes included postoperative opiate consumption and postoperative pain scores. Dichotomous outcomes included nausea, vomiting, pneumonia, delirium, and wound infection.

Results: A total of 3 RCTs comprising 235 patients were selected for inclusion in the meta-analysis. Cumulative morphine consumption at 48 h was not statistically significant between lidocaine and control groups. Postoperative pain was not statistically significant at any measured time points in the first and second day postoperatively. There was no statistical difference in postoperative complications including nausea, vomiting, pneumonia, delirium, or surgical site infection.

Conclusion: Our results indicated that current literature does not support the use of intravenous lidocaine as an adjunctive measure of pain management after spine surgery. Given the relatively few numbers of studies in this field, further randomized controlled trials are needed to make a definitive conclusion on the effectiveness of lidocaine in spine surgery patients.

Introduction

Lidocaine was first synthesized in 1943 under the label LL30 and noted by scientists to have a longer duration of action than procaine, lower toxicity, and more rapid onset, while being easier to preserve [1,2]. Soon afterwards it was tested in clinical trials before being used in dental procedures [1,3,4]. Lidocaine, also known as xylocaine or lignocaine, is now a commonly used local anesthetic agent included by the World Health Organization on its list of essential medicines [2,5]. Given its analgesic, anti-hyperalgesic, and anti-inflammatory properties in addition to immunomodulation capabilities related to surgical stress, lidocaine has been proposed as a component of multi-modal analgesia [6–11].

As a supplement to manage postoperative pain, the use of lidocaine has produced mixed results [12–15]. For example, addition of intravenous lidocaine has demonstrated reduction in postoperative pain scores and an opioid-sparing effect after abdominal and urological surgery [14,16]. However, these results have contrasted with a recent meta-analysis by Chang et al. that demonstrated no reduction in postoperative pain after breast surgery with the administration of intravenous

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lidocaine perioperatively [17]. In spine surgery, Takano et al. first described intraoperative topical administration of 1% 10 mL lidocaine applied directly to the surgical wound site prior to closure and noted that the addition of lidocaine significantly reduced pain scores and postoperative analgesic consumption compared to intravenous fentanyl but not compared to topical application of fentanyl [18].

Due to the small sample sizes and conflicting findings of previous studies, further studies are necessary to evaluate whether the addition of lidocaine reduces postoperative pain following spine surgery. This meta-analysis of randomized controlled trials was therefore performed to investigate the effect of supplementary intravenous lidocaine on postoperative pain following spine surgery. The primary outcome was postoperative opiate consumption. Secondary outcomes included postoperative pain scores and postoperative complications.

Materials and methods

This meta-analysis was performed using the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) statement as a guide [19]. There is no online protocol for this study. Randomized controlled trials were considered eligible for potential inclusion based on the PICOS criteria [20,21]. Eligible studies had (1) patients that underwent spine surgery, (2) were given intravenous lidocaine in addition to postoperative analgesics, (3) involved a comparison and control group, (4) measured postoperative pain and complications, and (5) involved general anesthesia. There were no restrictions based on publication year, language, or publication status (i.e. ongoing trials were not excluded). An outline of the eligibility criteria is documented in **Appendix A**.

Systematic search

The following databases were searched: United States National Library of Medicine PubMed/MEDLINE, Clinicaltrials.gov, Cochrane Library Central Register of Controlled Trials, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Clarivate Analytics Web of Science, and World Health Organization International Clinical Trial Registry Platform (WHO ICTRP). Results were last updated on June 7, 2017. Hand searches of reference lists were also performed. Authors of relevant studies were contacted for additional information where appropriate. Electronic search strategies were developed based on a previously published meta-analysis [22]. Search strategies for each database used in this meta-analysis are listed in **Appendix B**. The electronic search strategy for PubMed/MEDLINE is reproduced below.

1 lidocaine OR xylocaine OR lignocaine
2 pain OR analgesia OR analgesic OR analgesics
3 spine OR spinal OR spine surgery OR spinal surgery
4 #1 AND #2 AND #3
5 letter OR editorial OR news OR comment OR case reports OR note OR conference paper OR animals OR animal OR mice OR mouse
6 #4 NOT #5
7 #4 NOT #5 Filters: Randomized controlled trials

Study selection

Articles were screened by title and abstract by two authors according to the inclusion-exclusion criteria specified *a priori* in **Appendix A**. Discrepancies were resolved by a third author. The included articles were then screened by full-text review with discrepancies resolved by the same third author.

Data collection

Data was collected from studies included in the quantitative synthesis into a standardized data abstraction form. The corresponding authors of each article were contacted for additional data and/or clarification as necessary. The following study demographic elements were abstracted: first author, year of publication or study completion, type of surgery, dose of intravenous lidocaine, placebo, number of patients per study arm, primary postoperative analgesic, and mode of analgesic administration. Continuous outcomes included postoperative analgesic consumption and postoperative pain scores. Dichotomous outcomes included nausea, vomiting, pneumonia, delirium, and wound infection. Data for each outcome was abstracted by at least two studies. Eligible articles were also analyzed according to the Cochrane Risk of Bias screening tool at the study level prior to incorporation into quantitative synthesis [23]. To compare mean cumulative morphine consumption, the standard deviation was imputed for one study using the "same meta-analysis" method described by Furukawa et al. [24]. In addition, fentanyl consumption was converted to morphine equivalents for one study based on previously reported equianalgesic ratios (100 mg morphine equivalent to 1 mg fentanyl) [25]. Postoperative pain scores were converted from a 0-100 scale to a 0-10 scale for one study prior to comparison.

Statistical analysis

Standardized mean difference (SMD) and 95% confidence interval (CI) were used to compare continuous outcomes. Odds ratio (OR) and 95% CI were used to compare dichotomous outcomes. A comparison was considered statistically significant if $p < 0.05$. Between-studies heterogeneity was assessed using chi-squared test. If $p > 0.10$, the between-studies heterogeneity was considered statistically insignificant and the fixed effects statistical model was used. If $p < 0.10$, the between-studies heterogeneity was significant, and the random effects model was employed. To reduce bias in the selection of relevant articles, we searched relevant reference lists by hand. We also requested additional data if appropriate prior to comparison. There were no sensitivity or subgroup analyses. Review Manager 5.3.5 for Mac (The Cochrane Collaboration, Copenhagen, Denmark) was used to perform the analyses [26]. The Cochrane Handbook was used as a reference in this study [27].

Results

Systematic search and study selection

Searches of PubMed/MEDLINE (n=1694), Clinicaltrials.gov (n=3), Cochrane Library Central Register of Controlled Trials (n=713), CINAHL (n=488), Clarivate Analytics Web of Science (n=209), and WHO ICTRP (n=35) produced 3142 articles. Hand searches produced an additional 4 articles, bringing the total to 3146. After duplicates were removed (n=297), 2849 articles were screened for eligibility. Upon completion of screening, a total of 3 randomized controlled trials comprising of 235 patients were selected for inclusion in the meta-analysis [28–30]. Study selection is outlined in Fig. 1.

Study characteristics

Two trials included a single bolus, and all three involved a continuous infusion of intravenous lidocaine used as adjunctive analgesics. Primary postoperative analgesics included morphine and fentanyl administered via patient-controlled analgesia. Study characteristics are described in Table 1.

Statistical comparisons

Cumulative morphine consumption at 48 hours was not statistically significant between lidocaine and control groups (SMD = -1.69, 95% CI: -3.65 to 0.27, $p = 0.09$). Postoperative pain was not statistically significant in the first postoperative day at 2 hours (SMD = 0.08, 95% CI: -1.56 to 1.72, $p = 0.92$), 4 hours (SMD = 0.13, 95% CI: -1.35 to 1.62, $p = 0.86$), 6 hours (SMD = 0.45, 95% CI: -0.72 to 1.62, $p = 0.45$), 8 hours (SMD = 0.13, 95% CI: -0.55 to 0.81, $p = 0.72$), 12 hours (SMD = 0.00,

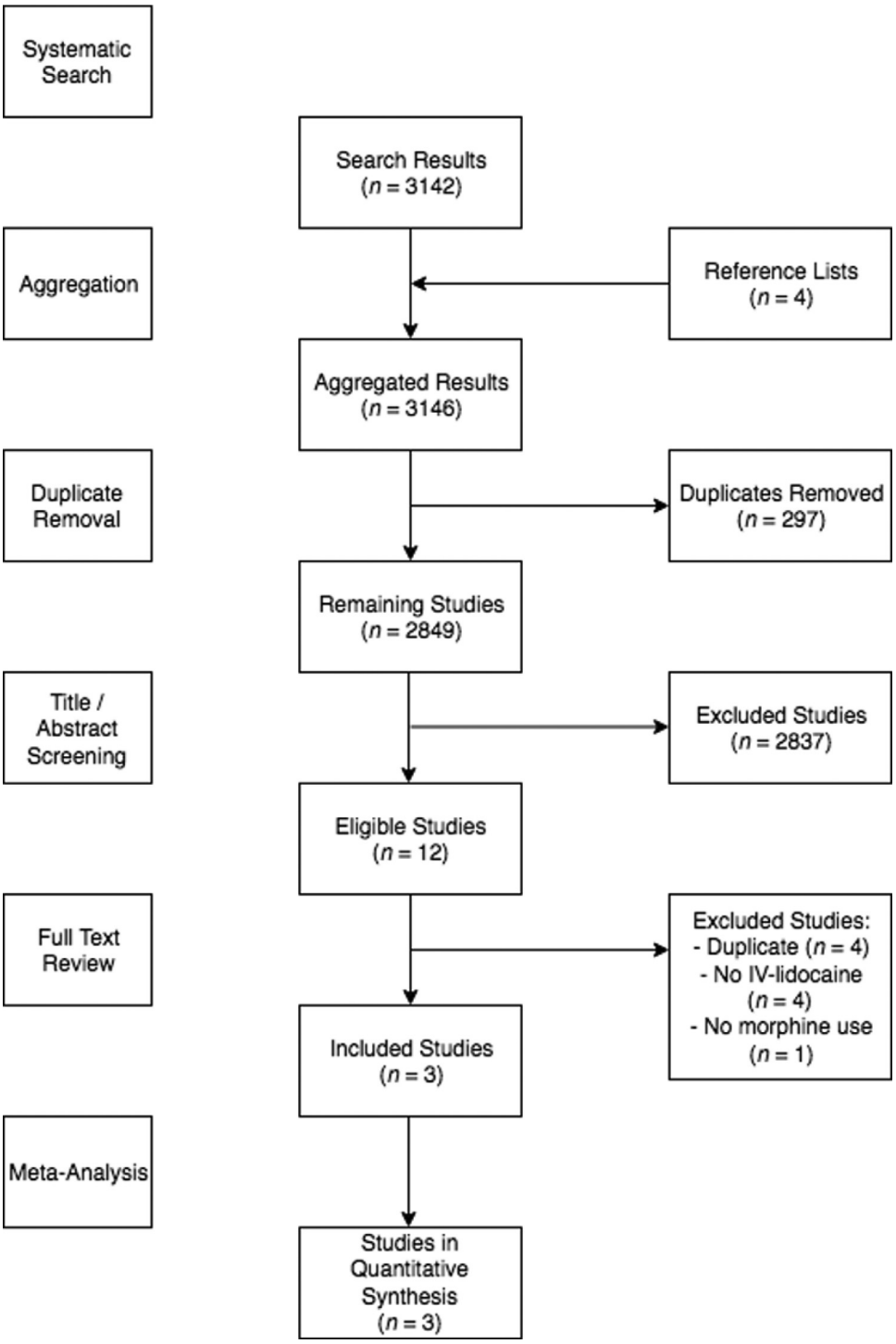

Fig. 1. Flow Diagram indicating methodology for meta-analysis. The initial search yielded studies. After aggregation from reference lists and removing duplicate studies, there were studies remaining. The remaining studies were screened by two authors independently with discrepancies solved by a third author. A total of 3 studies were identified to be included in the meta-analysis based on our pre-specified inclusion.

Table 1
Randomized controlled trial characteristics.

First Author	Year of Publication	Lidocaine Dose	Placebo	Spinal fusion	Instrumentation	Lidocaine group (*n*)	Control group (*n*)	Postoperative Analgesics	Mode of Administration
Kim	2013	1.5 mg/kg bolus & 2 mg/kg/hr	Saline	no	no	25	26	Morphine	PCA
Farag	2015	2 mg/kg/hr	Saline	yes	yes	57	58	Fentanyl	PCA
Dewinter	2017	1.5 mg/kg bolus & 1.5 mg/kg/hr	Saline	yes	yes	35	34	Morphine	PCA

PCA: patient-controlled analgesia

Table 2
Postoperative morphine equivalent consumption and pain scores.

Category	Studies (*n*)	Lidocaine group (*n*)	Control group (*n*)	SMD	95% CI	*P*
Postoperative Morphine Consumption (48 hours)	2	83	83	-1.69	-3.65 to 0.27	0.09
Postoperative Pain Scores (2 hours)	3	116	117	0.08	-1.56 to 1.72	0.92
Postoperative Pain Scores (4 hours)	3	118	117	0.13	-1.35 to 1.62	0.86
Postoperative Pain Scores (6 hours)	2	92	91	0.45	-0.72 to 1.62	0.45
Postoperative Pain Scores (8 hours)	3	118	117	0.13	-0.55 to 0.81	0.72
Postoperative Pain Scores (12 hours)	3	117	116	0.00	-0.91 to 0.91	1.00
Postoperative Pain Scores (24 hours)	3	118	117	-0.14	-0.65 to 0.37	0.60
Postoperative Pain Scores (48 hours)	3	118	117	-0.22	-0.48 to 0.03	0.09

SMD: standardized mean difference; CI: confidence interval; P: p-value

Table 3
Postoperative complications.

Category	Studies (*n*)	Lidocaine Complications (*n*)	Control Complications (*n*)	Lidocaine group (*n*)	Control Group (*n*)	OR	95% CI	*P*
Nausea	3	38	32	110	113	1.40	0.73 to 2.71	0.31
Vomiting	3	21	15	110	113	1.59	0.76 to 3.34	0.22
Pneumonia	3	0	1	92	91	0.31	0.01 to 7.99	0.48
Delirium	2	1	0	92	91	3.00	0.12 to 76.24	0.51
Infection	2	1	0	83	82	3.05	0.12 to 76.54	0.50

OR: odds ratio; CI: confidence interval; P: p-value

95% CI: -0.91 to 0.91, $p = 1.00$), or 24 hours (SMD = -0.14, 95% CI: -0.65 to 0.37, $p = 0.60$). Postoperative pain scores were also not statistically different in the second postoperative day (SMD = -0.22, 95% CI: -0.48 to 0.03, $p = 0.09$). Postoperative morphine use and pain scores are described in Table 2. Nausea did not occur more often in either the lidocaine or control group (OR = 1.40, 95% CI: 0.73 to 2.71, $p = 0.31$). There was no statistical difference in vomiting (OR = 1.59, 95% CI: 0.76 to 3.34, $p = 0.22$), pneumonia (OR = 0.31, 95% CI: 0.76 to 3.34, $p = 0.48$), delirium (OR = 3.00, 95% CI: 0.12 to 76.24, $p = 0.51$), or surgical site infection (OR = 3.05, 95% CI: 0.12 to 76.54, $p = 0.50$). Postoperative complications are described in Table 3.

Discussion

Lidocaine has been discussed extensively in literature for its use as a local anesthetic agent in surgical procedures [12,13]. Its role as a systemic analgesic agent has been controversial with relatively few studies examining its intraoperative use for the goal of achieving effective term postoperative pain control [6–10,14]. This meta-analysis was performed to determine the effect of intraoperative intravenous lidocaine on postoperative opiate consumption in patients undergoing spinal surgery. A comprehensive search of multiple databases identified three randomized controlled trials that compared the use of intravenous lidocaine to placebo control on postoperative morphine equivalent consumption, patient perceived pain scores, and postoperative complications including nausea, vomiting, pneumonia, delirium, and surgical site infection. With regards to postoperative pain, there was no significant difference throughout the postoperative period (2, 4, 6, 8, 12, 24, and 48 h after spine surgery). These findings are consistent with our results indicating no significant reduction in cumulative morphine equivalent pain medication between both groups. With respect to postoperative complications, there were no differences between the lidocaine and placebo group.

Of the studies included, both Kim et al. and Farag et al. noted a significant reduction in postoperative morphine consumption as well as pain scores with the use of adjunctive intravenous lidocaine, while Dewinter et al. reported no significant differences in either parameter [28–30]. Although this meta-analysis found a reduction in cumulative morphine equivalent consumption in patients that received lidocaine, this reduction was not statistically significant. This outcome may be explained by the significant heterogeneity between the studies reported by Kim et al. and Farag et al., which differed in terms of administration of lidocaine, type of surgery performed, and the analgesic consumed postoperatively. Given the lack of a standardized dose for intravenous lidocaine, each of the 3 studies included used a different dosing regimen. The highest quantitative dosage was used by Kim et al., where patients were given 1.5 ml/kg of lidocaine bolus with an additional continuous infusion of 2.0 ml/kg/hr, while Farag et al. used solely a 2.0 ml/kg/hr continuous infusion, and Dewinter et al. used a 1.5 ml/kg bolus with a 1.5 ml/kg/hr continuous infusion [28–30]. Given no currently accepted standard dose for intravenous lidocaine, as well as variations in dosing regimens used in each study, it is possible that the dose given by Dewinter et al. was not sufficiently high enough to adequately control postoperative pain thereby contributing to the negative results [30]. A previous study examining the use of lidocaine in treatment of neuropathic pain suggests a possible threshold dose necessary for adequate analgesia [31]. Although the cumulative dose of lidocaine was high, the dose of lidocaine given as a continuous infusion was lower in the Dewinter study. As Kim et al. and Farag et al. both used a 33% higher continuous dose of lidocaine, it is possible that this contributed to the improved pain management with a resulting decrease in opiate consumption and patient perceived pain scores [28,29].

Additionally, the patient population enrolled in Dewinter et al., consisted of those undergoing spinal fusion, whereas the patients enrolled in Kim et al. were strictly undergoing elective laminectomies and discectomies. Given the surgically complex nature of spinal fusions requiring hardware instrumentation, relative to a discectomy or laminectomy, patients in Dewinter et al. may have had significantly higher baseline pain level [30]. This factor along with an overall lower cumulative dosage of lidocaine may explain the lack of benefit seen in terms of opiate reduction and patient perceived postoperative pain. In the study by Dewinter et al., the use of intra-operative morphine derivatives may have masked the morphine-sparing effect of lidocaine administration [31]. One other notable difference was the inclusion of adolescent patients in the trial published by Dewinter et al., which may contribute to the heterogeneity between trials.

Despite a comprehensive and systematic search of multiple databases, our study has a few limitations worth consideration. While we made every attempt to include all studies matching our inclusion criteria, there is a possibility that not all trials involving intraoperative adjunctive lidocaine use were included. Our results demonstrated a trend

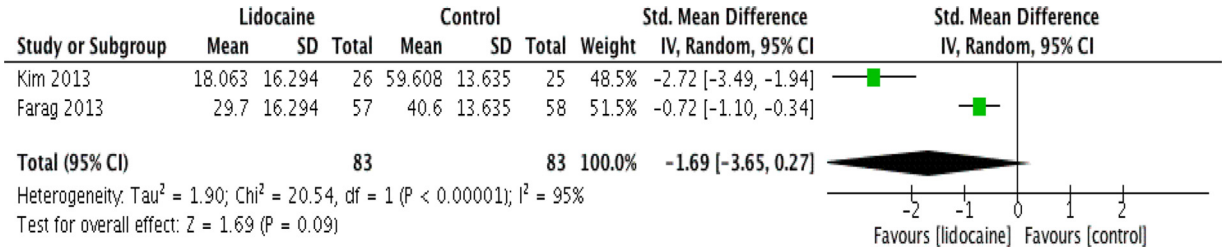

Fig. 2. Forrest plot outlining the effect of intraoperative intravenous lidocaine on postoperative morphine equivalent consumption. No significant differences were found between the lidocaine and control group (p = 0.09).

towards decreased postoperative morphine equivalent consumption in the lidocaine group Fig. 2. However, given the paucity of studies in this field as well as the relatively low sample sizes in each study included, it is possible that power of our analysis may not have been sufficient to detect significant difference between the adjunctive lidocaine and the control group given that no differences in morphine consumption, pain scores, as well as patient outcomes were seen. Additionally, each of the three studies utilized a different dosage of lidocaine [28–30].

Conclusion

In conclusion, our review and analysis of current literature did not find a significant difference in postoperative morphine consumption, subjective pain scores, and outcomes in spine surgery patients given intravenous adjunctive lidocaine as compared to placebo. Given that the need for an effective pain regimen with less reliance on opiates continues to remain a challenge for spine surgeons, there is an urgent need for further investigations into the role of integrating lidocaine into a multimodal model of postoperative pain control. Further randomized controlled trials with a larger sample of patients, as well as standardized dosage, timing, and method of administration of lidocaine all constitute avenues of future research and can better elucidate the role of lidocaine in postoperative pain management.

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The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Declaration of Competing Interest

Mr. Musa reports payment for physician education presentations from WebMD/Medscape. Arif Musa has received research support from the Southern California Clinical and Translation Sciences National Institutes of Health Team Building Award (UL1TR001855), the J. Robert Gladden Orthopaedic Society Stryker Medical Student Grant, and the Wayne State University School of Medicine Medical Student Research Fellowship.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.xnsj.2021.100079.

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