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Efficacy of lidocaine on preventing incidence and severity of pain associated with propofol using in pediatric patients

A PRISMA-compliant meta-analysis of randomized controlled trials

Bing-chen Lang, MS[a,b,c], Chun-song Yang, MS[a,b,c], Ling-li Zhang, MD[a,b,c,*], Wen-sheng Zhang, MD[d], Yu-zhi Fu, MS[a,b,c]

Abstract

Background: Propofol injection pain was considered as one conundrum during clinical anesthesia. The systematic review about the effect of lidocaine in reducing injection pain among children has not been established. The aim of the study was to systematically evaluate the efficacy and safety of such intervention.

Methods: The literature search was performed from the inception to the May 31, 2016 in PubMed, Ovid EMBASE, and Cochrane database. All randomized controlled trials that using lidocaine for propofol injection pain in children were enrolled. The primary outcome included the incidence of injection pain and the incidence of propofol injection pain in different degrees. The data were combined to calculate the relative ratio and relevant 95% confidence interval. A meta-analysis was performed following the guidelines of the Cochrane Reviewer's Handbook and the PRISMA statement.

Results: Data from the included 11 studies indicated that the incidence of injection pain was lower in lidocaine group than the incidence in saline control group and in propofol lipuro (medium- and long-chain triglycerides [MCT/LCT]) group (pain occurrence: 22.1% in lidocaine vs 66.8% in saline, RR with 95% 0.34 [0.26, 0.43], $I^2=38\%$; 30.5% in lidocaine vs 46.9% in propofol lipuro, RR with 95% 0.68 [0.46, 1.00], $I^2=9\%$). There was no difference between lidocaine and ketamine/alfentanil both in reducing pain occurrence and in reducing pain severity (pain occurrence: 29.7% in lidocaine vs 25.8% in ketamine, RR with 95% 1.47 [0.16, 13.43], $I^2=94\%$; 31.0% in lidocaine vs 30.7% in alfentanil, RR with 95% 1.01 [0.69, 1.46], $I^2=11\%$). And the reported side effects revealed that the safety of lidocaine in pediatric patients was acceptable.

Conclusion: Compared with ketamine and alfentanil, lidocaine would be served as one more effective treatment in consideration of its well-matched efficacy, acceptable accessibility, and reasonable safety. However, more high-quality evidences in pediatric patients are necessary.

Abbreviations: MCT/LCT = medium- and long-chain triglycerides, RCT = randomized controlled trial, RR = risk ratio.

Keywords: injection pain, lidocaine, meta-analysis, pediatrics, propofol

1. Introduction

As one of commonly used sedative drugs for intravenous administration, propofol featured its rapid onset, short duration, and reasonable recovery. However, the pain emerged during the iv infusion of propofol was experienced by up to 85% of pediatric patients,[1] and the induction was considered as one of the most painful stages during perioperative period. Additionally, owing to the small veins of children, the high incidence of propofol injection pain was associated with the high risk during pediatric

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B-cL and C-sY contributed equally to this work.

Ethical approval: All analyses were based on previous published studies; thus, no ethical approval and patient consent are required.

Authorship: BL, LZ, and WZ conceived of the design of the study; BL and CY participated in the literature search, study selection, data extraction, and quality assessment; YF performed the statistical analysis; and BL finished the manuscript. All authors read and approved the final manuscript.

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[a] Department of Pharmacy, West China Second University Hospital, Sichuan University, [b] Key Laboratory of Birth Defects and Related Diseases of Women and Children (Sichuan University), Ministry of Education, [c] Evidence-Based Pharmacy Center, West China Second University Hospital, [d] Department of Anesthesiology, Laboratory of Anesthesia and Critical Care Medicine, Translational Neuroscience Center, West China Hospital, Sichuan University, Chengdu, China.

[*] Correspondence: Ling-li Zhang, Department of Pharmacy, West China Second University Hospital, No. 20, Section 3, Renmin Nanlu, Chengdu 610041, Sichuan, China (e-mail: zhlingli@sina.com).

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anesthesia induction. Thus, alleviating the injection pain was considered as a thorny problem needs to be solved.

Various approaches have been tried out to alleviate propofol injection pain, such as adjustment of the temperature of infusion,[2] pretreatment with different medications including opiates, and local anesthetics at varying dosages. Nyman et al[3] tried to premix etomidate with propofol, and Lembert et al[4] chose the nitrous oxide as the medication. In fact, the confirmed effect and reasonable results have been reported with the intravenous administration of ketamine,[5] alfentanil,[6] newer propofol formulation (dissolved in a mixture of medium- and long-chain triglycerides [MCT/LCT]),[7,8] and especially lidocaine[9,10] in adult patients.

However, in contrast of the proved efficacy of using lidocaine and other pharmacological interventions in published systematic reviews about adult patients,[11–13] the relevant systematic review about the efficacy and safety in reducing injection pain of propofol between lidocaine and other medications in pediatric patients has not been established.

In order to evaluate the effects of adjunctive lidocaine and other medications administration on alleviating the propofol injection pain occurred in pediatric patients, the present meta-analysis was performed by aggregating the published randomized controlled trials (RCTs) comparing lidocaine and other frequently used pharmacological approaches in clinic. Moreover, the safety of these medications was also described.

2. Methods

Ethical approval and patient written informed consent are not required due to that this is a systematic review and meta-analysis of previously published studies. This meta-analysis was performed in accordance with the recommendations in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement[14] and the guidelines described in the Cochrane Handbook.

2.1. Inclusion and exclusion criteria

2.1.1. Participants. The patients were the children (less than 18 years old) with American Society of Anesthesiologists (ASA) physical status I or ASA II. And the types of patients included the children who experienced the propofol induction in different surgeries, diagnostic procedures, and outpatient treatment.

2.1.2. Interventions and comparisons. All studies that administered lidocaine intravenously for preventing pain on propofol injection were included. Comparisons included lidocaine versus saline control, lidocaine versus ketamine, lidocaine versus alfentanil, and lidocaine versus propofol lipuro (MCT/LCT).

2.1.3. Outcome measurements. Because of inconsistent pain scores used in these published literatures, the primary outcome was the number of patients reporting any pain (incidence of injection pain emergence); if the measurement scores among different studies were similar, the severity of pain (the incidence of propofol injection pain in different degrees) would also be evaluated. Moreover, the description of cardiorespiratory parameters or adverse events would be reviewed to evaluate the safety of the intervention if the enrolled clinical studies mentioned.

2.1.4. Studies. In consideration of the quality of literature, all RCTs published in English were included. Trials were excluded if the patients were adult, the medication administrated was not involving lidocaine, and data from the case reports, reviews, and the animal studies.

2.1.5. Search strategy. The literature search for published RCTs was conducted by 2 reviewers (BL and CY), and the databases included PubMed, Embase, and the Cochrane Library. The following search terms: "injection pain," propofol, lidocaine, pediatrics, adolescent, teenager, child, infant, children, preschool, kids were combined using "and" or "or" for searching for relevant studies. The search was restricted to human studies and the language of publications was restricted to English. The last literature search was performed in May 31, 2016.

2.1.6. Data extraction. All data were extracted by BL and CY independently. After screening of the titles and abstracts, full articles were obtained when information could not be ascertained. The information derived from literatures was collected and entered into a table which included the following contents: the general characteristics of studies, the types and general characteristics of patients, the sample size, and interventions and comparisons (Table 1). The disagreements were resolved by consensus through discussion among all authors.

2.1.7. Quality assessment. BL and CY independently evaluated the methodological quality of included studies by using the Cochrane Collaboration tool for assessing risk of bias in randomized trials.[15] There are 7 items to assess random sequence generation including allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias using high, low, or unclear risk of bias.[16]

2.2. Statistics analysis

All statistical analyses were performed using the Review Manager 5.0 software. Dichotomous data were analyzed by using the risk ratio (RR) with 95% confidence intervals, the Mantel Haenszel method (fixed or random models). I-square (I^2) test was performed to assess the impact of study heterogeneity on the results of the meta-analysis. According to the Cochrane review guidelines, if severe heterogeneity was present at $I^2 > 50\%$, the random effect models were chosen, otherwise the fixed effect models were used. If interventions involved 10 or more studies, the tunnel plots were used to visualize the reporting bias. Moreover, sensitivity analysis was conducted by deleting each study individually to evaluate the quality and consistency of the results.

3. Results

After search of the database mentioned above, 38 articles were identified by initial screening. Following the full-text review, 11 articles published in English were enrolled in the present systematic review.[17–27] The identification procedure of these eligible articles is described in Fig. 1. The studies from different regions were published from 1992 to 2013. The child age ranged from 2 months to 18 years. In these studies, the incidence of propofol injection pain was reported in 9 of them,[17–23,25,27] and the number of patients experienced injection pain in different degrees was reported in 6 of them.[18,20–23,25] Normal saline was used as the control in 4 studies,[18,19,21,23] ketamine was used as the comparison in 2 studies,[20,25] alfentanil was used as the comparison in 3 studies,[17,18,22] and propofol lipuro (MCT/LCT) was used as the comparison in 2 studies.[19,27] The grade measuring injection pain severity was selected

Table 1

The general characteristics of the enrolled studies.

Study (reference)	Year	Type of patients	Patient age range, years	Patients enrolled (n)	Intervention	Comparison	Grade of pain severity	Outcome
Kwak et al[22]	2009	Elective surgery	3–10	120	Propofol (LCT) mixed with lidocaine (1%)	Alfentanil 15 μg/kg + propofol (LCT)	4-point scale	①②③
Beyaz et al[26]	2011	Elective surgery	3–15	120	Intravenous 1 mg/kg lidocaine + propofol (LCT)	Propofol (LCT)	Modified Eastern Ontario Children's Hospital pain scale (mCHEOPS)	–
Barbi et al[20]	2003	Gastroscopy	1–18	122	Propofol (LCT) mixed with 2 mL lidocaine (1%)	Propofol Lipuro (MCT/LCT) Ketamine (5 mg/mL, 0.5 mg/kg) + propofol (LCT)	3-point Scale	①②③
Nyman et al[27]	2005	Pediatric outpatients	2–18	83	Propofol (LCT) mixed with lidocaine (1%)	Propofol lipuro (MCT/LCT)	4-point scale	①
Rahman Al-Refai et al[18]	2007	Adenotonsillectomy	5–12	335	Propofol (LCT) mixed with lidocaine (1%)	Propofol (LCT)	4-point scale	①②
Rochette et al[19]	2008	Elective surgery	<7	160	Propofol (LCT) mixed with lidocaine (1%)	Alfentanil 15 μg/kg + propofol (LCT) 1. Propofol (LCT) 2. Propofol Lipuro (MCT/LCT)	0–6 graded scale	①③
Depue et al[24]	2013	Painless diagnostic procedures	2 months–7 years	109	Intravenous 0.5 mg/kg lidocaine + propofol (LCT)	Propofol (LCT)	FLACC scale	③
Kaabachi et al[25]	2007	Orthopedic, plastic surgery, or urological procedures	1–12	116	Propofol (LCT) mixed with lidocaine (1%)	Ketamine (5 mg/mL, 0.5 mg/kg) + propofol (LCT)	3-point scale	①②③
Borazan et al[23]	2012	Elective orthopedic and otolaryngological surgery	6–13	120	Propofol (LCT) mixed with lidocaine (1%)	Propofol (LCT)	4-point scale	①②③
Hiller and Saarnnaa[17]	1992	Otolaryngological surgery	Not mentioned	100	Propofol (LCT) mixed with lidocaine (1%)	Alfentanil 15 μg/kg + propofol (LCT)	4 grade	①③
Bilotta et al[21]	2006	Invasive diagnostic or therapeutic interventional hematological procedures	2 months–10 years	358	Intravenous 2 mg/kg lidocaine	Propofol (LCT)	4-point scale	①②③

① The incidence of propofol injection pain; ② the incidence of propofol injection pain in different degrees; and ③ the description about side effect occurred in pediatrics patients. MCT/LCT = medium- and long-chain triglycerides.

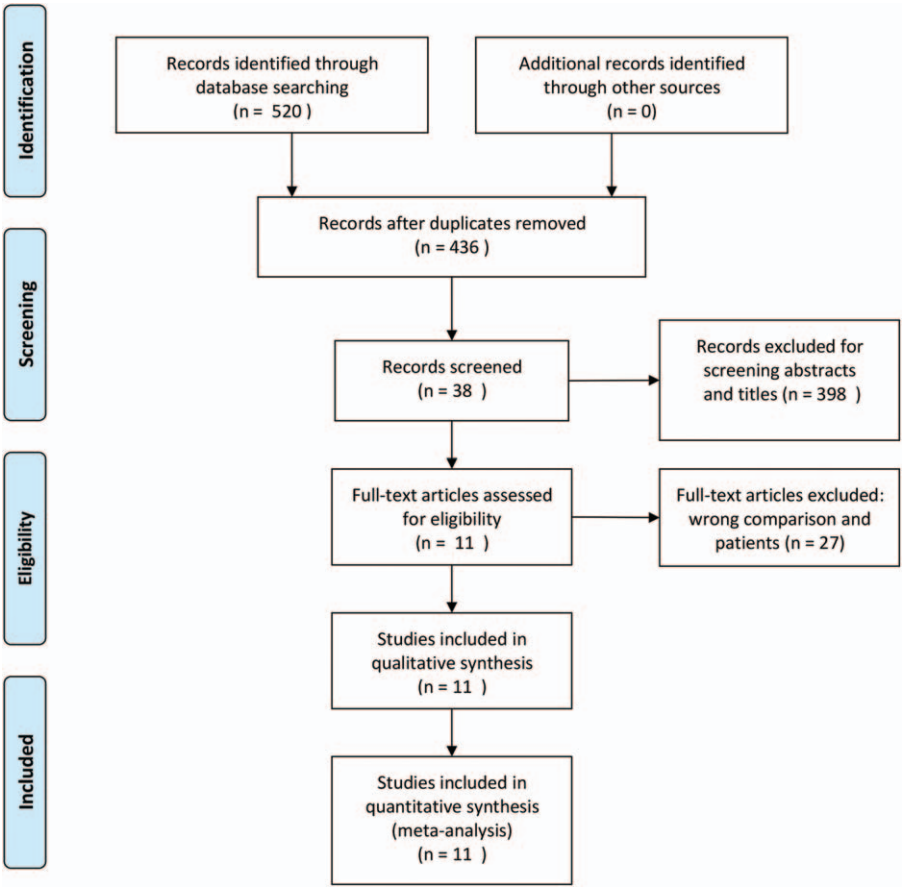

Figure 1. Flow chart of literature screening and the selection process.

inconsistently, 4-point scale was chosen in 6 studies, 3-point scale was used in 2 studies, and 0–6 graded scale, FLACC Scale, and mCHEOPS were used in 1 study, respectively. The general characteristics of the enrolled characters are shown in Table 1.

3.1. Quality assessment

According to the Cochrane Collaboration tool for assessing risk of bias, the 7 items including random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias of these including RCTs were evaluated. A total of 73% (8/11) studies used an adequate method of random sequence generation,[19–23,25,27] 64% (7/11) of the studies mentioned "allocation concealment" with the description of using opaque, sealed envelopes. Three studies[18,20,26] did not mention the blinding procedure of participants and personnel, and only 2 studies[20,26] did not mention the blinding procedure of outcome assessment. The risk of bias assessment tool is shown in Fig. 2.

4. Incidence of injection pain associated with propofol induction

4.1. Lidocaine versus saline

A total of 448 pediatric patients were included in the study, and 231 of them were given the lidocaine intravenously to alleviate the pain produced by propofol induction. Compared with the placebo (saline), intravenous administration of lidocaine definitely reduced the incidence of injection pain which was described as the number of pain occurrence (the incidence of pain: 22.1% in lidocaine vs 66.8% in saline, RR with 95% 0.34 [0.26, 0.43], $I^2 = 38\%$). The I^2 of 38% indicated that the substantial heterogeneity was not existed, thus the fixed effect model was used. The result is shown in Fig. 3.

4.2. Lidocaine versus ketamine

The study included a total of 238 pediatric patients, and 118 of them were given the lidocaine intravenously to alleviate the injection pain. And the incidence of pain occurrence indicated that there were no difference between the using of lidocaine and the using of ketamine (the incidence of pain: 29.7% in lidocaine vs 25.8% in ketamine, RR with 95% 1.47 [0.16, 13.43], $I^2 = 94\%$). The heterogeneity was substantial and the number of studies was limited, and the random effect was used. The result is shown in Fig. 4.

4.3. Lidocaine versus alfentanil

The study included a total of 230 pediatric patients, and 116 of them were given the lidocaine intravenously. The incidence of pain occurrence indicated that there were no difference between the using of lidocaine and alfentanil (the incidence of pain: 31.0% in lidocaine vs 30.7% in alfentanil, RR with 95% 1.01 [0.69, 1.46], $I^2 = 11\%$). The I^2 of 11% indicated that the substantial heterogeneity was not existed, thus the fixed effect model was used. The result is shown in Fig. 5.

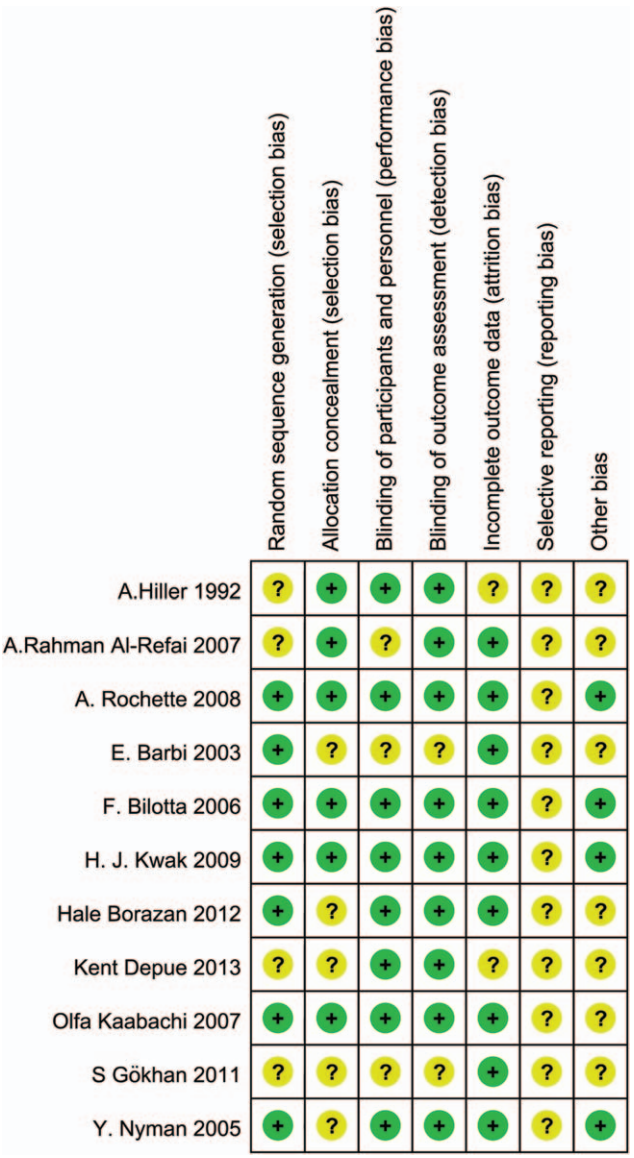

Figure 2. Risk of bias assessment of included studies.

4.4. Lidocaine versus propofol lipuro (MCT/LCT)

A total of 163 pediatric patients were included in the study, and 82 of them were given the lidocaine intravenously to alleviate the pain. Compared with the propofol lipuro (MCT/LCT), intravenous administration of lidocaine had the efficiency in reducing injection pain (the incidence of pain: 30.5% in lidocaine vs 46.9% in propofol lipuro, RR with 95% 0.68 [0.46, 1.00], $I^2=9\%$). The I^2 of 9% indicated that the heterogeneity was not existed, thus the fixed effect model was used. The result is shown in Fig. 6.

5. Severity of injection pain associated with propofol induction

Considered as the inconsistent score/grade used in measuring the severity of pain among pediatric patients in these included studies, the number of pediatric patients who experienced slight, moderate, and the severe pain was reviewed respectively to evaluate the severity of injection pain when the similar pain measurement was used between the different studies.

5.1. Lidocaine versus saline

A 4-point scale was used in 3 of the studies, and the score 2, score 3, and score 4 symbolized slight, moderate, and severe pain individually. Compared with the placebo (saline), the incidence of moderate and severe pain occurred in pediatric patients who received intravenous administration of lidocaine was significantly lower (the incidence of severe pain: 1.58% in lidocaine vs 15.64% in saline control, RR with 95% 0.12 [0.04, 0.35], $I^2=0\%$; the incidence of moderate pain: 6.84% in lidocaine vs 31.84%, RR with 95% 0.24 [0.10, 0.54], $I^2=50\%$), and the difference of occurrence rate of slight pain in between lidocaine group and control group was not significant (the incidence of slight pain: 13.68% in lidocaine vs 21.23% in saline, RR with 95% 0.65 [0.42, 1.03], $I^2=0\%$). The I^2 of 0% indicated that the heterogeneity was not existed, thus the fixed effect model was used, while the I^2 of 50% indicated that the heterogeneity was existed, the random effect model was chosen. The details are shown in Figs. 7–9.

5.2. Lidocaine versus ketamine

A 3-point scale was used in the 2 studies, and the high-grade pain was defined as score 3, the moderate-grade pain was defined as score 2. The incidence of both high-grade pain and moderate pain occurrence indicated that there were no difference between the using of lidocaine and the using of ketamine (the incidence of severe pain: 10.2% in lidocaine vs 25.8% in ketamine, RR with 95% 2.16 [0.03, 176.34], $I^2=88\%$; the incidence of moderate pain: 19.49% in lidocaine vs 18.33% in ketamine, RR with 95% 1.21 [0.27, 5.39], $I^2=84\%$). However, the heterogeneity was substantial, and the limited number of involving studies showed the unreliability of the result (Figs. 10 and 11).

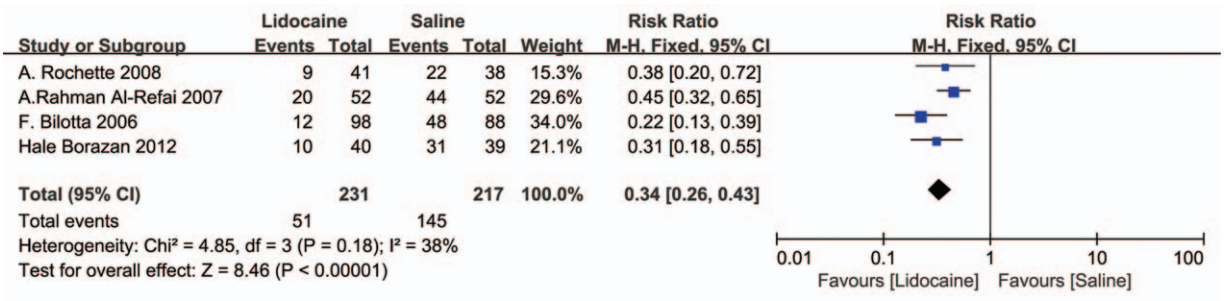

Figure 3. Effect of lidocaine versus saline control in reducing the incidence of propofol injection pain.

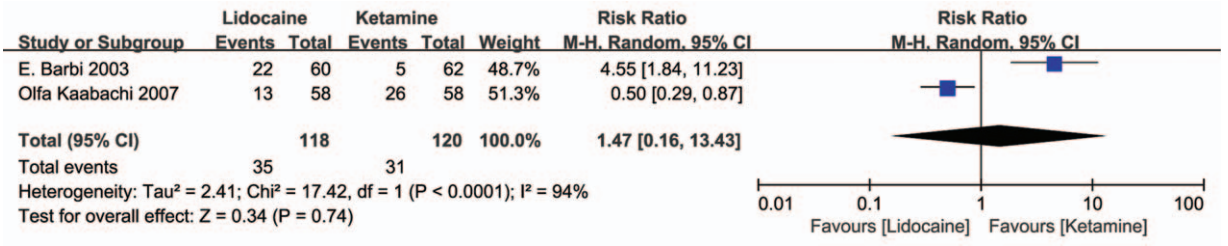

Figure 4. Effect of lidocaine versus ketamine in reducing the incidence of propofol injection pain.

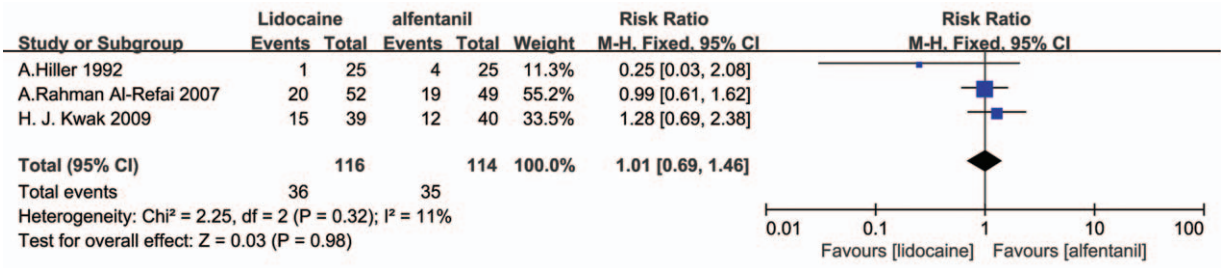

Figure 5. Effect of lidocaine versus alfentanil in reducing the incidence of propofol injection pain.

Figure 6. Effect of lidocaine versus propofol lipuro (medium- and long-chain triglycerides [MCT/LCT]) in reducing the incidence of propofol injection pain.

Figure 7. The incidence of severe pain in group lidocaine versus group saline control.

5.3. Lidocaine versus alfentanil

A 4-point scale was used in 2 of the studies. The incidence of severe pain, moderate pain, and slight pain occurrence indicated that there were no difference between the using of lidocaine and alfentanil (the incidence of severe pain: 3.3% in lidocaine vs 5.6% in alfentanil, RR with 95% 0.58 [0.14, 2.37], $I^2=0\%$; the incidence of moderate pain: 11.0% in lidocaine vs 6.7% in alfentanil, RR with 95% 1.61 [0.61, 4.21], $I^2=10\%$; the incidence of slight pain: 24.2% in lidocaine vs 22.5% in alfentanil, RR with 95% 1.08 [0.63, 1.83], $I^2=0\%$). The I^2 of 0% and 10% indicated that the heterogeneity was not existed, thus the fixed effect model was used. The result is shown in Figs. 12–14.

6. The side effects

A total of 8 studies[11,13,14,16,17–25] mentioned the side effects occurred during the anesthesia. The reported side effects in

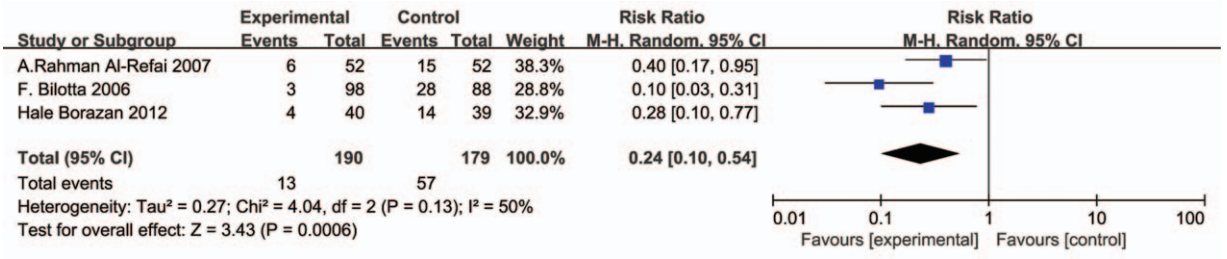

Figure 8. The incidence of moderate pain in group lidocaine versus group saline control.

Figure 9. The incidence of slight pain in group lidocaine versus group saline control.

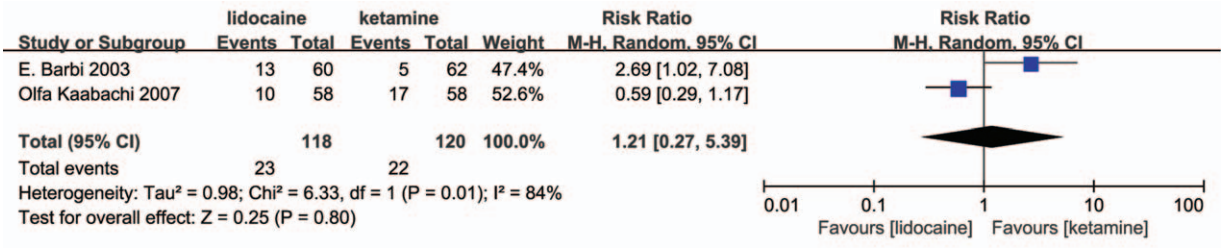

Figure 10. The incidence of the severe pain in group lidocaine versus group ketamine.

Figure 11. The incidence of moderate pain in group lidocaine versus group ketamine.

literatures were sporadic and diverse, thus we tried to describe the details of them (Table 2). According to the records, the mean heart rate and mean arterial pressure from most of patients receiving lidocaine intravenously were maintained within normal limit, and there was no hypotension or bradycardia during the study period. None of the patients suffered from hypoxemia, desaturation, apnea, and chest wall rigidity during the induction of anesthesia. However, 1 child received lidocaine[25] and 1 child received ketamine[20] developed laryngospasm. Especially, iv premedication with lidocaine injected at a dose of 2 mg/kg frequently induced bouts of coughing in infants.[21] And benign cutaneous rashes occurred in 3 pediatric patients (2 received propofol–saline and 1 received propofol lipuro [MCT/LCT]–saline).[19] And the transient severe bradycardia (heart rate fall more than 50% from the preceding value) occurred in 2 children and junctional rhythm occurred in 7 children who received the alfentanil.[17]

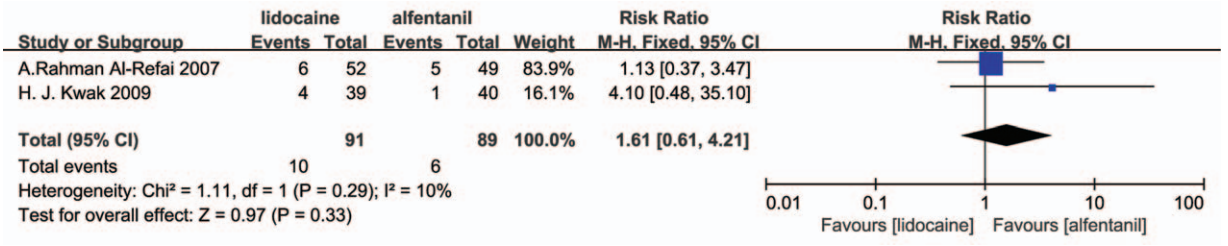

Figure 12. The incidence of the severe pain in group lidocaine versus group alfentanil.

Figure 13. The incidence of moderate pain in group lidocaine versus group alfentanil.

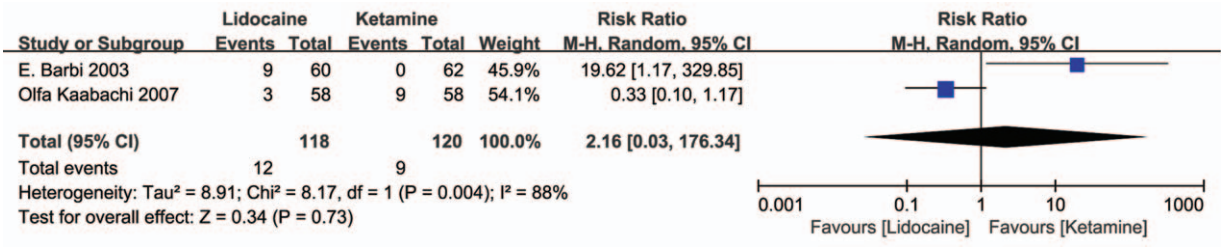

Figure 14. The incidence of slight pain in group lidocaine versus group alfentanil.

7. Discussion

Our study indicated that intravenous administration of lidocaine should be a reasonable approach to alleviate propofol injection pain occurred in pediatric patients. Especially in comparison to the controlled medicine such as ketamine and alfentanil, lidocaine would be served as one more effective treatment in consideration of its well-matched efficacy, acceptable accessibility, and reasonable safety.

Injection pain was always deemed as one common but thorny problem during propofol induction, and it was ranked 7th in 33 outcomes of clinical anesthesia by expert anesthesiologists,[28] according to the frequency they believe that the outcomes occurrence and the importance they expect patients to understand. To increase quality of clinical anesthesia and treatment, reducing the incidence and severity of the top items should be prioritized. However, the potential mechanism of the injection pain associated with the using of propofol was still unclear. The insolubility and the application of emulsion was once thought to be the culprit of the injection pain, thus, the alteration in concentration,[29] infusion rate,[30] and the research about the water-soluble propofol prodrugs[31] had been considered by clinical scientists. Actually, it should be admitted that the pharmacological interventions played an important role in reducing the propofol injection pain in current clinical anesthesia.

Table 2

The description of side effects occurred in included studies.

Type of medication	Side effects occurred in clinical trials	Description
Lidocaine	Laryngospasm; coughing	One child developed laryngospasm; injection (2 mg/kg) frequently induced bouts of coughing in infants.
Ketamine	Laryngospasm	One child developed laryngospasm.
Alfentanil	Transient severe bradycardia; junctional rhythm	Two children developed transient severe bradycardia; 7 children developed junctional rhythm.
MCT/LCT propofol	Benign cutaneous rashes	Two received propofol–saline and 1 received MCT/LCT propofol–saline.

MCT/LCT = medium- and long-chain triglycerides.

However, to our knowledge, about the comparison of efficacy and safety between these pharmacological interventions, no information is available in children. And our study firstly reviewed the studies about these drugs which were used frequently in clinical anesthesia.

The literature screening in our present study was strictly followed the thorough strategies and inclusion criteria. To comprehensively evaluate the practical clinical value of using lidocaine, the randomized controlled studies performed in pediatric patients about comparison including lidocaine versus ketamine, lidocaine versus alfentanil, and lidocaine versus MCT/LCT propofol were enrolled in the present study.

And the risk of bias assessment tool devised by the Cochrane Collaboration showed that 11 studies included were at different risk. And we also found that inconsistency of reported outcome existed in these studies. The incidence of injection pain associated with the using of propofol did not report in 2 studies,[24,26] and the measurement scores of pain severity among these trials were varied including 3-point scale, 4-point scale, and 6-point scale, etc. Therefore, our study reviewed the trials used the same pain score, and collected the number of pediatric patients who experienced different grade pain to evaluate the efficacy of using lidocaine and other medications in alleviating the severity of injection pain.

As same as the previous reports in adult patients, the results indicated that the using of lidocaine intravenously had confirmed effect in alleviating the injection pain both in incidence and the severity (especially the severe pain and the moderate pain) in pediatric patients (Figs. 3, 7, 8). Although the published literatures have been reported that the application of propofol lipuro (MCT/LCT) was effective in reducing the injection pain, the present study indicated that the using of lidocaine exhibited existed but not obvious superiority in solving the problem (Fig. 6).

And there was no difference in reducing pain incidence and pain severity between lidocaine and ketamine/alfentanil. Thereinto, in view of the factor about drug regulation, the iv administration of lidocaine should be the reasonable and convenient option for its accessibility and affordability. However, it was worth noting that the substantial heterogeneity in the comparison between lidocaine and ketamine would affect the reliability of the outcome. And it may be derived from the opposite conclusion of the only 2 RCTs;[20,25] therefore, more evidence with high quality would be necessary to determine which was the preferred option in reducing the injection pain in children.

In addition, our study also provides the findings about the safety of the using of lidocaine, ketamine, alfentanil, and propofol lipuro (MCT/LCT). The results from the existing trials indicated that the specific cases of side effect cases occurred in vary degrees including coughing, laryngospasm, and even transient severe bradycardia. However, there was insufficient evidence currently to presume the complete safety of these different pharmacological interventions. By contrast, lidocaine seemed more applicable, especially considered as the coughing before anesthesia induction is advantageous in infants and children as it clears secretions from the upper airway.[21]

Overall, the comparatively determinate conclusion was that the application of lidocaine intravenously should be considered as one promising approach in decreasing the injection pain occurred in pediatric patients from many different perspectives including efficiency, safety, and resource availability. The limitation of our study was the limited numbers of the RCTs performed in children. Given that the actual effects and the clinical application value of such intervention in pediatric anesthesia should be evaluated in depth, more high-quality evidences in pediatrics are necessary.

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