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The Efficacy and Safety of Dexmedetomidine Combined with Bupivacaine on Caudal Epidural Block in Children: A Meta-Analysis

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Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Background: This meta-analysis was conducted to evaluate the analgesics effect and safety of dexmedetomidine (DEX) combined with bupivacaine (BU) on caudal epidural block.

Material/Methods: Published studies were identified using the PubMed, EMBASE, Web of Science, and the Cochrane Library from inception until October 2017. Relative risk (RR), the standardized mean difference (SMD), and the corresponding 95% confidence interval (CI) were calculated using the STATA 12.0.

Results: Ten randomized controlled trials (RCTs) were selected for this meta-analysis, involving a total of 691 patients. There was a longer duration of postoperative analgesia in children receiving DEX (SMD=3.19, 95% CI: 2.16–4.22, $P<0.001$). Furthermore, there was a lower number of patients requiring rescue analgesics in the (BU) + (DEX) group (6 hours: RR=0.09, 95% CI: 0.05–0.17, $P<0.001$; 12 hours: RR=0.50, 95% CI: 0.32–0.79, $P=0.003$; 24 hours: RR=0.66, 95% CI: 0.51–0.85, $P=0.002$). Finally, the occurrence of adverse events, between BU and DEX + BU group, was not statistically significant (RR=0.96, 95% CI: 0.58–1.58, $P>0.05$).

Conclusions: DEX seems to be a promising adjuvant to BU increase duration of caudal analgesia without an increase in side effects in children. However, the result may be influenced by clinical heterogeneity. More large-scale, multicenter, approaching, double-blinded RCTs are required to confirm our results.

MeSH Keywords: Bupivacaine • Children • Dexmedetomidine • Meta-Analysis • Randomized Controlled Trial

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Background

Postoperative pain is one of the most untreated medical problems, and an annoying subjective sensation for patients, especially in children. A variety of methods have evolved for supposing postoperative pain relief in pediatric patients to provide a better quality of sleep and prolong the duration of sedation [1]. Caudal epidural block is normally a safe technique performed in pediatric anesthesia. The main disadvantage of a caudal block is the shortest duration of analgesia after a single injection, it works for only for 4 to 8 hours [2,3], even with the use of bupivacaine (BU), levobupivacaine, or ropivacaine. Therefore, various adjuvants, such as morphine [4], ketamine [5,6], ephedrine [6], clonidine and neostigmine [7,8], opioids [9–11], and dexmedetomidine (DEX) [12] have been investigated to caudal local anesthetics.

DEX is a powerful and highly selective α_2 adrenergic agonist that has been defined as a safe and effective additive in many anesthetic applications [13], and is being used increasingly in children [14,15]. Substantial studies have shown that DEX added to BU in caudal epidural block can prolong sedation time and reduce side effects, but this conclusion is still controversial [16,17]. However, there are still some concerns regarding its safety [18]. The purpose of this meta-analysis was to assess the efficacy and safety of DEX in addition to caudal analgesia in children undergoing lower abdominal, perineal, and lower limb surgeries, and to help provide a reliable basis for the selection of surgical anesthesia in children.

Material and Methods

Search strategies and study selection

This meta-analysis was reported in accordance with the PRISMA-P Statement [19]. Published studies were identified using the databases of PubMed, Embase, Cochrane Library, and Web of Science from their inception until October 2017. We used the following combined keywords and MeSH terms: 'dexmedetomidine' AND 'Bupivacaine' AND 'children' OR 'Pediatric' OR 'child' OR 'childhood' OR 'Toddler' OR 'Adolescence' OR 'Infancy'. We also detected further studies by scanning the reference list of retrieved researches.

A study was considered eligible for our meta-analysis if it included the following criteria: 1) for patients, only general anesthesia patients, American Society of Anesthesiologists (ASA) I–II, aged less than 12 year undergoing lower abdominal, perineal, and lower limb surgeries, we applied no type of surgery restrictions; 2) for study types, only RCTs with a concrete randomized method and double-blind clinical trials; 3) for interventions, only if BU was involved in caudal epidural block, the control group received BU (or levobupivacaine) alone and the comparison group received BU (or levobupivacaine) + DEX; 4) for outcomes, the primary efficacy endpoints was duration of analgesia (the time of first postoperative rescue analgesics required), secondary efficacy endpoints was incidence of patients to first analgesics administration at 6 hours,12 hours and 24 hours; the primary safety endpoints included side effect of nausea and vomiting. If any of these principles were not met, the study was excluded.

Data extraction and quality assessment

Two investigators independently reviewed publications for eligibility, with disagreements resolved by a third agent. Studies that met inclusion criteria were selected for further analysis. We extracted the following data from each selected study: total number of participants, age, surgery style, blocking methods, and ASA. The Cochrane Collaboration tool was used to estimate the risk of bias in the inclusion studies, which classifies the risk for bias as low, unclear, or high [20].

Statistical analysis

The primary outcomes of our analysis were the duration of analgesia, which was a continuous variable, and data was pooled together in the form of standardized mean difference (SMD) with 95% confidence interval (CI). When SMD >0 and $P<0.05$, the anesthetic effect of DEX + BU group (DEX add to BU in general anesthesia patient) was better than that of BU group (only BU). For secondary outcomes and side effects, in the case of qualitative data, we used risk ratio (RR) with 95% CI. When RR >1 and $P<0.05$, the side effects of DEX + BU group were considered to be higher than that of BU group.

The Cochran Q statistic with chi-square test and the Higgins I^2 test were used to determine the heterogeneity between-study variability. The Cochran's Q Test $P<0.05$ or $I^2>50\%$ or more indicate significant heterogeneity, and the data will be analyzed through the random effect model. On the contrary, the fixed effect model will be chosen. Influence analysis was also conducted to regulate whether an individual study affected the aggregate result or not. We assessed publication bias by funnel plots and Egger's test. Statistical analyses were performed using Stata 12.0 and Review Manager 5.3.

Results

The literature search found 198 documents, of which 159 studies were excluded after our review of titles and abstracts. The full text of 39 remaining citations was screened, and finally 10 articles (12 studies) including 691 patients were included [1,16,17,21–27]. The flow chart of the meta-analysis is

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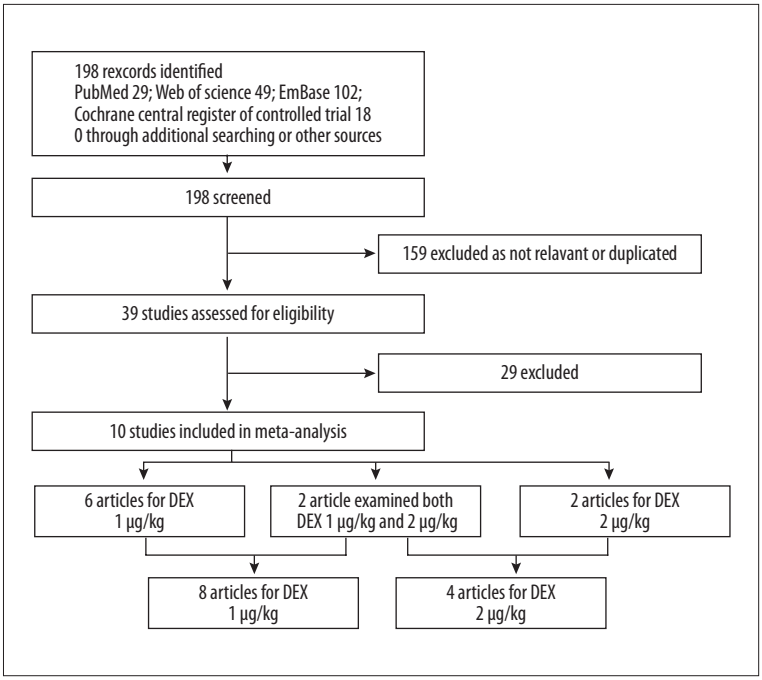

Figure 1. Flow chart of study selection.

presented in Figure 1. The characteristics of the included studies are listed in Table 1, and the methodological quality of the evaluation results are presented in Figure 2. In the DEX + BU trials, 2 different doses of DEX (1 μg/kg and 2 μg/kg) were investigated. Therefore, we did a dose grouping in order to reduce heterogeneity at the time of the merger.

Primary outcomes: duration of analgesia

The merged effect analysis showed that combining DEX + BU can significantly extend the duration of analgesia with a mean time of 13.83 hours in the DEX + BU group compared to 5.81 hours in the BU group (SMD=3.19, 95% CI: 2.16–4.22, I^2=96.1%). DEX at 1 μg/kg and 2 μg/kg was associated with extending the time to first supplemental analgesics (SMD=3.76, 95% CI: 2.16–5.37, I^2=97.4% and SMD=2.30, 95% CI: 1.73–2.87, I^2=64.7% respectively), and there were no significantly differences with 1 μg/kg DEX versus 2 μg/kg DEX (SMD=0.43, 95% CI: –0.09–0.94, I^2=48.4%) (Figure 3).

Secondary outcomes: number of patients who received rescue analgesia

Secondary efficacy endpoints were the incidence of patients to first analgesics administration at 6 hours, 12 hours and 24 hours. From the meta-analysis, DEX + BU was significantly more effective than BU alone (6 hours: RR=0.09, 95% CI: 0.05–0.17, I^2=33.9%; 12 hours: RR=0.50, 95% CI: 0.32–0.79, I^2=81.4%; 24 hours: RR=0.66, 95% CI: 0.51–0.85, I^2=85.9%). The results of subgroup analysis are shown in Table 2.

Adverse events: the incidence of nausea and vomiting

Nausea and vomiting are common side effects of sacral anesthesia in children and are used to evaluate safety. The incidence of nausea and vomiting was described in 7 studies, the doses of DEX were 2 μg/kg and 1 μg/kg, respectively. The pooled results of the adverse events between the BU only group and the DEX + BU group were not statistically significant (P>0.05), (RR=0.96, 95% CI: 0.58–1.58). All the observed I^2 were 0% (Figure 4).

Sensitivity analysis for the primary outcomes

We did a sensitivity analysis for duration of analgesia. When these trials were removed individually, significant differences were still found in duration of analgesia (Figure 5), suggesting that the pooled data results are robust.

Publication bias for the primary outcomes

Funnel plot and Egger's publication bias plot revealed strong asymmetry (Figure 6), suggesting potential publications bias.

Discussion

There were several chief observations from this meta-analysis. The use of DEX combined with BU in caudal epidural block had a statistically significant effect on the duration of analgesia compared to using BU alone. The DEX + BU group had a longer time before patients needed first supplemental analgesic

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Table 1. Characteristics of the included studies.

First author	Year	Surgery style	N	Age	ASA	Inhaled anesthesia	Blocking methods	Anesthesia position	Anesthesia needle type	Control group	Case group	Pain trigger
Lei	2014	Infraumbilical surgeries	80	1–6 y	I–II	8% sevoflurane + 8 L/min oxygen	Caudal analgesia	Lateral decubitus position	23 G needle	1 mL/kg levobupivacaine 0.25%	Levobupivacaine 0.25% + 2 μg/kg DEX	FLACC >3
Meenakshi	2016	Paediatric infraumbilical surgeries	90	6 m–8 y	I–II	Oxygen and nitrous oxide in 1: 1 ratio and halothane 1–3%	Caudal analgesia	Lateral decubitus position	---	1 mL/kg bupivacaine 0.25%	1 mL/kg of 0.25% bupivacaine + 1 or 2 μg/kg DEX	FLACC >4
Elfawal	2016	Lower limb surgeries (lower extremity lengthening, correction of lower extremity deformities)	60	1–7 y	I–II	Sevoflurane in oxygen/air (FiO2 50%)	Caudal analgesia	Lateral decubitus position	23 G needle	0.75 mL/kg levobupivacaine 0.25% diluted in 0.9% NS	0.75 mL/kg levobupivacaine + 1 μg/kg DEX	FLACC >4
Goyal	2016	Elective infraumbilical surgeries	100	2–10 y	I–II	Sevoflurane	Caudal analgesia	Left lateral position	---	1 mL/kg bupivacaine 0.25%	1 mL/kg bupivacaine 0.25% + 1 μg/kg DEX	---
El-Hennawy	2009	Lower abdominal surgeries	40	6 m–6 y	I–II	Sevoflurane delivered in oxygen	Caudal analgesia	Lateral decubitus position	23 G needle	1 mL/kg bupivacaine 0.25%	1 mL/kg bupivacaine 0.25% + 2 μg/kg DEX	FLACC >4
Saadawy	2008	Unilateral inguinal hernia repair/ orchidopexy	60	1–6 y	I–II	0.5–2% sevoflurane and 70% nitrous oxide in oxygen	Caudal analgesia	Lateral position	23-G short-beveled needle	1 mL/kg bupivacaine 2.5 mg/mL	bupivacaine 2.5 mg/mL, 1 mL/kg + 1 μg/kg DEX	OPS ≥4
Al-Zaben	2015	Infra-umbilical surgery	91	1–6 y	I	Sevoflurane	Caudal analgesia	Lateral decubitus position	23-G short-beveled needle	1 mL/kg bupivacaine 0.25%	bupivacaine 0.25% at a dose of 0.8 mL/kg + 1 μg/kg or 2 μg/kg DEX	OPS ≥4
Al-Zaben	2016	Elective lower abdominal and perineal surgeries	50	1–6 y	I	8% sevoflurane in 100% oxygen via facemask	Caudal analgesia	Left lateral position	22-G needle	1 mL/kg caudal 0.25% bupivacaine	1 mL/kg caudal 0.25% bupivacaine + 1 μg/kg DEX	OPS ≥4
Xiang	2012	Unilateral inguinal hernia repair/ orchidopexy	60	1–6 y	I	---	Caudal analgesia	Left lateral position	22-G needle	1 mL/kg bupivacaine 0.25%	1 mL/kg bupivacaine 0.25% + 1 μg/kg DEX	CHIPPS >3
Kannojia	2017	Urogenital surgery	60	2–7 y	I–II	Sevoflurane	Caudal analgesia	Lateral decubitus position	23 G shot needle	0.5 mL/kg bupivacaine 0.25%	0.5 mL/kg bupivacaine 0.25% + 1 μg/kg DEX	CHEOP scale >6

m – month; y – year; --- – null; ASA – American Society of Anesthesiology; DEX – dexmedetomidine; CHIPPS – Children and Infants Postoperative Pain Scale; FLACC – face, legs, activity, cry, consolability; OPS – Objective Pain Score; CHEOPS – Children's Hospital of Eastern Ontario Pain Scale.

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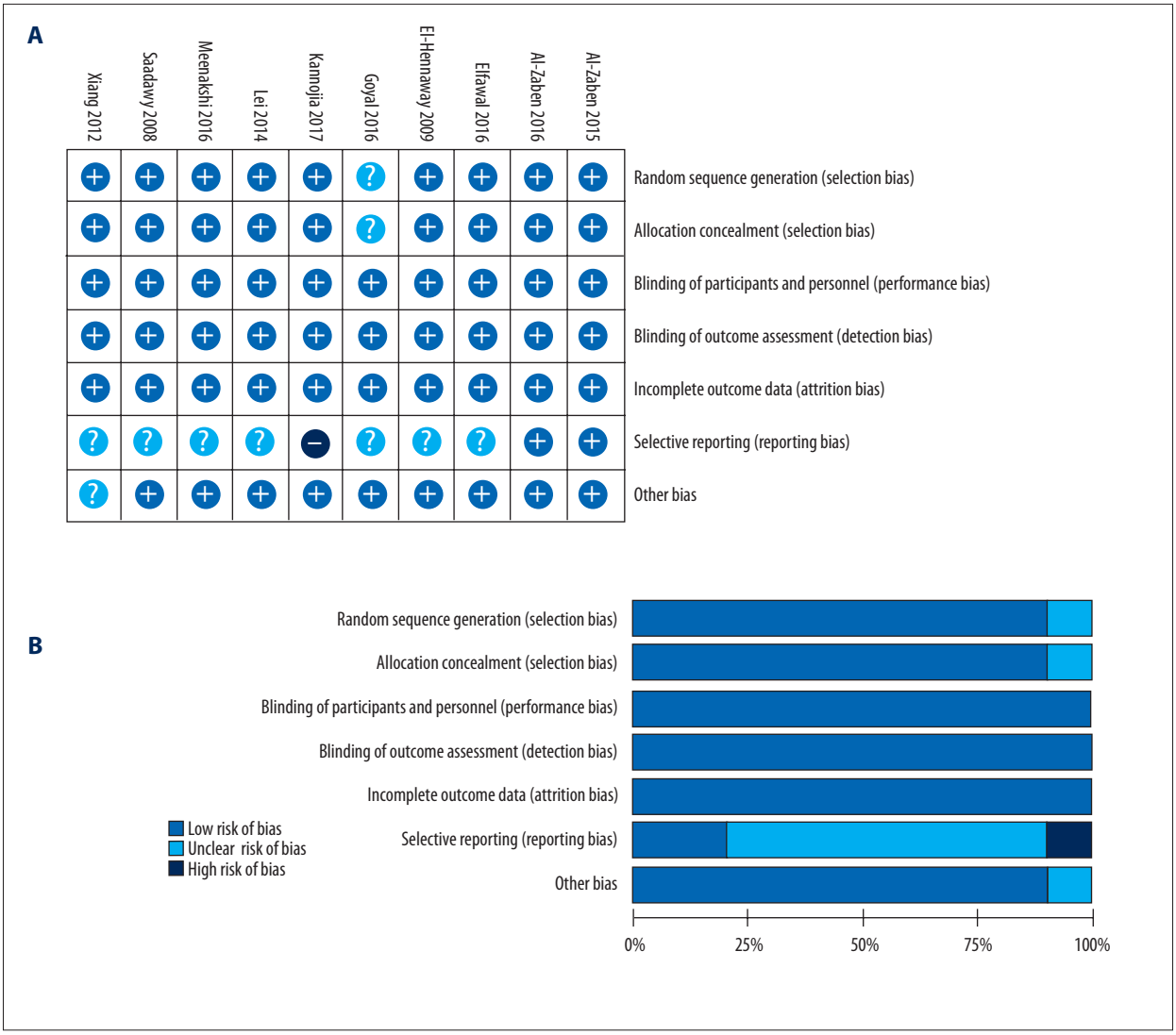

Figure 2. Risk of bias graph of the included trials. (**A**) Summary of the risk of bias in 7 domains in the 10 RCTs. (**B**) Representation of the overall risk of bias in the 7 domains.

and fewer patients who received rescue analgesia, compared to the BU group, and did not show a difference in the incidence of nausea and vomiting. There were no significantly differences with DEX at 1 μg/kg versus 2 μg/kg. However, there was significant heterogeneity among the studies; therefore, the quality of the results was low.

Our meta-analysis results agree with earlier studies concerning the effectiveness of DEX in prolonging the duration of postoperative analgesia [28,29], and reducing the number of patients who needed rescue analgesia. Attributable to the possible influence of data heterogeneity, further studies were required to determine the analgesics effect of different concentrations of DEX used in caudal block. We conducted an additional meta-analysis on defined anesthetic drugs BU or levobupivacaine, and conducted a subgroup analysis of the dosage of DEX. This study found that 1 μg/kg or 2 μg/kg DEX was associated with extending the time to first supplemental analgesics. Two other studies compared different doses of DEX (1 μg/kg and 2 μg/kg) and the results were not identical. Al-Zaben et al. [21] concluded a 1 μg/kg dose of caudal DEX achieved equivalent extension of postoperative analgesia to 2 μg/kg dose, with shorter duration of postoperative sedation and lower incidence of other side effects. Meenakshi et al. [17] found that 1 μg/kg DEX was as effective as 2 μg/kg DEX and had a better safety profile.

Although we have done a dose-grouping on DEX (with 1 μg/kg or 2 μg/kg) to reduce the heterogeneity, the results for time to first supplemental analgesics of DEX with 1 μg/kg showed significant heterogeneity (I^2=97.4%). While the exact cause could not be detected, we doubt that the differences in the

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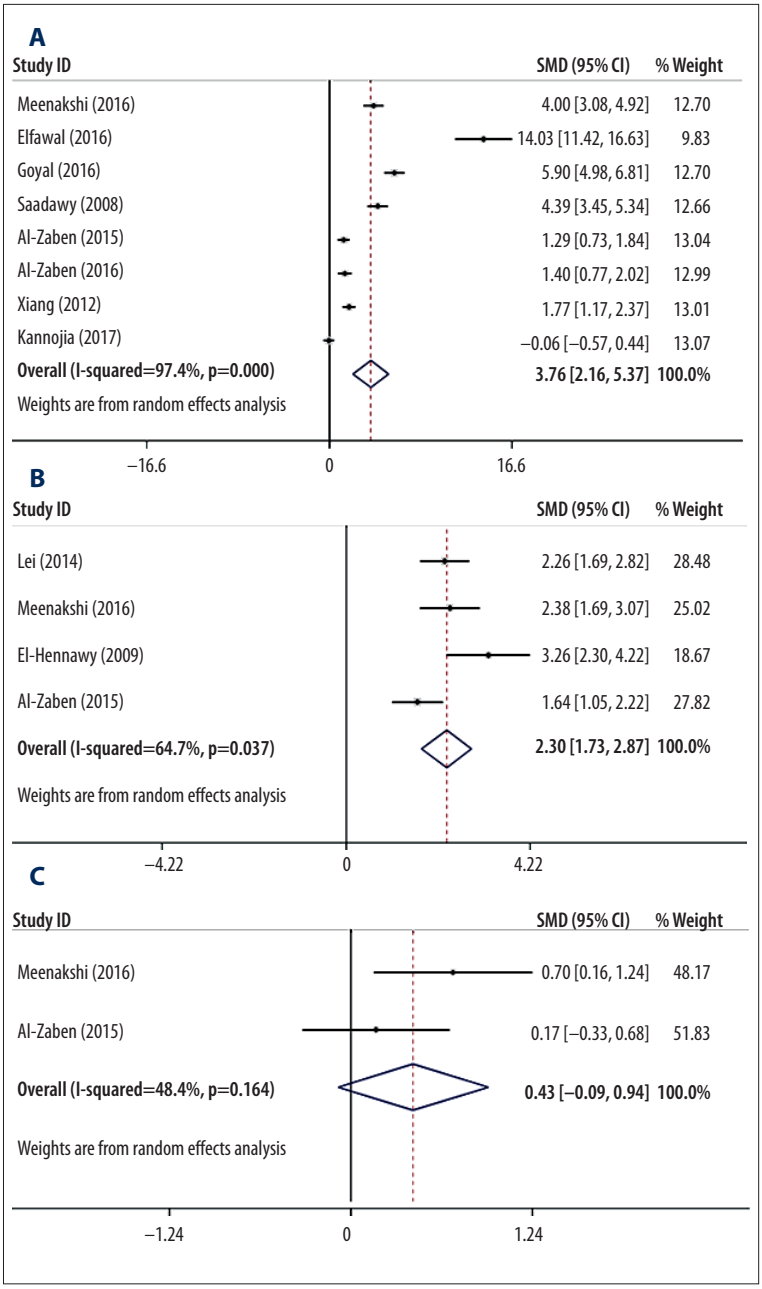

Figure 3. Forest plot for the duration of analgesia. (**A**) BU + DEX with 1 µg/kg versus BU alone; (**B**) BU + DEX with 2 µg/kg versus BU alone; (**C**) BU + DEX with 2 µg/kg versus BU + DEX with 1 µg/kg. DEX – dexmedetomidine; BU – bupivacaine.

age range of children among the studies was one of the reasons. In the articles, the age range of the participating children was heterogeneous. The age ranges in the Meenakshi et al. study and the Goyal et al. study was different from the other studies (6 months to 8 years of age versus 2 years to 10 years of age). We conducted subgroup analysis based on age range and found that as the heterogeneity decreased, so did the difference in the age range, which might be one of the sources of the heterogeneity.

We doubted that another reason for the heterogeneity could be the indications for different operation. The pain response in extreme surgery and abdominal surgery will be different from other indications. The operation criteria used in the Elfawal et al. study was lower limb surgeries, whereas the other studies used lower abdominal surgeries. We also doubted that the use of levobupivacaine or BU made a difference in terms of motor response generation and duration of drug action. Elfawal et al. used levobupivacaine; in our influence analysis, when this trial was removed, no significant reduction in heterogeneity was found.

Furthermore, α_2-adrenergic agonists have been studied for effects of hypotension and tachycardia on hemodynamics and

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Table 2. Number of patients requiring a rescue analgesia.

Time to first analgesic administration	Does of DEX	RR (95% CI)	P of RR	I^2	P
6 hour	Overall	0.093 (0.051, 0.170)	<0.001	33.90%	0.169
	1 μg/kg	0.096 (0.049, 0.191)	<0.001	44.2%	0.128
	2 μg/kg	0.085 (0.025, 0.291)	<0.001	45.8%	0.175
12 hour	Overall	0.502 (0.321, 0.786)	0.003	81.4%	<0.001
	1 μg/kg	0.326 (0.123, 0.869)	0.025	91.3%	<0.001
	2 μg/kg	0.559 (0.432, 0.723)	<0.001	0.0%	0.622
24 hour	Overall	0.657 (0.507, 0.853)	0.002	85.9%	<0.001
	1 μg/kg	0.642 (0.497, 0.831)	0.001	63.8%	0.04
	2 μg/kg	0.695 (0.424, 1.138)	0.148	92.6%	<0.001

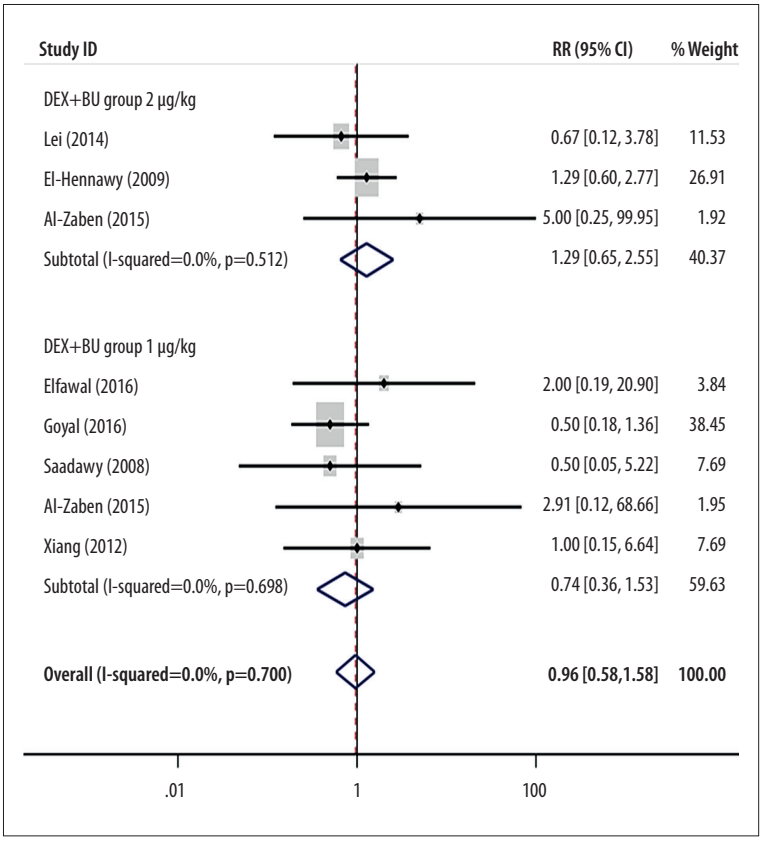

Figure 4. Forest plot for side effect.

reduced incidence of postoperative nausea [30]. The introduction of DEX, one of the highly selective α_2-adrenergic agonists, has further broadened the use of α_2-adrenergic agonists in recent years [31,32]. In the 10 studies included in our meta-analysis, no serious side effects were described. Even though the incidence of nausea and vomiting between the BU group and the DEX + BU group were not statistically significant, we did find that as the dosage of DEX increased, the incidence of nausea and vomiting increased. However, 2 articles reported that a 2 μg/kg dose caudal DEX compared to a 1 μg/kg dose of caudal DEX had a higher incidence of other side effects.

There were several limitations to our study. Although we used dose-grouping for DEX to reduce heterogeneity, the heterogeneity in some studies was still large. Furthermore, the influence of publication bias cannot be ignored; the methodological

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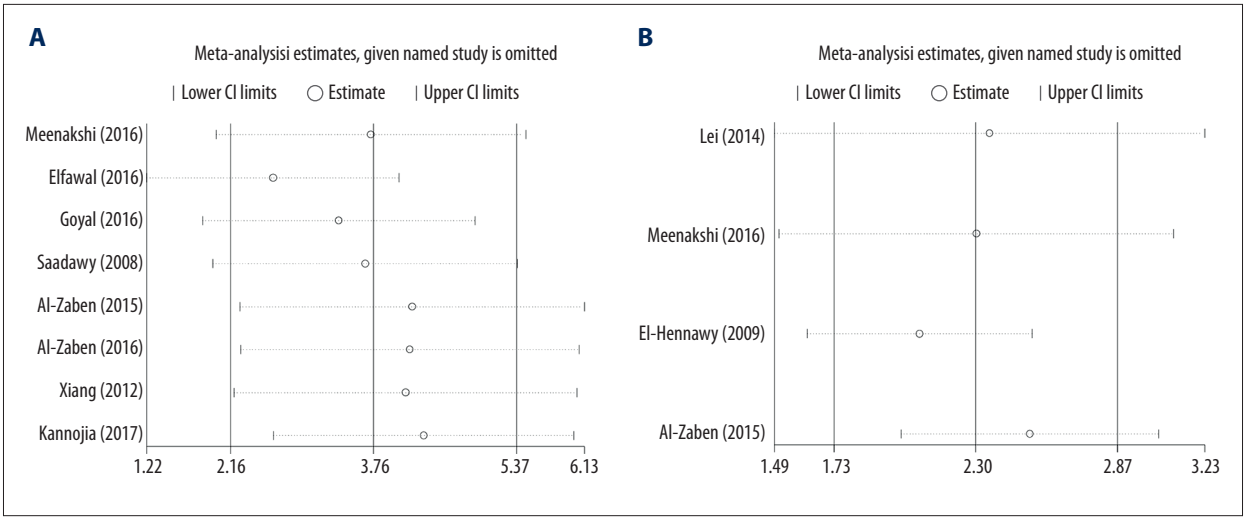

Figure 5. The result of influence analysis. (**A**) DEX with 1 μg/kg; (**B**) DEX with 2 μg/kg. DEX – dexmedetomidine; BU – bupivacaine.

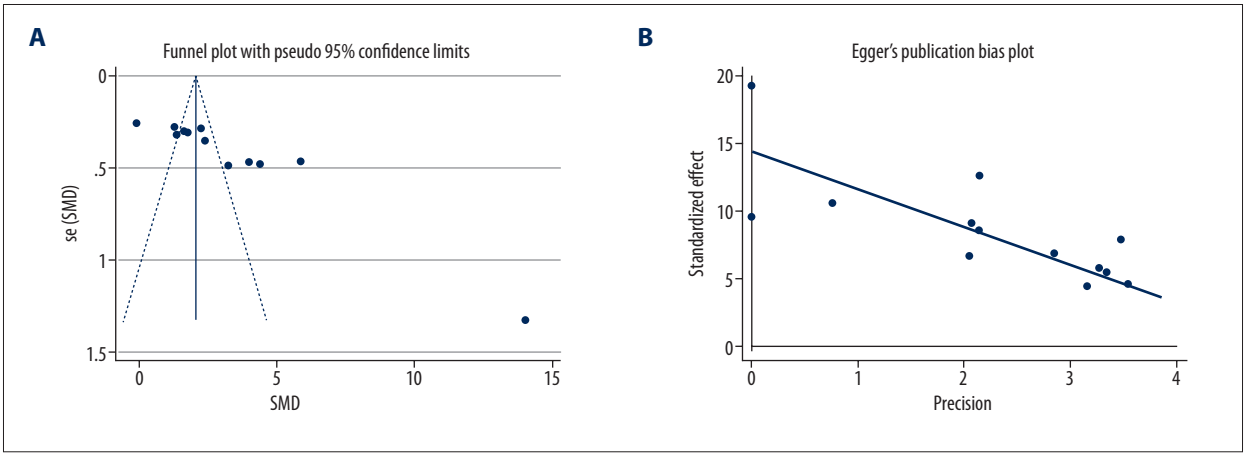

Figure 6. Publication bias. (**A**) Funnel plot with pseudo 95% confidence limits; (**B**) Egger's publication bias plot.

quality of our results representing reporting bias was unclear for the included studies, and the Funnel plot and Egger's publication bias plot revealed strong asymmetry. The different methods used in studies for postoperative pain assessment and the triggers used for rescue analgesics might have introduced bias into some outcomes, especially for the duration of analgesia. Thus, some results of our research might be influenced by bias. The concentration and dose of BU administered caudally varied between the studies and this might have influenced the postoperative analgesic effect.

Conclusions

DEX seems to be a promising adjuvant to BU to increase the duration of caudal analgesia without an increase in side effects in a pediatric patients. However, the results of our meta-analysis might have been influenced by clinical heterogeneity and insufficient data. More large-scale, multicenter, double-blinded RCTs are required to confirm our results.

Conflict of interest

None.

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