

# Dexmedetomidine Addition For Pediatric Hernia Repair: A Meta-Analysis of Randomized Controlled Studies

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## Research

**Keywords:** dexmedetomidine, pain control, pediatric hernia repair, randomized controlled trials.

**Posted Date:** June 30th, 2020

**DOI:** <https://doi.org/10.21203/rs.3.rs-38078/v1>

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## Abstract

**Introduction:** The efficacy of dexmedetomidine addition for pain control after pediatric hernia repair remains controversial. We conduct a systematic review and meta-analysis to explore the influence of dexmedetomidine addition on pain management for pediatric hernia repair.

**Methods:** We search PubMed, EMBASE, Web of Science, EBSCO, and Cochrane library databases through March 2020 for randomized controlled trials (RCTs) assessing the effect of dexmedetomidine addition on pain management for pediatric hernia repair. This meta-analysis is performed using the random-effect model.

**Results:** Six RCTs are included in the meta-analysis. Overall, compared with control group for pediatric hernia repair, dexmedetomidine addition is associated with significantly reduced analgesic consumption (SMD=-1.0; 95% CI=-1.40 to -0.61; P<0.00001) and number of rescue analgesics (SMD=0.16; 95% CI=0.06 to 0.41; P=0.0002), prolonged time to first analgesia (SMD=8.16; 95% CI=4.58 to 11.73; P<0.00001) and decreased the incidence of emergence agitation (RR=0.12; 95% CI=0.03 to 0.44; P=0.001), but has no obvious impact on pain scores at 1 h (SMD=-2.00; 95% CI=-5.78 to 1.79; P=0.30) or 2 h (SMD=-0.73; 95% CI=-2.33 to 0.87; P=0.37).

**Conclusions:** Dexmedetomidine addition is beneficial to pain control after pediatric hernia repair.

## Introduction

Hernia repair has become the most common surgical procedures in children, but may result in severe post-operative pain [1–4]. About 12.4% of pediatric patients were estimated to experience persistent post-herniorrhaphy pain. Chronic pain occurs in 5–10% of patients with inguinal herniorrhaphy [5]. Insufficient pain control may result in increased blood pressure, tachycardia, insomnia and behavioral disorders [3, 5, 6].

Many methods have been developed for perioperative pain management in children, they mainly include single shot caudal block, wound infiltration with local anesthetics, transverse abdominal plane block, oral or intravenous analgesics [7–9]. For example, ilioinguinal/iliohypogastric nerve block has good effect on post-operative pain with minimal risk and low cost [10]. It can achieve the comparable efficacy to caudal block [11]. Dexmedetomidine, a strong  $\alpha_2$  adrenergic agonist, has a sympatholytic, sedative, analgesic effect and is effective in many anesthetic and analgesic techniques [12, 13]. The addition of dexmedetomidine to wound infiltration with ropivacaine was reported to reduce post-operative pain after inguinal herniorrhaphy [14–16].

Recently, several studies have investigated the efficacy of dexmedetomidine supplementation for pediatric hernia repair, but the results are conflicting [11, 17–19]. This systematic review and meta-analysis of RCTs aims to assess the impact of dexmedetomidine supplementation on pain control after pediatric hernia repair.

## Materials And Methods

This systematic review and meta-analysis are performed based on the guidance of the Preferred Reporting Items for Systematic Reviews and Meta-analysis statement and Cochrane Handbook for Systematic Reviews of Interventions [20, 21]. No ethical approval and patient consent are required because all analyses are based on previous published studies.

### Literature search and selection criteria

We systematically search several databases including PubMed, EMBASE, Web of Science, EBSCO, and the Cochrane library from inception to March 2020 with the following keywords: "esketamine", and "depression". The reference lists of retrieved studies and relevant reviews are also hand-searched and the process above is performed repeatedly in order to include additional eligible studies.

The inclusion criteria are presented as follows: (1) study design is RCT, (2) children patients underwent hernia repair, and (3) intervention treatments are dexmedetomidine addition spray versus placebo.

### Data extraction and outcome measures

Some baseline information is extracted from the original studies, and they include first author, number of patients, age, female, weight, duration of surgery and detail methods in two groups. Data are extracted independently by two investigators, and discrepancies are resolved by consensus. We have contacted the corresponding author to obtain the data when necessary.

The primary outcomes are analgesic consumption and number of rescue analgesics. Secondary outcomes include time to first analgesia, emergence agitation, pain scores at 1 h and 2 h.

### Quality assessment in individual studies

The methodological quality of each RCT is assessed by the Jadad Scale which consists of three evaluation elements: randomization (0-2 points), blinding (0-2 points), dropouts and withdrawals (0-1 points) [22]. One point would be allocated to each element if they have been conducted and mentioned appropriately in the original article. The score of Jadad Scale varies from 0 to 5 points. An article with Jadad score  $\leq 2$  is considered to be of low quality. The study is thought to be of high quality if Jadad score  $\geq 3$  [23].

### Statistical analysis

We assess standard mean difference (SMD) with 95% confidence interval (CI) for continuous outcomes (analgesic consumption, time to first analgesia, pain scores at 1 h and 2 h), and risk ratio (RR) with 95% CI for dichotomous outcome (number of rescue analgesics and emergence agitation). Heterogeneity is evaluated using the  $I^2$  statistic, and  $I^2 > 50\%$  indicates significant heterogeneity [24]. The random-effects model is used for all meta-analysis. We search for potential sources of heterogeneity for significant heterogeneity. Sensitivity analysis is performed to detect the influence of a single study on the overall estimate via omitting one study in turn or performing the subgroup analysis. Owing to the limited number (<10) of included studies, publication bias is not assessed. Results are considered as statistically significant for  $P < 0.05$ . All statistical analyses are performed using Review Manager Version 5.3 (The Cochrane Collaboration, Software Update, Oxford, UK).

## Results

### Literature search, study characteristics and quality assessment

Figure 1 shows the detail flowchart of the search and selection results. 315 potentially relevant articles are identified initially. Finally, six RCTs are included in the meta-analysis [11, 13, 17–19, 25].

The baseline characteristics of six included RCTs are shown in Table 1. These studies are published between 2015 and 2020, and the total sample size is 332. The dose of dexmedetomidine ranged from 0.3  $\mu\text{g}/\text{kg}$  to 1.0  $\mu\text{g}/\text{kg}$ .

Table 1  
Characteristics of included studies

NO.	Author	Dexmedetomidine group						Control group			
		Number	Age	Female (n)	Weight (kg)	Duration of surgery (min)	Methods	Number	Age	Female (n)	Weight (kg)
1	Shahhosseini 2020	30	41.80 $\pm$ 22.79 months	-	14.67 $\pm$ 3.79	-	5 ml bupivacaine 0.25% with dexmedetomidine 0.3 $\mu\text{g}/\text{kg}$	30	38.33 $\pm$ 18.05 months	-	15.48 $\pm$ 5.08
2	Azemati 2019	30	27.97 $\pm$ 20.78 months	-	-	-	1 $\mu\text{g}/\text{kg}$ dexmedetomidine plus local infiltration of 0.2 mL/kg bupivacaine 0.5% at the incision site before surgery	30	17.53 $\pm$ 14.77 months	-	-
3	Yao 2018	30	2.9 $\pm$ 1.5 years	1	15.4 $\pm$ 2.9	34.3 $\pm$ 6.5	1 mL/kg of caudal 0.25% levobupivacaine and intravenous 1 $\mu\text{g}/\text{kg}$ dexmedetomidine in 20 mL saline	30	2.8 $\pm$ 1.8 years	1	14.7 $\pm$ 3.3
4	Karan 2018	30	5.91 $\pm$ 2.65 years	3	18.7 $\pm$ 7.11	29.1 $\pm$ 4.64	ilioinguinal-iliohypogastric nerve block with ropivacaine 0.2% with adjunct dexmedetomidine 1 $\mu\text{g}/\text{kg}$	30	5.93 $\pm$ 2.72 years	2	17.83 $\pm$ 6.54
5	Sun 2017	25	26.1 $\pm$ 9.7 months	5	13.4 $\pm$ 3.1	-	intravenous dexmedetomidine at 1.0 $\mu\text{g}/\text{kg}$	24	24.1 $\pm$ 11.1 months	8	12.9 $\pm$ 2.7
6	Lundblad 2015	22	5.55 (2.3–7.8), median (range) years	5	20.5 (12–26)	23.5 (12–43)	ilioinguinal/iliohypogastric nerve block with plain ropivacaine 0.197% plus with adjunct dexmedetomidine 0.3 $\mu\text{g}/\text{kg}$	21	5.3 (1.7–7.9) years	8	19.6 (12–34)

Among the six included RCTs, two trials reported analgesic consumption [19, 25], two trials reported number of rescue analgesics and time to first analgesia [18, 19], two trials reported emergence agitation [18, 25], as well as two trials reported pain scores at 1 h and 2 h [17, 19]. Jadad scores of the six included studies vary from 3 to 5, and all six studies have high-quality based on the quality assessment.

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### Primary outcomes: analgesic consumption and number of rescue analgesics

The random-effect model is used for the analysis of primary outcome. The results find that compared to control group for pediatric hernia repair, dexmedetomidine addition is associated with significantly reduced analgesic consumption (SMD=-1.0; 95% CI=-1.40 to -0.61;  $P < 0.00001$ ) with no heterogeneity among the studies ( $I^2=0\%$ , heterogeneity  $P=0.72$ , Figure 2) and number of rescue analgesics (SMD=0.16; 95% CI=0.06 to 0.41;  $P=0.0002$ ) with no heterogeneity among the studies ( $I^2=0\%$ , heterogeneity  $P=0.93$ , Figure 3).

## Sensitivity analysis

There is no heterogeneity for the primary outcome, and thus we do not perform the meta-analysis via omitting one study or subgroup analysis to detect the heterogeneity.

## Secondary outcomes

In comparison with control intervention for pediatric hernia repair, dexmedetomidine addition can substantially increase time to first analgesia (SMD=8.16; 95% CI=4.58 to 11.73; P<0.00001; Figure 4) and decrease the incidence of emergence agitation (RR=0.12; 95% CI=0.03 to 0.44; P=0.001; Figure 5), but shows no obvious effect on pain scores at 1 h (SMD=-2.00; 95% CI=-5.78 to 1.79; P=0.30; Figure 6) or 2 h (SMD=-0.73; 95% CI=-2.33 to 0.87; P=0.37; Figure 7).

## Discussion

Local anesthetics such as bupivacaine and ropivacaine were used for peripheral nerve block, sympathetic nerve block, local infiltration, epidural and caudal blocks [11, 26–28]. Combination dexmedetomidine with bupivacaine or ropivacaine can prolong the analgesic effect [14, 29, 30]. In a prospective randomized study involving 60 patients with the age between 6 months to 6 years scheduled for unilateral inguinal herniorrhaphy, the duration of analgesia is significantly higher in patients receiving bupivacaine with dexmedetomidine in comparison to patients receiving bupivacaine alone, but the frequency of analgesic consumption in the first 24 h and total dose of analgesic consumption had no significant difference in the two groups [11].

However, this meta-analysis finds that dexmedetomidine addition can substantially reduce the analgesic consumption and number of rescue analgesics for pediatric hernia repair in comparison to control intervention. In sixty children with the age range of 12 to 72 months for unilateral inguinal herniorrhaphy, dexmedetomidine in addition to bupivacaine reduced the hernia sac traction response and increased the analgesia time postoperatively [31]. Dexmedetomidine addition to ropivacaine was reported to prolong the period of first analgesia demand compared to ropivacaine alone in children undergoing inguinal herniorrhaphy [13]. Our meta-analysis also confirms the prolonged time to first analgesia after dexmedetomidine addition for pediatric hernia repair. In addition, the emergence agitation is obviously reduced after adding dexmedetomidine.

In another study on 120 patients undergoing laparoscopic cholecystectomy, visual analogue score (VAS) was far lower in dexmedetomidine and bupivacaine group ( $1.80 \pm 0.36$ ) than tramadol and bupivacaine ( $3.01 \pm 0.48$ ) and plain bupivacaine group ( $4.5 \pm 0.92$ ) ( $P < 0.001$ ) [32]. The mixture of dexmedetomidine and bupivacaine on forty children with abdominal cancer surgeries was reported to reduce postoperative pain significantly up to 19 hours and increase the duration of sedation [32]. However, this meta-analysis revealed the similar pain scores at 1 h and 2 h between dexmedetomidine addition and control intervention for pediatric hernia repair. The efficacy of dexmedetomidine addition for pain control may be compromised by the analgesic consumption during the surgery. In sixty children aged between 2–11 years scheduled for elective herniotomy, adjunct dexmedetomidine  $1 \mu\text{g}/\text{kg}$  was associated with substantially reduced pain scores after 6 h compared to control intervention [19].

Several limitations exist in this meta-analysis. Firstly, our analysis is based on only six RCTs, and more RCTs with large sample size should be conducted to explore this issue. Next, although there is no significant heterogeneity, different doses and combination methods of dexmedetomidine addition may produce some bias. Finally, some unpublished and missing data may lead to some bias for the pooled effect.

## Conclusion

Dexmedetomidine addition benefits to pain control after pediatric hernia repair.

## Abbreviations

randomized controlled trials: RCTs

mean differences: MDs

confidence intervals: CIs

risk ratios: RRs

## Declarations

### Ethical Approval and Consent to participate

Not applicable.

### Consent for publication

Not applicable.

### Availability of supporting data

Not applicable.

### Competing interests

The authors declare no conflict of interest.

## Funding

Not applicable.

## Authors' contributions

Bo Liu conducted the design, Wei Liu conducted the study planning, data analysis and data interpretation, Liang Yuan wrote and revised the article. All authors read and approved the final manuscript.

## Acknowledgements

None.

## Authors' information

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## Figures

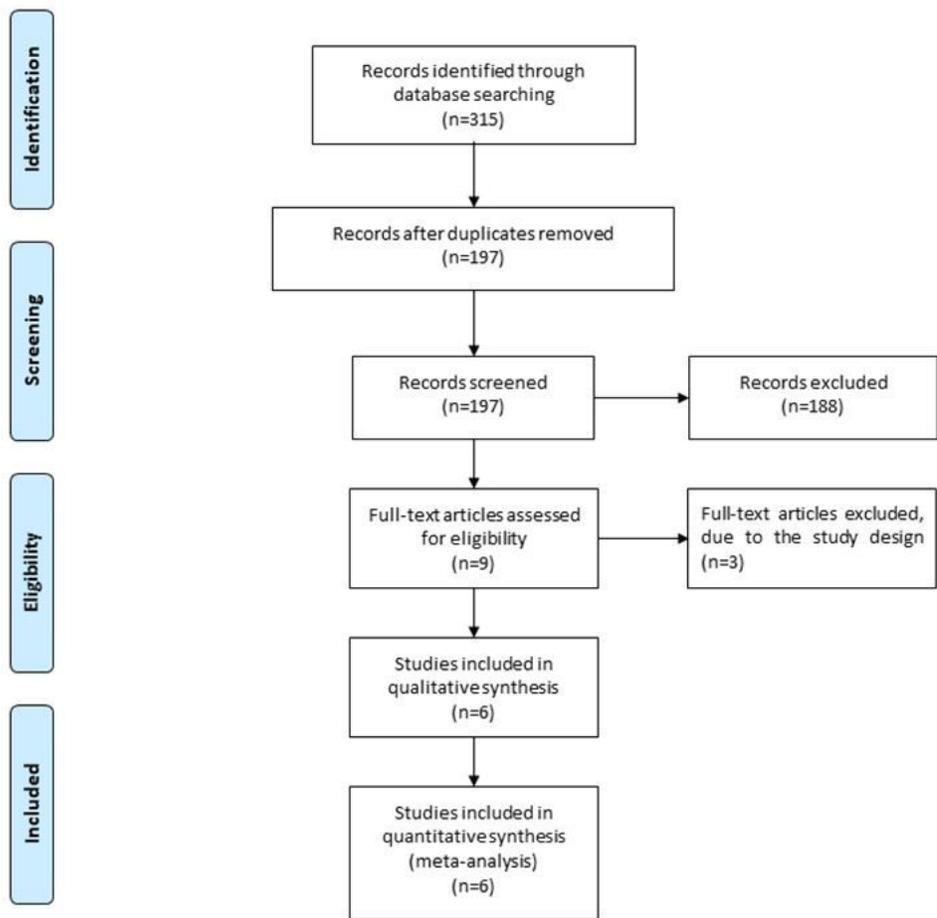


Figure 1

Flow diagram of study searching and selection process.

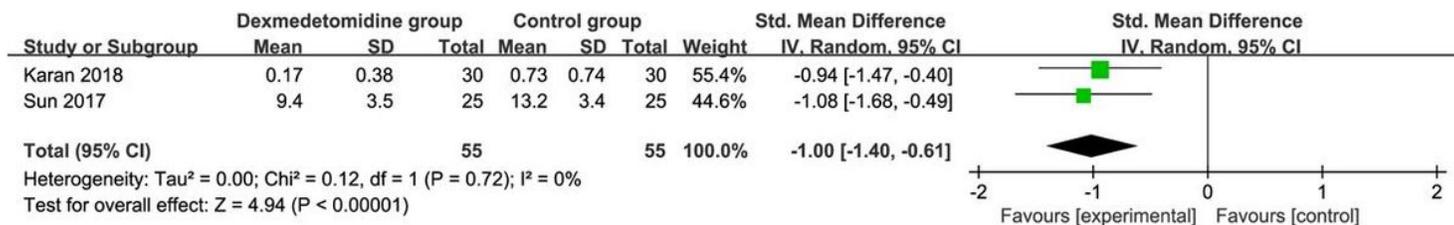


Figure 2

Forest plot for the meta-analysis of analgesic consumption.

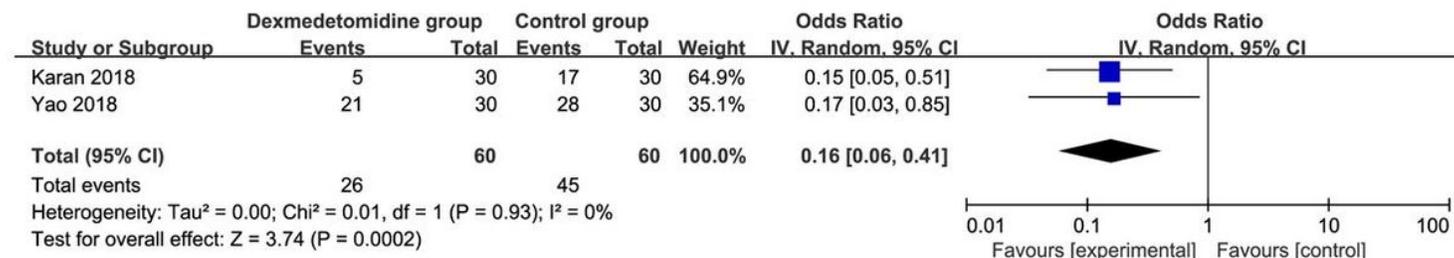


Figure 3

Forest plot for the meta-analysis of number of rescue analgesics.

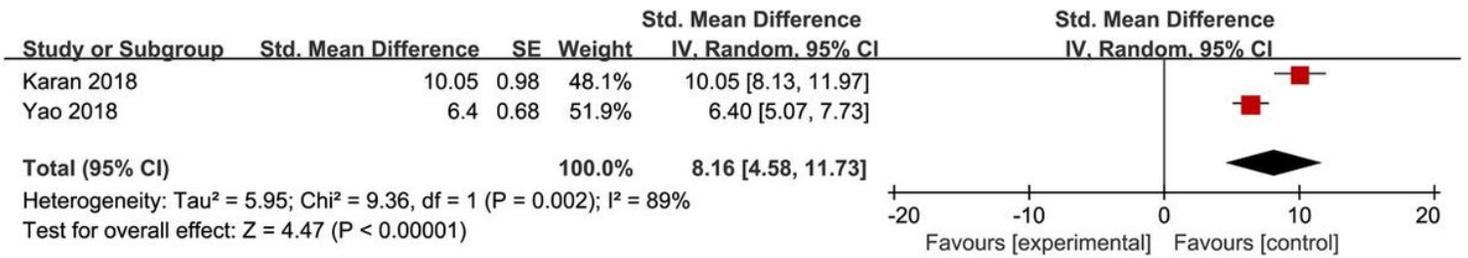


Figure 4

Forest plot for the meta-analysis of time to first analgesia.

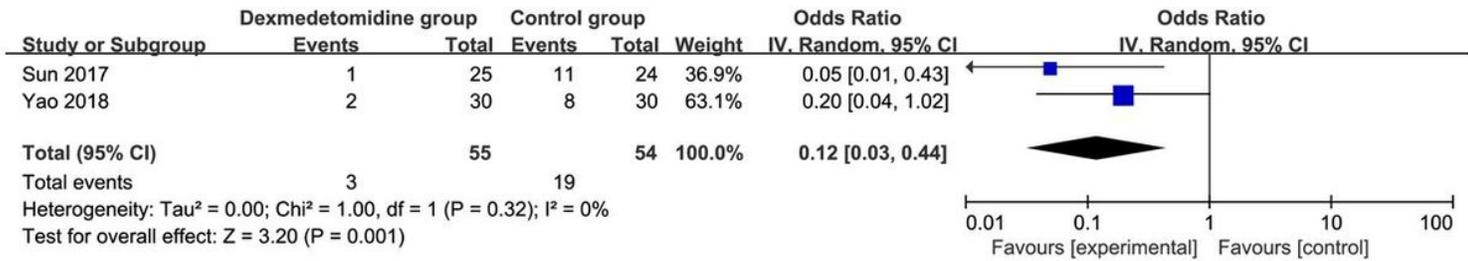


Figure 5

Forest plot for the meta-analysis of emergence agitation.

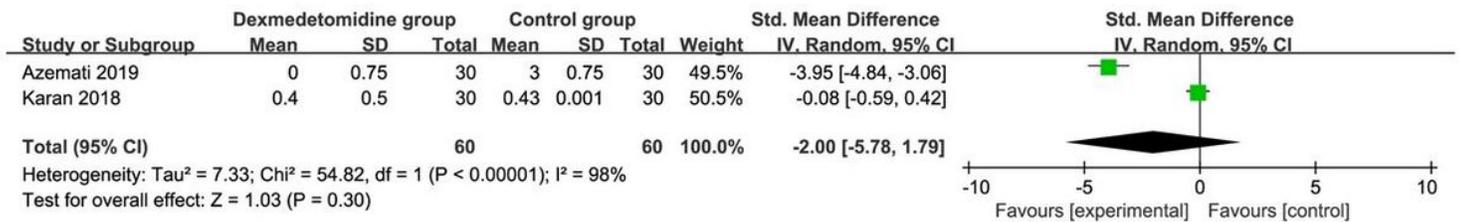


Figure 6

Forest plot for the meta-analysis of pain scores at 1 h.

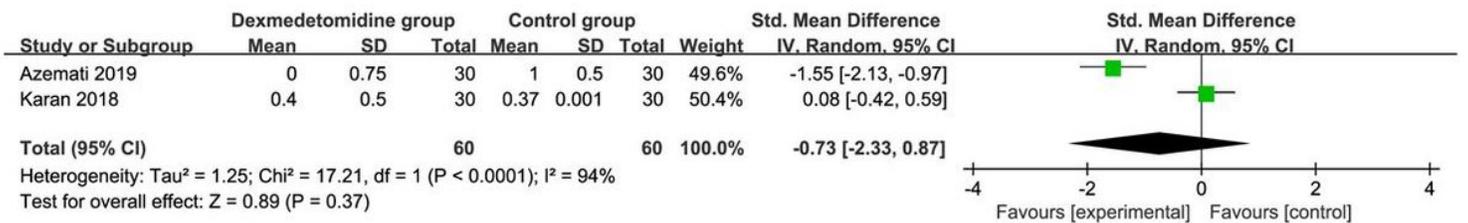


Figure 7

Forest plot for the meta-analysis of pain scores at 2 h.