Effect of dexmedetomidine and propofol sedation on the prognosis of children with severe respiratory failure: a systematic review and meta-analysis

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Background: During treatment of acute respiratory failure (ARF) in children, sedation can reduce pain, improve tolerance, and reduce the incidence of adverse events, so selecting an appropriate sedation strategy is very important for improving prognosis and quality of life. Both dexmedetomidine and propofol have good sedative effects, so we investigated the application of these drugs in critically ill children with ARF by literature search and meta-analysis.

Methods: We searched Embase, The Cochrane Library, PubMed, Ovid, Clinicaltrials.org, and Google Scholar for randomized controlled trials (RCTs) preferentially but not exclusively, and used RevMan 5.4 to analyze the screened literature.

Results: Seven studies were included in the quantitative meta-analysis, with a total of 1,188 patients. There was no significant difference in the effect of dexmedetomidine and propofol on the duration of tracheal intubation in children with ARF [mean difference (MD) =–0.05; 95% confidence interval (CI): (–0.42, 0.32); Z=0.26; P=0.79], but dexmedetomidine sedation could reduce the intensive care unit (ICU) stay in children with ARF [MD =–0.62; 95% CI: (–1.08, –0.16); Z=2.65; P=0.008], and shorten the total hospital stay [MD =–1.94; 95% CI: (–2.63, –1.25); Z=5.48; P<0.00001]. There was no significant effect on mortality between the two groups [odds ratio (OR) =0.48; 95% CI: (0.19, 1.25); Z=1.50; P=0.13]. The incidence rate of bradycardia with dexmedetomidine sedation was higher than with propofol [OR=12.30; 95% CI: (2.28, 66.47); Z=2.92; P=0.004], and the incidence of hypotension was also higher [OR =6.99, 95% CI: (1.22, 39.86); Z=2.19; P=0.03].

Discussion: Compared with propofol, dexmedetomidine can significantly reduce the ICU stay and hospital stay. However, bradycardia and hypotension may occur during the use of dexmedetomidine, which requires close attention and timely intervention.

Keywords: Dexmedetomidine; propofol; pediatric respiratory failure

Introduction

Respiratory failure in children is defined as dyspnea due to various causes of respiratory physiological dysfunction, and acute respiratory failure (ARF) is common (1,2). Pediatric respiratory failure is a clinically critical illness that can cause death in children in the pediatric intensive care unit (PICU). In addition to effective control of the primary disease (pulmonary infection, cerebral edema), oxygen therapy should be given to patients with respiratory insufficiency, and tracheal intubation and mechanical ventilation (MV) should be given when necessary (3). During treatment, sedative therapy can reduce the pain and subjective discomfort caused by MV, improve the tolerance of the pediatric patient, reduce the incidence of accidental removal of ventilation catheters, ultimately reduce cardiovascular and respiratory instability, shorten the PICU admission time and total hospital stay, and reduce mortality (4,5). However, prolonged sedation may also lead to adverse effects such as memory and cognitive impairment, respiratory depression, and changes in cardiovascular dynamics; therefore, the selection of an appropriate sedation strategy is important for improving the prognosis and quality of life (6). Dexmedetomidine, a highly potent and selective pharmacological α2-adrenergic receptor agonist, is widely used for clinical surgical anesthesia and intensive care unit (ICU) sedation because of its good analgesic, sedative, and anti-sympathetic effects (7). However, there is still a lack of evidence on whether its use is superior to other commonly used sedative drugs (e.g., midazolam and propofol) in the treatment of MV children with respiratory failure. Kim *et al.* (8) compared the outcomes between dexmedetomidine as a tranquilizer and propofol in the course of pediatric MRI, but there is no clinical comparison in children with respiratory failure yet. A recent meta-analysis by Dong (9) compared dexmedetomidine with other sedative drugs in MV, but the included patients were all adults, not children. In this study we summarized the relevant studies to on the application of dexmedetomidine for sedative effect in the treatment of ARF in children. We present the following article in accordance with the PRISMA reporting checklist (available at https://tp.amegroups.com/article/view/10.21037/tp-22-20/rc).

Methods

Database and search strategy

We searched Embase, The Cochrane Library, PubMed, Ovid, and additionally searched the clinical experimental research in Clinicaltrials.org. We also used the search function of Google Scholar to search for other possibly relevant literature. We set the search time from database construction to November 2021 and used the keyword combination of (dexmedetomidine OR DEX) AND (propofol) OR (sedation) OR (respiratory failure OR acute respiratory failure OR ARF) OR (Mechanical ventilation OR MV).

Literature inclusion criteria

(I) Study type: English language only, and randomized controlled trials (RCTs) preferred. (II) Study subjects: all patients were admitted to a PICU, aged <18 years, with respiratory failure caused by primary disease (pneumonia infection, cerebral edema, pulmonary edema), with hypoxemia or hypercapnia as the main symptom. (III) Intervention measures: all children were given MV and either dexmedetomidine or propofol to expected depth of sedation (i.e., two cohorts or groups). (IV) At least one expected outcome indicator: length of hospital stay, mortality, PICU stay, duration of MV, adverse reaction rate, and complete data are available.

Literature exclusion criteria

(I) Subjects were mainly adults; (II) investigations, case analysis and review of non-RCT; (III) incomplete or no data.

Literature screening

After literature retrieval, all studies were imported into Endnote X9 software for exclusion of duplicate literature. Next, two researchers read the title and abstract for further screening. If the original text was not available, the correspondence author was contacted by email and telephone to obtain the full text.

Literature quality evaluation and risk of bias assessment

The analysis tool RevMan 5.4 provided by the Cochrane Collaboration was used to assess the risk of bias of the included articles. We used Jadad scale to evaluate the quality of the study, and a score of more than 3 was regarded as a high-quality study.

Outcome indicators

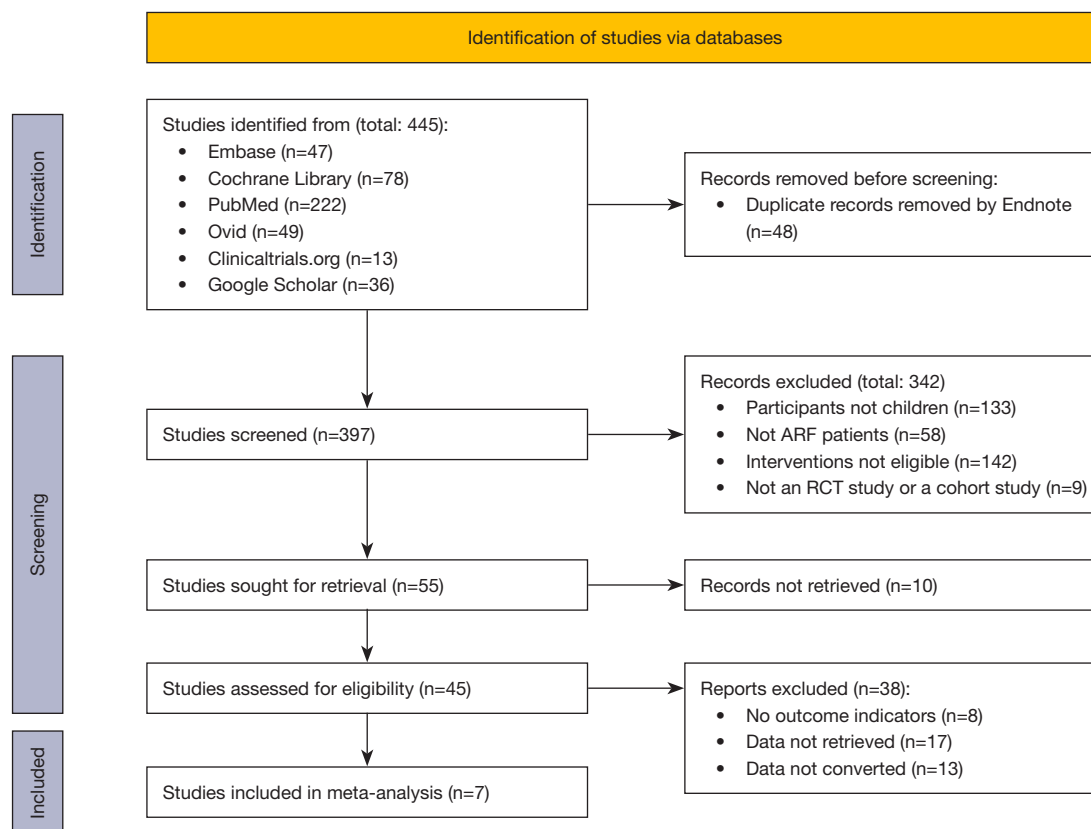We only counted and analyzed the six most common

Figure 1 Literature selection flow chart. ARF, acute respiratory failure.

outcome indicators: (I) duration of endotracheal intubation; (II) ICU length of stay; (III) length of hospital stay; (IV) mortality; (V) incidence of adverse reactions (bradycardia); (VI) incidence of adverse reactions (hypotension).

Data extraction

Two researchers independently extracted the relevant data: author, publication year and month, grouping method, number of cases in each group, age of children, sex ratio, weight, primary disease diagnosis, complications, intervention methods and sedative dose. After data extraction, the results of each researcher were cross-checked and any differences generated were discussed and finally determined.

Statistical methods

(I) Meta-analysis software was RevMan 5.4. (II) Continuous variables were statistically analyzed by inverse variance, effect size is reported using mean difference (MD) and

95% confidence interval (CI), and effect size is reported as odds ratio (OR) and 95% CI for binary variables; P<0.05 indicated the results were statistically significant. (III) Forest plot descriptive statistics were used for comparisons. (IV) Literature heterogeneity was analyzed by I^2 analysis and Q test; heterogeneity of results was indicated by I^2>50% or P<0.1; the OR value was obtained using a random-effects or fixed-effects model as applicable. (V) If the heterogeneity analysis suggested heterogeneity between studies, a heterogeneity source survey was performed using a case-by-case exclusion method, and general description analysis was adopted when the heterogeneity source could not be judged. (VI) Sensitivity analysis was performed by comparing the random-effect and fixed-effect results. (VII) Funnel plot was used to indicate publication bias.

Results

Literature screening

The flow chart of literature selection is shown in *Figure 1*: 7

Table 1 Basic characteristics, intervention measures and outcome indicators of included literature

Author	Publication year	Type	Primary disease	Age (years)	E/C (n)	Experiment group	Control group	Outcome	Jadad Score
Erickson *et al.* (10)	2020	RCT	MV children with ARF	1–13	29/28	Dexmedetomidine 1.0 µg/kg/h	Propofol (maximum dose 4 mg/kg/h)	①②③ ④⑤⑥	3
Curley *et al.* (11)	2015	Cluster-randomized trial	Children with ARF	2–18	287/171	Dexmedetomidine 1.0 µg/kg/h	Propofol with lowest effective dose	①② ③④	3
Shehabi *et al.* (12)	2013	RCT	Children with ARF	1–17	16/21	Dexmedetomidine 0.1–1.5 µg/kg/h	Propofol (maximum 1–4 mg/kg/h)	②③④	3
Tosun *et al.* (13)	2006	RCT	Children with ARF	1–16	22/22	0.7 g/kg/h of dexmedetomidine and 1 mg/kg/h of ketamine	100 µg/kg/min of propofol and 1 mg/kg/h of ketamine	⑤⑥	3
Mogahd *et al.* (14)	2017	RCT	MV children with ARF after 3 CABG	1–18	35/35	Dexmedetomidine 0.2–0.7 µg/kg/h	Propofol 25–50 µg/kg/min	①②	3
Ruokonen *et al.* (15)	2009	RCT	Children with ARF	1–17	41/44	Dexmedetomidine 0.3–1.4 µg/kg/h	Propofol 0.5–3 mg/kg/h	②⑤⑥	4
Jakob *et al.* (16)	2012	RCT	Children with ARF	1–18	223/214	Dexmedetomidine 0.2–1.4 µg/kg/h	Propofol 0.3–4.0 mg/kg/h	①②	4

Outcomes: ① duration of endotracheal intubation; ② ICU length of stay; ③ length of hospital stay; ④ mortality; ⑤ bradycardia; ⑥ hypotension. E/C, experiment/control; RCT, randomized controlled trial; MV, mechanical ventilation; ARF, acute respiratory failure; CABG, coronary artery bypass graft; ICU, intensive care unit.

studies with a total of 1,188 patients were finally included in the quantitative meta-analysis (10-16). Basic characteristics, intervention measures and outcome indicators of all studies are shown in *Table 1*.

Literature quality and bias evaluation

All studies (10-16) were RCTs in the type of random grouping and all described the generation method of random sequence. However, the allocation concealment method was not described in all the literature (12,14), the others used sealed opaque envelopes to conceal the numbers. The studies (10-13) clearly indicated that the blind method was not implemented, which might introduce bias to the final results. All studies recorded the dropout cases in detail, without significant selective reporting bias and other biases, as shown in *Figures 2,3*.

Meta-analysis

Tracheal intubation time (days)

A total of 4 studies (10,11,14,16) reported the tracheal intubation time after the intervention of the two sedatives,

with statistical heterogeneity in the literature (I^2=59%; P=0.06). Random-effects model was used. Meta-analysis showed no significant difference in the effect of dexmedetomidine and propofol on the tracheal intubation time in children with ARF [MD =–0.05; 95% CI: (–0.42, 0.32); Z=0.26; P=0.79], as shown in *Figure 4*.

ICU length of stay (days)

A total of 6 studies (10-12,14-16) reported ICU admission time after the intervention of the two sedatives. There was statistical heterogeneity between them (I^2=61%; P=0.03). Random-effects model was used. Meta-analysis showed that dexmedetomidine reduced ICU admission time in children with ARF compared with propofol [MD =–0.62; 95% CI: (–1.08, –0.16); Z=2.65; P=0.008], as shown in *Figure 5*.

Length of hospital stay (days)

A total of 3 studies (10-12) reported the total hospital stay after the intervention of the two sedatives. There was no statistical heterogeneity (I^2=0%; P=0.81). The fixed-effects model was used. Meta-analysis showed that using dexmedetomidine for sedation reduced the total hospital stay of children with ARF compared with propofol
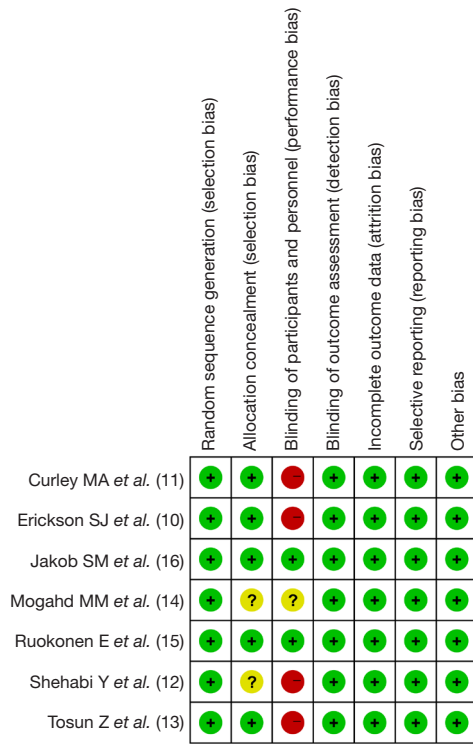
264

Xiao et al. Dexmedetomidine for the prognosis of children with SRF

Figure 2 Summary of literature bias (10-16).

[MD =−1.94; 95% CI: (−2.63, −1.25); Z=5.48; P<0.00001], as shown in *Figure 6*.

Mortality

A total of 3 studies (10-12) reported deaths after the intervention of the two sedatives. There was no statistical heterogeneity (I^2=0%; P=0.79). The fixed-effects model was used. Meta-analysis results showed that the effect of dexmedetomidine sedation compared with propofol on mortality was not statistically significant [OR =0.48; 95% CI: (0.19, 1.25); Z=1.50; P=0.13], as shown in *Figure 7*.

Adverse reactions

A total of 3 studies (10,13,15) reported the incidence rate of adverse reactions (bradycardia and hypotension) after the intervention of the two sedatives.

There was no statistical heterogeneity among the literature for bradycardia (I^2=0%; P=0.74). The fixed-effects model was used. Meta-analysis results showed that the incidence rate of bradycardia with dexmedetomidine sedation was higher than with propofol [OR =12.30; 95% CI: (2.28, 66.47); Z=2.92; P=0.004], as shown in *Figure 8*.
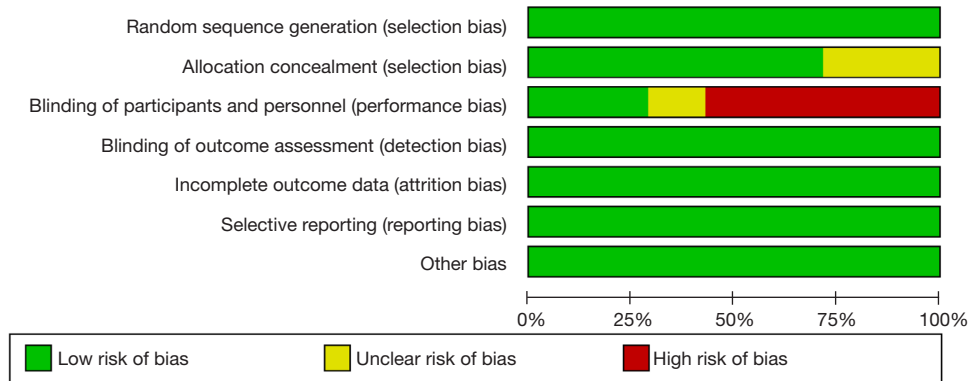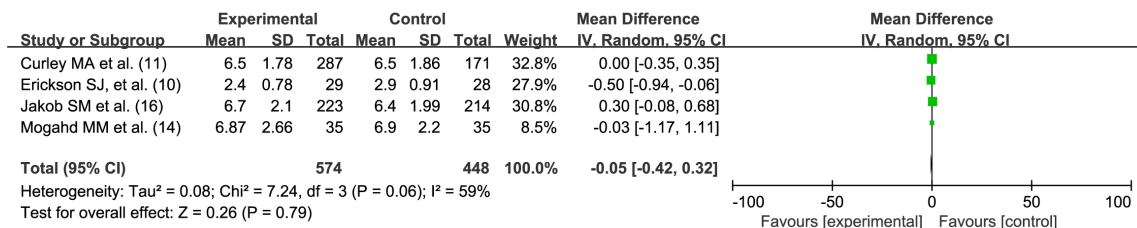

Figure 3 Literature bias plot.

Figure 4 Comparison of the effects of dexmedetomidine and propofol sedative on tracheal intubation time in children with ARF (10,11,14,16). ARF, acute respiratory failure; CI, confidence interval; SD, standard deviation.
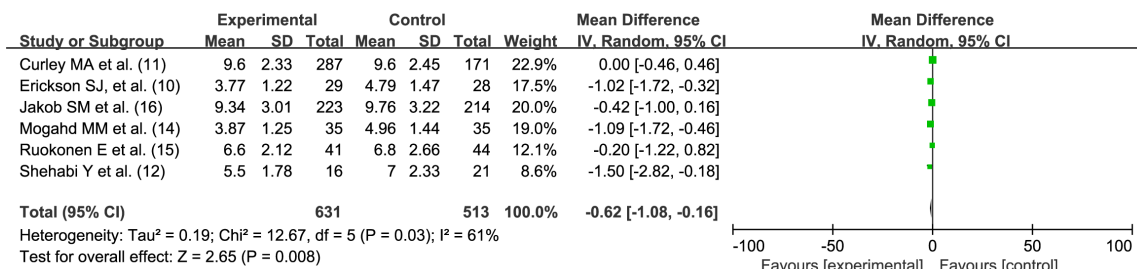
Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Curley MA et al. (11)	9.6	2.33	287	9.6	2.45	171	22.9%	0.00 [-0.46, 0.46]
Erickson SJ, et al. (10)	3.77	1.22	29	4.79	1.47	28	17.5%	-1.02 [-1.72, -0.32]
Jakob SM et al. (16)	9.34	3.01	223	9.76	3.22	214	20.0%	-0.42 [-1.00, 0.16]
Mogahd MM et al. (14)	3.87	1.25	35	4.96	1.44	35	19.0%	-1.09 [-1.72, -0.46]
Ruokonen E et al. (15)	6.6	2.12	41	6.8	2.66	44	12.1%	-0.20 [-1.22, 0.82]
Shehabi Y et al. (12)	5.5	1.78	16	7	2.33	21	8.6%	-1.50 [-2.82, -0.18]
Total (95% CI)			**631**			**513**	**100.0%**	**-0.62 [-1.08, -0.16]**

Heterogeneity: Tau² = 0.19; Chi² = 12.67, df = 5 (P = 0.03); I² = 61%
Test for overall effect: Z = 2.65 (P = 0.008)

Figure 5 Comparison of the effect of dexmedetomidine and propofol sedative on ICU length of stay in children with ARF (10-12,14-16). ARF, acute respiratory failure; CI, confidence interval; SD, standard deviation.
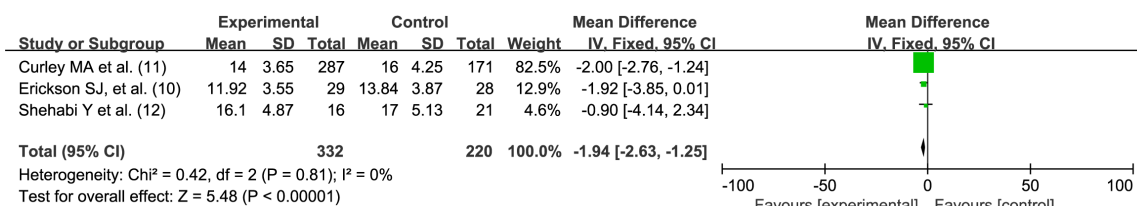
Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Curley MA et al. (11)	14	3.65	287	16	4.25	171	82.5%	-2.00 [-2.76, -1.24]
Erickson SJ, et al. (10)	11.92	3.55	29	13.84	3.87	28	12.9%	-1.92 [-3.85, 0.01]
Shehabi Y et al. (12)	16.1	4.87	16	17	5.13	21	4.6%	-0.90 [-4.14, 2.34]
Total (95% CI)			**332**			**220**	**100.0%**	**-1.94 [-2.63, -1.25]**

Heterogeneity: Chi² = 0.42, df = 2 (P = 0.81); I² = 0%
Test for overall effect: Z = 5.48 (P < 0.00001)

Figure 6 Comparison of the effect of dexmedetomidine and propofol sedative on length of hospital stay in children with ARF (10-12). ARF, acute respiratory failure; CI, confidence interval; SD, standard deviation.
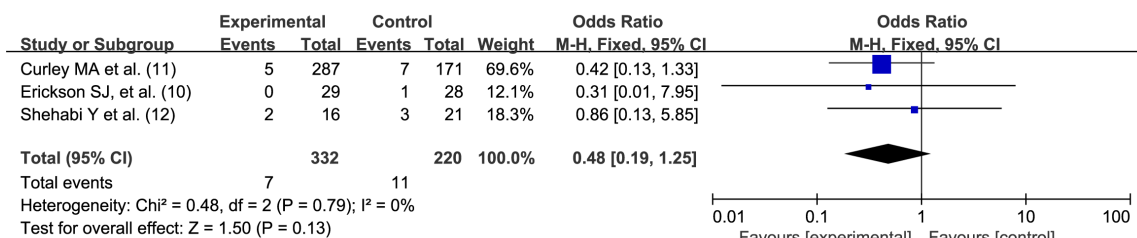
Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Curley MA et al. (11)	5	287	7	171	69.6%	0.42 [0.13, 1.33]
Erickson SJ, et al. (10)	0	29	1	28	12.1%	0.31 [0.01, 7.95]
Shehabi Y et al. (12)	2	16	3	21	18.3%	0.86 [0.13, 5.85]
Total (95% CI)		**332**		**220**	**100.0%**	**0.48 [0.19, 1.25]**
Total events	7		11			

Heterogeneity: Chi² = 0.48, df = 2 (P = 0.79); I² = 0%
Test for overall effect: Z = 1.50 (P = 0.13)

Figure 7 Comparison of the effect of dexmedetomidine and propofol sedative on mortality in children with ARF (10-12). ARF, acute respiratory failure; CI, confidence interval.
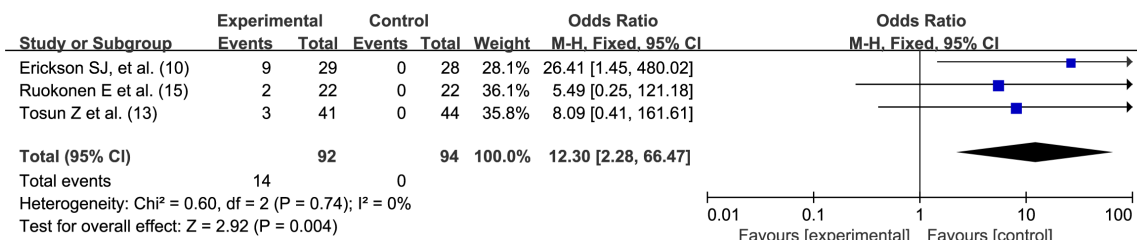
Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Erickson SJ, et al. (10)	9	29	0	28	28.1%	26.41 [1.45, 480.02]
Ruokonen E et al. (15)	2	22	0	22	36.1%	5.49 [0.25, 121.18]
Tosun Z et al. (13)	3	41	0	44	35.8%	8.09 [0.41, 161.61]
Total (95% CI)		**92**		**94**	**100.0%**	**12.30 [2.28, 66.47]**
Total events	14		0			

Heterogeneity: Chi² = 0.60, df = 2 (P = 0.74); I² = 0%
Test for overall effect: Z = 2.92 (P = 0.004)

Figure 8 Comparison of incidence rate of bradycardia after dexmedetomidine and propofol sedation in children with ARF (10,13,15). ARF, acute respiratory failure; CI, confidence interval.
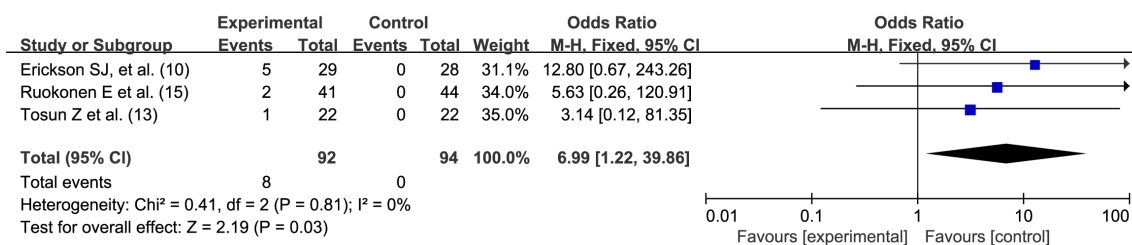
| Study or Subgroup | Experimental | | Control | | Weight | Odds Ratio M-H, Fixed, 95% CI | Odds Ratio M-H, Fixed, 95% CI |
	Events	Total	Events	Total			
Erickson SJ, et al. (10)	5	29	0	28	31.1%	12.80 [0.67, 243.26]	
Ruokonen E et al. (15)	2	41	0	44	34.0%	5.63 [0.26, 120.91]	
Tosun Z et al. (13)	1	22	0	22	35.0%	3.14 [0.12, 81.35]	
Total (95% CI)		92		94	100.0%	6.99 [1.22, 39.86]	
Total events	8		0				
Heterogeneity: Chi² = 0.41, df = 2 (P = 0.81); I² = 0%							
Test for overall effect: Z = 2.19 (P = 0.03)							

Figure 9 Comparison of incidence rate of hypotension after dexmedetomidine and propofol sedation in children with ARF (10,13,15). ARF, acute respiratory failure; CI, confidence interval.
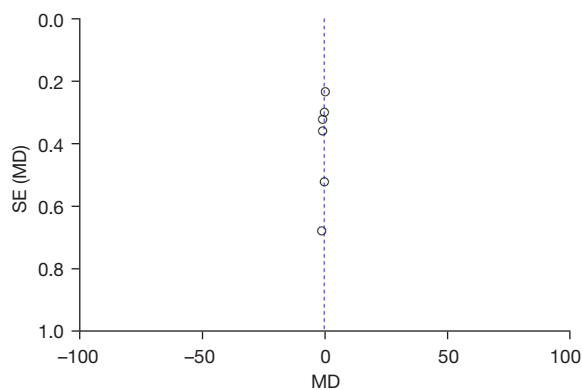
Figure 10 Funnel plot for indicators of ICU length of stay. ICU, intensive care unit; SE, standard error; MD, mean difference.

There was no statistical heterogeneity among the literature for hypotension (I^2=0%; P=0.81). The fixed-effects model was used. Meta-analysis results showed that the incidence rate of hypotension with dexmedetomidine sedation was higher than that with propofol [OR =6.99; 95% CI: (1.22, 39.86); Z=2.19; P=0.03], as shown in *Figure 9*.

Source of heterogeneity and sensitivity analysis
In the analysis of indicators of ICU length of stay, there was statistical heterogeneity among the studies (I^2=61%; P=0.03). The generation of heterogeneity can be related to the age and primary disease of the children. However, most of the included studies did not specify the mean age and primary disease type of the children, so we could not perform a subgroup analysis. However, there was little difference in the results between the random-effects model and the fixed-effects model, showing that the results had good stability (good sensitivity).

Analysis of publication bias
In the analysis of ICU admission time indicators, the

funnel plot (*Figure 10*) was essentially evenly distributed, suggesting that the publication bias was small.

Discussion

Using dexmedetomidine as the sedative could reduce the length of stay in the PICU and reduce the total length of hospital stay for children with ARF compared with propofol, but there was no statistically significant difference in the effects on MV time or mortality. Studies have shown that dexmedetomidine can significantly reduce the occurrence of delirium in elderly patients compared with propofol (17,18), but because no study reported this index in our study, it is impossible to determine the effect of dexmedetomidine on the occurrence of postoperative delirium in children.

Dexmedetomidine, as a highly selective α2-adrenergic receptor agonist, has a much greater affinity for α2 receptors than α1, and in addition to its sedative effect, also exerts analgesic effects by binding to α2 receptors in the spinal cord, thereby reducing the dose of opioids (19). Propofol is a short-acting anesthetic and commonly used in induction and maintenance of anesthesia in adults. When used as a sedative drug for patients undergoing artificial ventilation under intensive monitoring, the infusion rate should be adjusted according to the required depth of sedation. Generally, within 0.3–0.4 mg/kg/h should obtain a satisfactory sedative effect (20). Zhang *et al.* found that dexmedetomidine was superior to propofol in reducing ICU length of stay and reducing the risk of delirium for sedation in ICU patients, but adverse effects occurred when dexmedetomidine was administered at a loading dose or at a high infusion rate (21).

Adverse effects of dexmedetomidine are primarily cardiovascular, and it can cause bradycardia and hypotension by acting on the α2 receptors of the heart (22). In this study, dexmedetomidine was used as a sedative in children with

ARF, and the incidence rates of bradycardia and hypotension were higher than with propofol. Therefore, special attention should be paid to the safety of dexmedetomidine in critically ill pediatric patients, and if bradycardia or hypotension occurs, the infusion of dexmedetomidine should be reduced or discontinued immediately, fluid replacement should be increased, or vasoactive drugs should be administered (23).

Dexmedetomidine is widely used in clinical pediatric medicine, such as cardiac catheterization (24), magnetic resonance imaging (25), airway foreign body removal (26), and the application of dexmedetomidine sedation can reduce pain in children and improve their compliance. Piastra *et al.* stated in a case series that early use of dexmedetomidine in infants/children receiving a ventilator for ARF can be considered safe, with the ability to improve recruitment and support ventilator synchrony in patients (27).

The use of dexmedetomidine for sedation in pediatric patients requires special attention to dosage; Erkonen *et al.* reported a 2-year-old child with traumatic brain injury who developed hypertension several hours after dexmedetomidine infusion at 4 mg/kg/h (28). In the study by Sayed *et al.* (29), the investigators divided MV infants/children into high-dose and low-dose groups according to the dosage of dexmedetomidine. The low-dose group was given a dosage of 0.25 μg/kg for 10 min, followed by a maintenance dose rate of 0.25 μg/kg/h for 50 min, while the high-dose group was given a dosage of 0.5 μg/kg for 10 min, followed by a maintenance dose rate of 0.5 μg/kg/h for 50 min. Their results showed that the high-dose group had better depth of sedation, and shorter ICU and hospital stays, which suggested that a dose rate of 0.5 μg/kg/h was safe.

It has been suggested that dexmedetomidine is a better option from an economic point of view than standard sedatives when providing mild to moderate ICU sedation for more than 24 h (30), and the potential reason for its savings is mainly a reduction in extubation time.

In this study, the heterogeneity among the literature came from multiple aspects such as the age and disease characteristics of the children. The funnel plot suggested that the publication bias was small. Some of the studies included in this meta-analysis did not perform a blind method (10-13), the number of included studies was small, and the sample sizes were on average small.

Conclusions

A total of 1,188 patients in 7 studies were included in this meta-analysis. The results showed that the application of dexmedetomidine as the main sedative in the treatment of children with ARF could significantly reduce the PICU and hospital stays compared with propofol, but bradycardia and hypotension may occur during treatment, which requires close attention and timely intervention. However, due to the small number of included studies, this topic still needs to be deeply explored in a RCT.

Acknowledgments

Footnote

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