



Research article

The comparison of ketamine-dexmedetomidine (ketadex) and ketamine-propofol (ketofol) for procedural sedation in pediatric patients: A meta-analysis of randomized controlled trials



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ABSTRACT

Introduction: The combination of different agents used for procedural sedation allows a greater range of desirable effects while minimizing side effects. The ketamine-dexmedetomidine combination (ketadex) and ketamine-propofol combination (ketofol) are successful examples. The purpose of this meta-analysis was to compare the safety and efficacy of ketadex with ketofol used for procedural sedation in pediatric patients.

Methods: We searched Pubmed, Cochrane Controlled Register of Trials, and Embase from inception to June 2022. Studies were independently evaluated for inclusion criteria and exclusion criteria by two reviewers. Outcome measures for safety comparison were the incidence of hypotension, bradycardia, respiratory depression, nausea, vomiting, and agitation; Outcome measure for efficacy comparison was clinicians' satisfaction. In addition, we compared the recovery time of ketadex and ketofol.

Results: Nine studies were included in this meta-analysis. Compared with ketofol, ketadex sedation in pediatric patients had lower risk of respiratory depression (RR: 0.51, 95% CI: 0.34–0.76, $P = 0.0009$). However, ketadex displayed significant effect on recovery time (MD: 8.38 min, 95% CI: 7.55–9.22 min, $P < 0.00001$). Ketadex had similar incidence of hypotension (RR: 0.95, 95% CI: 0.33–2.67, $P = 0.92$) and bradycardia (RR: 1.80, 95% CI: 0.64–5.06, $P = 0.26$) compared to those with ketofol. Clinicians' satisfaction rate of ketadex and ketofol were both high (RR: 0.93, 95% CI: 0.69–1.25, $P = 0.62$). Also, no significant difference was observed between ketadex and ketofol on the incidence of nausea, vomiting, and agitation.

Conclusions: Both ketadex and ketofol can provide effective sedation and maintain stable hemodynamics. In consideration of good safety profile in respiratory problems, we suggest ketadex is a better option for procedural sedation in pediatric patients.

1. Introduction

Unlike adults, children are more anxious and uncooperative in clinical procedures, especially when it's invasive and painful. Deep sedation and general anesthesia are helpful to keep the child immobile and facilitate the procedures [1]. Compared with general anesthesia, deep sedation is preferred as it allows children to breathe spontaneously via a natural airway with quick recovery [2]. A wide variety of medication treatments, either alone or in combination, have been used for procedural sedation [3]. Considering safety and efficacy, it's a great challenge for clinicians to choose an optimal sedative technique.

Although propofol, dexmedetomidine, and ketamine are commonly used for procedural sedation, each of these agents has some unwanted

side effects. The most important disadvantage of propofol is the possibility of causing hypotension and dose-dependent respiratory depression [4]. Dexmedetomidine has analgesic property but can induce hypotension and bradycardia [5]. Ketamine has advantages in increasing the blood pressure and heart rate via sympathetic activation and preserving respiratory activity [6]. Since ketamine has opposing cardiovascular influences to dexmedetomidine and propofol, the ketamine-dexmedetomidine combination (ketadex) and ketamine-propofol combination (ketofol) may be helpful in maintaining hemodynamically stable and reducing potential side effects of each drug.

Several studies have compared ketadex and ketofol for procedural sedation in children. However, their results reported conflicting findings.

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Some investigators preferred ketadex, whereas others believed ketofol was a better option. Meta-analysis is a statistical technique widely recognized as the best in the aggregation and quantification of therapeutic effects from multiple studies [7]. Up to now, there have been no relevant systematic reviews and meta-analysis. This meta-analysis aimed to compare the safety and efficacy of ketadex and ketofol used for procedural sedation in pediatric patients.

2. Materials and methods

This meta-analysis was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and the guidelines described in the Cochrane Handbook.

2.1. Search strategy

Two authors independently searched Pubmed, Cochrane Controlled Register of Trials, and Embase from inception to June 2022. To avoid the omission of relevant studies, we selected the “All Fields” option rather than “Title/Abstract.” In addition, reference lists and citing articles from included studies were screened. The search strategy was constructed using a combination of the following words: (ketamine OR ketalar) AND (propofol) AND (dexmedetomidine) OR (ketadex) OR (ketofol) AND (child OR infant OR pediatric OR kid OR adolescent).

2.2. Inclusion and exclusion criteria

Studies meeting the following criteria were eligible for inclusion: (1) randomized controlled trials; (2) studies that recruited pediatric patients (aged 0–18 years) requiring sedation to undergo any diagnostic or therapeutic procedure; and (3) studies that evaluated safety and efficacy of intravenous ketadex and ketofol. Studies meeting the following criteria were excluded: (1) studies using routes such as intranasal, intramuscular, or oral to administer ketamine or dexmedetomidine; (2) studies that did not report any of our prespecified outcomes.

2.3. Data extraction

Data extraction was performed independently by two authors using a prespecified data extraction form designed by PFG. Disagreements between reviewers were resolved by discussion with a third reviewer. The following information was extracted from the eligible articles: primary author, type of surgery, patient characteristics (ages and number), type and dosage of sedative agents, clinicians' satisfaction, recovery time, the occurrence of related adverse events (hypotension, bradycardia, respiratory depression, agitation, nausea and vomiting).

2.4. Quality assessment

Two reviewers independently assessed the quality of the included studies according to Cochrane Collaboration's risk of bias tool [8], which includes seven items: (1) random sequence generation (selection bias); (2) allocation concealment (selection bias); (3) blinding of participants and personnel (performance bias); (4) blinding of outcome assessment (detection bias); (5) incomplete outcome data (attrition bias); (6) selective reporting (reporting bias); and (7) other bias. We assigned a judgment of high, low, or unclear risk for each item. Any disagreements were resolved by discussion among all authors.

2.5. Statistical analysis

Data of selected studies were analyzed using Review Manager 5.3 (Cochrane Collaboration, Oxford, UK). The incidence of dichotomous data was performed using the risk ratio (RR) with 95% confidence interval (CI) and analyzed by Mantel-Haenszel method. Continuous

outcomes were described as mean difference (MD) with 95% CI. Heterogeneity was quantified with I-squared (I^2) statistic in all the measured outcomes. The I^2 value of 25%, 50%, and 75% as cut-off points represented low, moderate, and high degrees of heterogeneity [9]. If $I^2 < 50\%$ and $P > 0.1$, a fixed-effects model was used; otherwise, a random-effects model was selected. A funnel plot was not performed because of the limited number of studies ($n < 10$). A P -value less than 0.05 was considered statistically significant.

3. Results

3.1. Study selection

A flow diagram summarized the detailed steps of our study selection was described in Figure 1. Our initial search yielded 838 studies from Pubmed, Cochrane Controlled Register of Trials, Embase, and other sources. 676 studies remained after adjusting for duplicates. After screening the titles and abstracts, 664 studies were determined to be not relevant to this meta-analysis. After screening the full text, 3 studies did not report relevant outcomes. Finally, 9 studies involving 565 children were included in this meta-analysis [2, 10, 11, 12, 13, 14, 15, 16, 17].

3.2. Study characteristics

The characteristics of included studies are presented in Table 1. All of the nine enrolled studies were single-center randomized controlled trials published between 2006 and 2021. The age of the patients ranged from 1 month to 17 years old. The studies involved cardiac catheterization (3 studies), gastrointestinal endoscopy (2 studies), burn wound management (1 study), tooth extraction (1 study), bone marrow biopsy or lumbar puncture (1 study), and emergency department procedures (1 study). These included studies compared the efficacy or safety of ketadex versus ketadex for procedural sedation. Furthermore, 4 studies used a continuous infusion of ketamine, dexmedetomidine, or propofol to maintain sedation, 5 studies used a bolus of these drugs to achieve satisfying sedative level.

3.3. Quality assessment

Risk of bias summary is outlined in Figure 2. All of the nine studies were randomized trials and six studies adequately reported allocation concealment. Furthermore, the participants were blinded to the intervention because most of them were preschoolers or school-aged children. Three studies blinded the observers, three studies described the observers were not blind to the intervention. Moreover, two studies' protocols were available and their prespecified outcomes had been reported. Thus we considered they had low risk of bias with selective reporting.

3.4. Respiratory adverse events

In the included studies, respiratory depression was defined as oxygen saturation (SpO_2) less than 95%, 94%, 92%, 90%, or decreased more than 5 points compared with baseline. As shown in Figure 3, based on the combined data of eight RCTs (508 children), the incidence of respiratory depression was 9.4% in the ketadex group and 19.3% in the ketofol group. Thus, ketadex was associated with a significantly lower incidence of hypoxia than ketofol (RR: 0.51, 95% CI: 0.34–0.76, $P = 0.0009$). There was no heterogeneity among the results ($I^2 = 0\%$).

3.5. Cardiovascular adverse events

Hypotension events were reported in four studies (225 children). After pooling these studies, no difference was found in the risk of hypotension between the two groups (RR: 0.95, 95% CI: 0.33–2.67, $P = 0.92$) (see Figure 4 A). Statistical heterogeneity was found to be moderate ($I^2 = 52\%$).

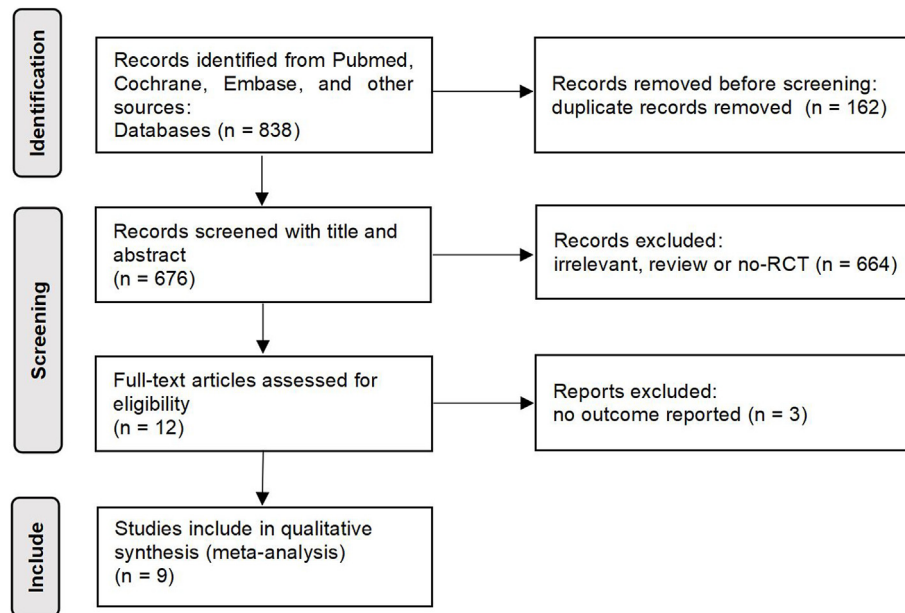


Figure 1. Flowchart of study selection process.

Table 1. Characteristics of included studies.

Author (Year)	Age	Procedure	ketadex/ ketofol	Dose of ketadex	Dose of ketofol	Outcomes
Ali (2015) [10]	1-12 y	Cardiac catheterization	29/30	Beginning: 1 mg/kg K+1 µg/kg D Maintenance: 1 mg/kg K when required	Beginning: 1 mg/kg K+50 µg/kg/min P Maintenance: 1 mg/kg K when required	1. Adverse events 2. Recovery time
Amer (2020) [11]	2-7 y	Gastrointestinal endoscopy	60/60	Beginning: 1 mg/kg K+0.5 µg/kg D Maintenance: 0.5 µg/kg D when required	Beginning: 1 mg/kg K+1 mg/kg P Maintenance: 1 mg/kg P when required	1.Adverse events 2.Clinicians' satisfaction
Azizkhani (2021) [12]	3-17 y	Emergency department procedures	31/31	Beginning: 1 mg/kg K+0.7 µg/kg D Maintenance: 0.25 mg/kg K when required	Beginning: 0.5 mg/kg K+0.5 mg/kg P Maintenance: 0.25 mg/kg K when required	1.Adverse events
Canpolat (2012) [13]	8-60 m	Burn wound management	30/30	Beginning: 1 mg/kg K+0.5 µg/kg D Maintenance: 0.5 µg/kg D when required	Beginning: 1 mg/kg K+1 mg/kg P Maintenance: 1 mg/kg P when required	1.Adverse events 2.Clinicians' satisfaction 3. Recovery time
Canpolat (2017) [14]	2-8 y	Tooth extraction	30/30	Beginning: 1 mg/kg K+0.5 µg/kg D Maintenance: 0.25 µg/kg D when required	Beginning: 1 mg/kg K+1 mg/kg P Maintenance: 0.5 mg/kg P when required	1.Adverse events 2.Clinicians' satisfaction 3. Recovery time
Mogahed (2017) [15]	2-12 y	Gastrointestinal endoscopy	30/30	Beginning: 1 mg/kg K+1 µg/kg D Maintenance: K-D mixture when required	Beginning: 1 mg/kg K+1 mg/kg P Maintenance: K-P mixture when required	1.Adverse events 2.Clinicians' satisfaction
Shaaban (2014) [16]	6-12 y	Bone marrow biopsy or lumbar puncture	20/20	Beginning: 0.5 mg/kg K+0.5 µg/kg D Maintenance: 0.5 µg/kg/h D	Beginning: 0.5 mg/kg K+2 mg/kg P Maintenance: 50 µg/kg/min P	1.Adverse events
Sree (2017) [2]	1 m-12 y	Cardiac catheterization	31/29	Beginning: 1 mg/kg K+1 µg/kg D Maintenance: 0.5 µg/kg/h D	Beginning: 1 mg/kg K+1 mg/kg P Maintenance: 100 µg/kg/min P	1.Adverse events 2.Recovery time
Tosun (2006) [17]	4 m-16 y	Cardiac catheterization	22/22	Beginning: 1 mg/kg K+1 µg/kg D Maintenance: 1 mg/kg/h K+0.7 µg/kg/h D	Beginning: 1 mg/kg K+1 mg/kg P Maintenance: 1 mg/kg/h K+100 µg/kg/min P	1.Adverse events 2.Recovery time

K ketamine; D dexmedetomidine; P propofol.

Bradycardia events were reported in three studies (164 children). Pooled analyses suggested that the incidence of bradycardia was comparable between the two groups (RR: 1.80, 95% CI: 0.64–5.06, $P = 0.26$) (see Figure 4 B). There was no heterogeneity among the results ($I^2 = 0\%$).

3.6. Nausea and vomiting

Three studies (240 children) reported nausea and vomiting and the incidence was 13.3% in the ketadex group and 6.7% in the ketofol group.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Ali 2015	+	+	+	?	+	?	?
Amer 2020	+	+	+	⊖	+	+	?
Azizkhani 2021	+	?	+	+	+	+	?
Canpolat 2012	+	?	+	+	+	?	?
Canpolat 2017	+	?	+	?	+	?	?
Mogahed 2017	+	+	+	?	+	?	?
Shaaban 2014	+	+	+	+	+	?	?
Sree 2019	+	+	+	⊖	+	?	?
Tosun 2006	+	+	+	⊖	+	?	?

Figure 2. Risk of bias summary.

After pooling data from these studies, subjects with ketadex had a similar incidence of nausea and vomiting to those with ketofol (RR: 2.00, 95% CI: 0.90–4.45, $P = 0.09$). There was no heterogeneity among the results ($I^2 = 0\%$).

3.7. Agitation

Four studies (206 children) reported agitation and the incidence was 7.8% in the ketadex group and 13.6% in the ketofol group. After pooling data from these four studies, subjects with ketadex had a similar incidence of agitation to those with ketofol (RR: 0.59, 95% CI: 0.26–1.31, $P = 0.19$). Statistical heterogeneity was found to be low across these studies ($I^2 = 35\%$).

3.8. Clinicians' satisfaction

Four studies (300 children) measured the satisfaction of clinicians. Clinicians' satisfaction rate was 74.0% in the ketadex group and 77.3% in the ketofol group. Pooled analyses suggested that the clinicians' satisfaction was statistically similar between the two groups (RR: 0.93, 95% CI: 0.69–1.25, $P = 0.62$). The degree of heterogeneity was found to be high across these studies ($I^2 = 82\%$).

3.9. Recovery time

Five studies (281 children) measured recovery time by using Steward recovery score but with different endpoints, of which three studies used a score of 6, while another two studies used a score of 7. In comparison with ketofol, the use of ketadex significantly prolonged the recovery time (MD: 8.38 min, 95% CI: 7.55–9.22 min, $P < 0.00001$). Statistical heterogeneity was found to be low across these studies ($I^2 = 38\%$).

4. Discussion

Nowadays, there have been diverse agents that we can choose for procedural sedation. The ideal sedative agent consists of rapid onset, short duration, easy to administer, adequate sedation, cardiovascular stability, and no respiratory depression [18]. Unfortunately, there is no such agent. Each agent has advantages but is also associated with some side effects. To get desired effects of different drugs, more and more clinicians prefer a combination of two or more agents. These agents create synergistic sedative effects via different receptors in the central nervous system, including GABA receptor, N-methyl-D-aspartate (NMDA) receptor, and alpha-2 receptor. The use of more agents at smaller doses allows a greater range of desirable effects while minimizing side effects [19].

Ketamine acts as a non-competitive NMDA receptor antagonist in the central nervous system. Due to its rapid onset and short duration without

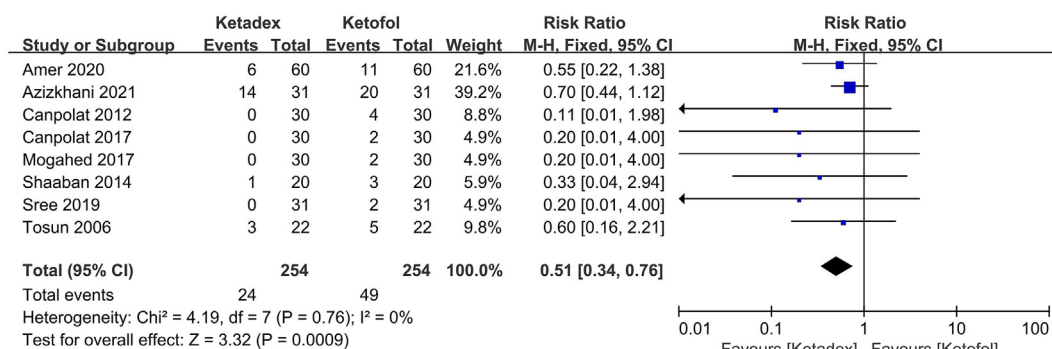


Figure 3. Forest plot of studies comparing ketadex and ketofol in respiratory depression.

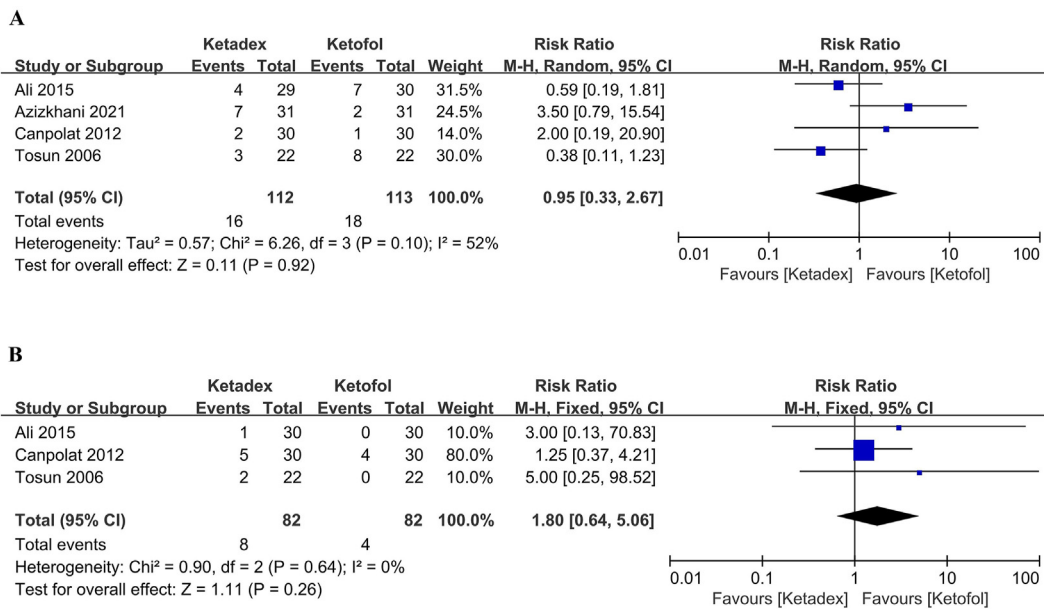


Figure 4. Forest plot of studies comparing ketadex and ketofol in cardiovascular adverse events: A, hypotension; B, bradycardia.

affecting respiratory function, ketamine is frequently used for procedural sedation and analgesia in children [20]. However, ketamine causes high incidence of adverse events, including cardiovascular stimulation, nausea, vomiting, and agitation [21]. To reduce the adverse events of ketamine, researchers explored ketadex and ketofol. Several meta-analysis have been conducted to compare ketadex or ketofol with ketamine alone. Li et al. found that ketadex resulted in better sedation outcomes than ketamine alone [22]. Similarly, Hu et al. confirmed that ketofol sedation had a lower frequency of adverse events than ketamine [23]. Nevertheless, evidence is required to determine whether ketadex or ketofol is the preferred medication for procedural sedation. Hence, we conducted this meta-analysis.

In this meta-analysis, ketadex sedation in pediatric patients had a significantly lower risk of respiratory depression when compared with ketofol. However, ketadex was associated with a longer recovery time. Ketadex had a similar incidence of cardiovascular adverse events compared to those with ketofol. The efficacy profile of ketadex and ketofol appeared to be similar. Also, no significant difference was observed between ketadex and ketofol in the incidence of nausea, vomiting, and agitation.

The analysis about the risk of respiratory depression suggested that ketadex is safer than ketofol. Although ketamine does not promote respiratory depression, airway events occur more frequently with propofol than dexmedetomidine. Similar to our findings, Kim et al. concluded that dexmedetomidine showed fewer desaturation events compared with propofol for children during MRI [24]. The most serious adverse effect of propofol is dose-dependent respiratory depression: decreasing tidal volume, minute ventilation, and increasing PaCO₂. The usual induction dose of propofol of 1–3 mg/kg results in most patients becoming apneic for a few minutes [4]. On the contrary, dexmedetomidine can maintain airway patency and tone, even at higher than recommended doses (3 µg/kg/h) and even in children with obstructive sleep apnoea [25]. These advantages make dexmedetomidine an attractive choice for procedural sedation, particularly for children with difficult airway [26].

Of the trials that evaluated cardiovascular adverse events, there was no difference between the two groups in the incidence of hypotension or bradycardia. It's well known that ketamine has opposing cardiovascular influences to dexmedetomidine and propofol. Their side effects on the cardiovascular system could be reduced by administering a combination of them at smaller doses. There is evidence that no matter

whether ketadex or ketofol can provide more stable hemodynamics than a single agent. A meta-analysis found that, in comparison with either ketamine or dexmedetomidine, ketadex sedation provided more stable heart rate and blood pressure [22]. Another meta-analysis also found that ketofol was associated with less incidence of cardiovascular adverse events compared to propofol alone [27]. Therefore, drug combination therapy should be advocated in clinical practice rather than a single-agent approach.

Reaching the desired level of sedation and good cooperation of children are important factors for clinicians' satisfaction. In the present meta-analysis, clinician satisfaction rates were high in both groups, which may be due to the synergistic sedative effect of different agents. However, it must be noted that heterogeneity was found to be substantial across these studies. The small number of studies and different procedures might have led to the result. Recovery time was significantly longer in the ketadex group in comparison with the ketofol group. This can be explained by the pharmacokinetics of propofol and dexmedetomidine. Propofol has a three times shorter half-life (30–60 min) than dexmedetomidine (2–3 h) [28].

No difference was found between groups in the incidence of nausea and vomiting. The antiemetic action of propofol is well known and has been widely described [29]. Nevertheless, recent clinical studies have demonstrated that dexmedetomidine also has an antiemetic effect [30]. Emergence agitation is a troublesome clinical situation for pediatric anesthesiologists that frequently occurs in preschool-aged children [31]. Although ketamine may lead to agitation, the incidences of emergence agitation in ketadex group and ketofol group were both very low in this meta-analysis. One reason is that the sedative effect of propofol and dexmedetomidine can prevent agitation [32, 33]. Another reason is that combining ketamine with propofol or dexmedetomidine can further reduce the dosage of ketamine.

Some limitations of the present meta-analysis should be noted. First, there were only nine studies included in our meta-analysis. They used different standards to define respiratory depression. Second, sedation score is the most appropriate reference to evaluate the efficacy of sedation, but little data were available in the included studies. Although we use clinicians' satisfaction rate as an alternative, the heterogeneity was found to be substantial. Last, three studies did not blind the observers and the detection bias was considered to be high. The different colors of propofol and dexmedetomidine make blinding more difficult.

5. Conclusions

Compared with ketofol, ketadex produced a lower incidence of respiratory depression but was associated with a longer recovery time. Both ketadex and ketofol can provide effective sedation and maintain stable hemodynamics. In consideration of good safety profile in respiratory problems, we suggest ketadex is a better option for procedural sedation in pediatric patients.

Declarations

Author contribution statement

Peng-fei Gao, Yang Ji: Conceived and designed the experiments; Performed the experiments; Wrote the paper.

Shi-yue Li, Yue Li: Contributed reagents, materials, analysis tools or data; Wrote the paper.

Le Zhao, Qiang Luo: Analyzed and interpreted the data; Wrote the paper.

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Data availability statement

Data will be made available on request.

Declaration of interest's statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

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