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CE - SYSTEMATIC REVIEWS AND META-ANALYSIS

A meta-analysis of randomized controlled trials: combination of ketamine and propofol versus ketamine alone for procedural sedation and analgesia in children

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Abstract
Although ketamine has been used for procedural sedation and analgesia, some researchers have assessed ketamine–propofol as a better alternative because of its reduced adverse events. The goal of this review was to compare adverse events between ketamine–propofol and ketamine for procedural sedation and analgesia in children. We searched the literature from their inception to May 2018 without the restriction of language. We included all randomized controlled trials comparing ketamine–propofol with ketamine for procedural sedation and analgesia in children. The meta-analysis was conducted using the Stata software. A total of six studies involving 693 individuals were included. Pooling of data showed that subjects with ketamine–propofol had similar incidence of respiratory adverse events compared to those with ketamine (RR 1.16, 95% CI 0.68–1.98). However, ketamine–propofol was effective in reducing cardiovascular adverse events compared to ketamine (RR 0.11, 95% CI 0.04–0.31). Ketamine–propofol was also effective in reducing psychomimetic adverse events compared to ketamine (RR 0.39, 95% CI 0.16–0.93). In regard to nausea and vomiting, ketamine–propofol was significantly effective (RR 0.43, 95% CI 0.25–0.74). In addition, we could not demonstrate differences in efficacious sedation between ketamine–propofol and ketamine. Although our study was not able to demonstrate differences in efficacious sedation between ketamine–propofol and ketamine, we confirmed that ketamine–propofol sedation had a lower frequency of adverse events compared to ketamine sedation in children.

Keywords Ketamine · Ketamine–propofol · Analgesia · Meta-analysis

Introduction

Invasive diagnostic and treatment process has become a routine in each clinical department, how to effectively relieve patient's pain in the process of diagnosis and treatment is a thorny problem for each physician. Therefore, the provision of moderate sedation during procedures is an important part of medicine practice.

The preferred medications used for procedural sedation should be both effective and safe. Only in this way could ensure that every patient has a predictable induction and a prompt recovery and no complications.

Common medication treatments for procedural sedation include the use of an opioid analgesic, such as fentanyl, in combination with sedative and amnestic agent, such as propofol. Ketamine as an effective solitary agent is accepted for the treatment of procedural sedation, since it has both sedative and analgesic effects [1–4].

Although propofol and ketamine are commonly used for procedural sedation, each has advantages and disadvantages. Many researchers have found that propofol is associated with some adverse events, such as hypotension, loss of airway reflexes, hypoventilation, and apnea [5, 6]. Ketamine has advantages in maintaining airway reflexes, but causes hypertension and tachycardia, as well as vomiting and emergence delirium [7, 8].

Here, we gathered data from all randomized controlled trials comparing ketamine–propofol with ketamine for procedural sedation and analgesia. In addition, a meta-analysis was conducted to investigate the evidence for or against ketamine–propofol as a better alternative for procedural

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sedation and analgesia. Understanding the effect of ketamine–propofol sedation compared to ketamine sedation would help in determining preferred medications used for procedural sedation.

Materials and methods

Data sources

We searched The Cochrane Library, PubMed, Medline, Embase, China National Knowledge Infrastructure for all randomized controlled trials of ketamine–propofol versus ketamine alone for procedural sedation and analgesia published up to July, 2018. In our literature search, we had no any restriction of language, and the following keywords were included: ketofol, ketamine, ketanest, ketalar, procedural sedation, and analgesia.

Inclusion and exclusion criteria

Studies meeting the following criteria were eligible for inclusion: (1) randomized controlled trials; (2) any nonelective painful procedures in children; and (3) any adverse events could be compared between ketamine–propofol and ketamine for procedural sedation and analgesia. Studies meeting the following criteria were excluded: (1) studies that used different sedative or analgesic agents (e.g., benzodiazepines, opioids) were excluded and (2) overlapping with other studies or overlapping with data from the same authors.

Quality assessment

Two authors independently assessed risk of bias of all included studies according to the Cochrane Collaboration's tool for assessing risk of bias, and discrepancies were resolved by discussion. Risk of bias tables for every study (see Table 1) included the following domains: random sequence generation, allocation concealment, blinding of participants/personnel, blinding of outcomes assessment, incomplete outcome data, and selective outcome reporting.

Data extraction

For each included study, we extracted the main characteristics, such as name of the first author, publication year, study design, number of patients in the analysis, sex of patients, ages of patients, painful procedures, and endpoints. Two researchers were required to independently extract all these data.

Measure of effect and statistical analysis

The main outcomes, such as time endpoints, adverse events were estimated to compare the effect of ketamine–propofol with ketamine in procedural sedation and analgesia. The time endpoint outcomes were continuous data, reported as mean procedure time/recovery time. The adverse outcomes were binary count data, reported as risk ratio (RR). RR was calculated by dividing the "risk of adverse events in ketamine–propofol group" by the "risk of adverse events in ketamine group".

Data were entered into Stata meta-analysis program (Stata 12.0, StataCorp, College Station, Texas), pooled using random-effects models. We estimated the percentage of variability contribution to heterogeneity with the I^2statistic. I^2 values of $\geq 50\%$ indicated substantial heterogeneity. All p values were calculated from two-tailed tests of statistical significance with a type I error rate of 5%. Egger's test was used to assess the publication bias.

Results

Characteristics of studies

After searching the Cochrane Library, PubMed, Medline, Embase, China National Knowledge Infrastructure, a total

Table 1 Quality assessment of all included trials in our study

Study	Random sequence generation	Allocation concealment	Blinding of participants/personnel	Blinding of outcomes assessment	Incomplete outcome data	Selective outcome reporting
Shah 2011 [9]	Low	Low	Low	High	Low	Low
Canpolat 2016 [10]	Low	Unclear	Unclear	High	Low	Low
Kinsara 2017 [11]	Low	Unclear	Unclear	High	Low	Low
Stevic 2017 [12]	Low	Unclear	High	High	Low	Low
Weisz 2017 [4]	Low	Low	Unclear	High	Low	Low
Yalçın 2018 [13]	Low	Low	Low	High	Low	Low
Summary score	Low risk of bias	Unclear risk of bias	Unclear risk of bias	High risk of bias	Low risk of bias	Low risk of bias

of 957 records were identified. However, only 49 studies were preliminarily assessed. Then, reviewing the full texts of those studies, 7 studies were eligible for inclusion and 42 studies were excluded. Among these excluded studies, 5 were duplications, 6 were animal studies, 1 was adult study, 17 were excluded for studies assessing other medications, and 14 were irrelevant studies. Six randomized controlled studies with a total of 693 individuals were finally included into the meta-analysis (see Fig. 1). The main characteristics of those six studies are listed in Table 2.

Differences in endpoints between ketamine and ketamine-propofol

Time endpoints

Although time endpoints (e.g., procedure time, recovery time, and sedation time) were reported in most included studies, we could not pool these outcomes due to the heterogeneity of these outcomes. In the study reported by Canpolat et al. [10], procedure time and recovery time did not differ between ketamine–propofol sedation group and ketamine sedation group. However, Stevic et al. [12] found that reported procedure time and recovery time were statistically different in ketamine–propofol sedation group compared to ketamine sedation group. In addition, Yalçın et al. [13] found that procedure time was not different between ketamine–propofol sedation group and ketamine sedation group, but recovery time significantly longer in ketamine sedation group than ketamine–propofol sedation group (Table 3).

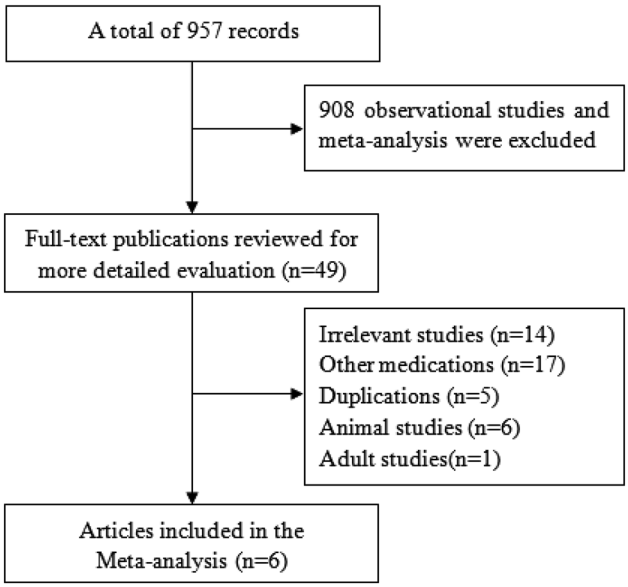

Fig. 1 Flowchart of study selection process

Respiratory adverse events

Data on respiratory adverse events were extracted in five included studies. After pooling data from these five studies, subjects with ketamine had similar incidence of respiratory adverse events than those with ketamine–propofol (RR 1.16, 95% CI 0.68–1.98) (see Fig. 2). I^2 showed no heterogeneity among these studies.

Cardiovascular adverse events

Data on cardiovascular adverse events (e.g., hypotension, tachycardia) were extracted in three included studies. After pooling these three studies, subjects with ketamine had significant higher incidence of cardiovascular adverse events than those with ketamine–propofol (RR 0.11, 95% CI 0.04–0.31) (see Fig. 3). I^2 showed no heterogeneity among these studies.

Psychomimetic adverse events

Data on psychomimetic adverse events (e.g., agitation and hallucination) were reported in five included studies. After pooling these five studies, subjects with ketamine had significant higher incidence of psychomimetic adverse events than those with ketamine–propofol (RR 0.39, 95% CI 0.16–0.93) (see Fig. 4). I^2 showed no heterogeneity among these studies.

Nausea and vomiting

Data on nausea and vomiting were extracted in four included studies. After pooling these four studies, subjects with ketamine had significant higher incidence of nausea and vomiting than those with ketamine–propofol (RR 0.43, 95% CI 0.25–0.74) (see Fig. 5). I^2 showed no heterogeneity among these studies.

Discussion

Procedural sedation and analgesia (PSA) is an appropriate method of managing sedatives or dissociative agents to patients undergoing unpleasant procedures. Since first described in North America, physicians administered PSA using medications from morphine and whiskey to the chloroform. More recently, agents used in anaesthesia and intensive care are increasingly applied in clinical departments prompting expressions of concern for patient safety.

Although many agents are available for physicians to administrate PSA, each has advantages and disadvantages. In addition, different clinical situations may need a different agent. The preferred medications used for PSA should be both effective and safe: has minimal effect on

Table 2 Main characteristics of those seven studies in our meta-analysis

Study	patients	Dose of K–P	Dose of ketamine	Route of treatment	Procedure	Endpoints/Outcomes
Shah (2011)	67 K-P, 69 K	0.5 mg/kg K, 0.5 mg/kg P	0.5 mg/kg	Intravenous	Orthopedic	Adverse events, time endpoints (i.e., procedure time, recovery time, and sedation time)
Canpolat (2016)	20 K-P, 20 K	0.5 mg/kg K, 0.5 mg/kg P	1 mg/kg	Intravenous	Tooth extraction	Adverse events, time endpoints (i.e., procedure time, recovery time, and sedation time)
Kinsara (2017)	29 K-P, 32 K	0.5 mg/kg K, 0.5 mg/kg P	1 mg/kg	Intravenous	Fracture/dislocation	Adverse events, time endpoints (i.e., procedure time, recovery time, and sedation time), efficacy, satisfaction of patients /providers
Stevic (2017)	100 K-P, 103 K	1 mg/kg K-P	1 mg/kg	Intravenous	scar	Adverse events, time endpoints (i.e., procedure time, recovery time, and sedation time)
Weisz (2017)	87 K-P, 96 K	0.5 mg/kg K, 0.5 mg/kg P	1 mg/kg	Intravenous	Fracture/dislocation	Adverse events, time endpoints (i.e., procedure time, recovery time, and sedation time), satisfaction of patients /providers
Yalçın (2018)	25 K–P, 25 K	0.6 mg/kg K–P	1 mg/kg	Intravenous	Dental treatment	adverse events, endpoints (i.e., procedure time, recovery time, and sedation time),satisfaction of patients /providers

Table 3 Procedure time and recovery time as reported by the included trials

Study	No. of patients		Procedure time(min)		Recovery time(min)	
	K–P	K	K–P($X \pm SD$)	K($X \pm SD$)	K–P($X \pm SD$)	K($X \pm SD$)
Canpolat (2016)	20	20	6.60 ± 2.30	6.50 ± 2.30	15.50 ± 7.10	11.20 ± 5.10
Stevic (2017)	100	103	7.74 ± 4.58	4.78 ± 3.09	14.46 ± 3.37	9.69 ± 3.27
Yalçın (2018)	25	25	7.64 ± 2.83	6.24 ± 3.24	11.96 ± 2.32	19.44 ± 5.48

hemodynamics; preserves protective reflexes; provides amnesia, relaxation, and analgesia; has a rapid onset and offset; and is titratable and reversible.

Two pharmacologic approaches might be used to apply in the administration of PSA. One is the single agent approach in which a single agent meets the sedation requirements of a given clinical situation (e.g., methohexital for a shoulder dislocation). The other is a balanced agent approach in which two or more agents are titrated together to achieve the desired clinical effect. Ketamine has been recommended for PSA, but which causes high incidence of adverse events. Some researchers have assessed the coadministration of ketamine and propofol as a better alternative because of its reduced adverse events [14, 15]. Here, we gathered data from all randomized controlled trials comparing ketamine–propofol with ketamine for PSA.

Our results suggested that subjects with ketamine–propofol had similar incidence of respiratory adverse events compared to those with ketamine. However, ketamine–propofol was effective in reducing cardiovascular adverse events compared to ketamine. Ketamine–propofol was also effective in reducing psychomimetic adverse events compared to

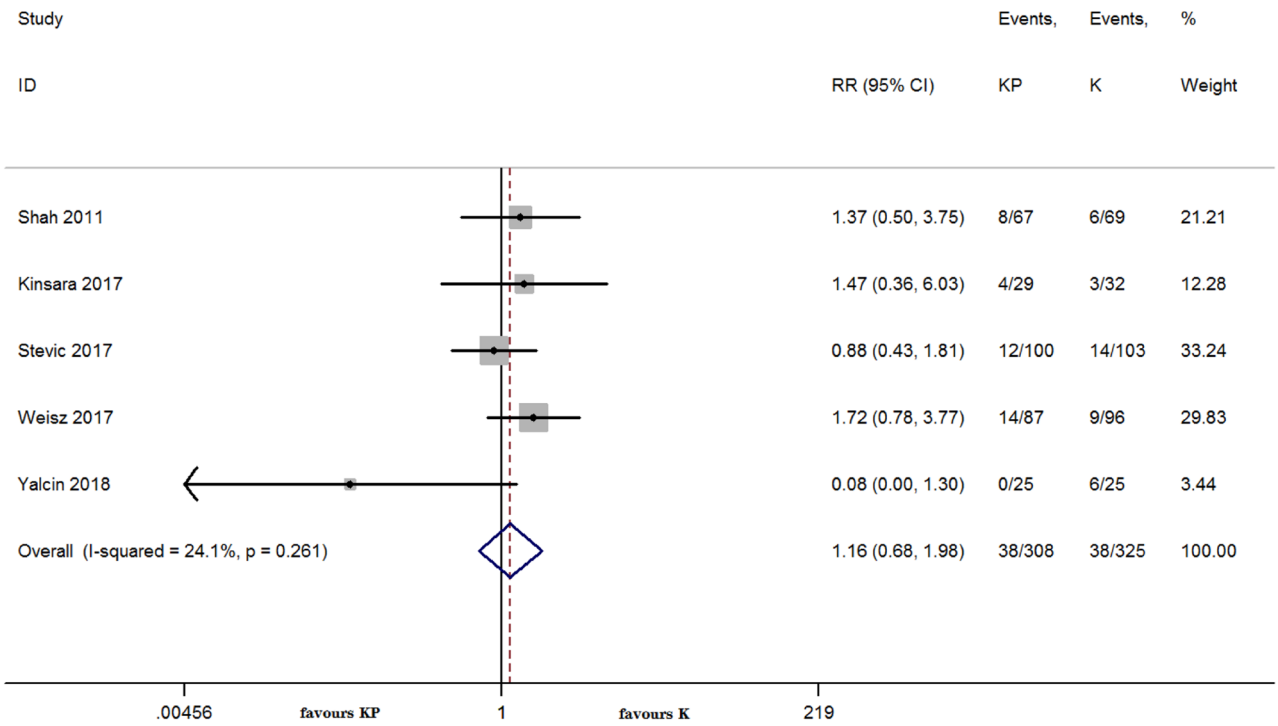

Fig. 2 Forest plot of studies comparing ketamine–propofol with ketamine in respiratory adverse events

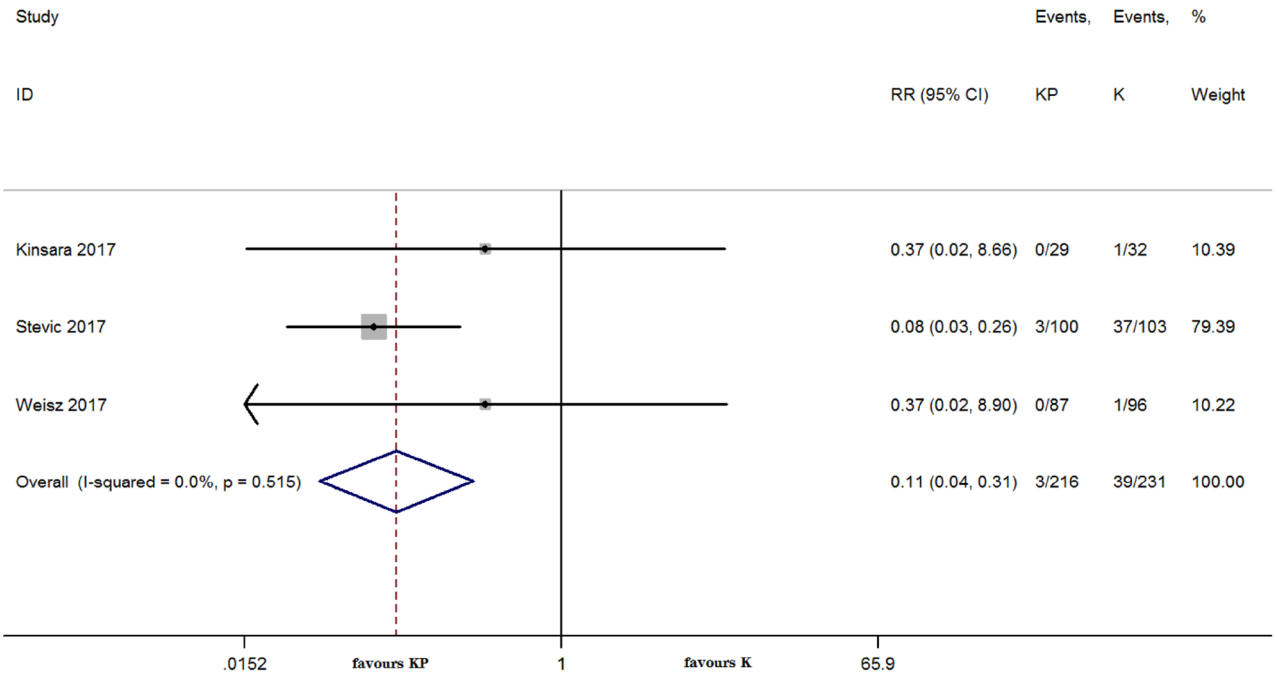

Fig. 3 Forest plot of studies comparing ketamine–propofol with ketamine in cardiovascular adverse events

ketamine. In regard to nausea and vomiting, subjects with ketamine–propofol had significant lower incidence of than those with ketamine, in which revealed ketamine–propofol had lower incidence of adverse respiratory events in patients undergoing PSA compared to ketamine alone.

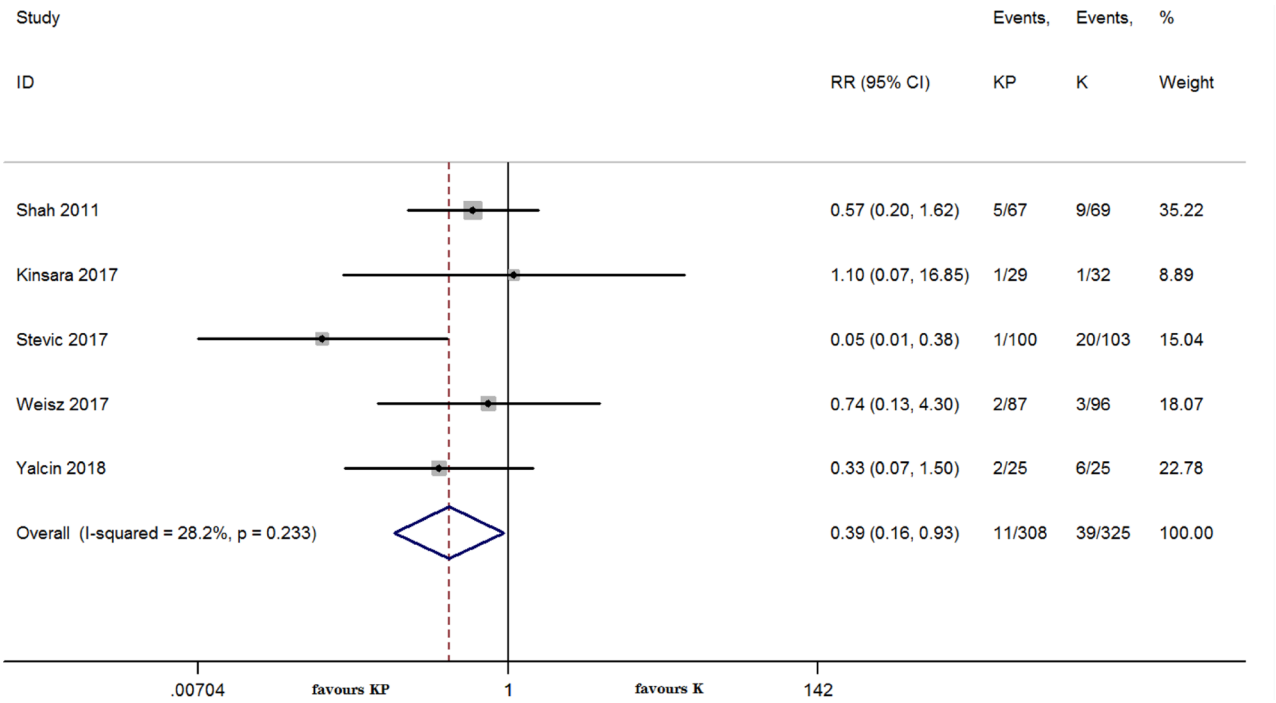

Fig. 4 Forest plot of studies comparing ketamine–propofol with ketamine in psychomimetic adverse events

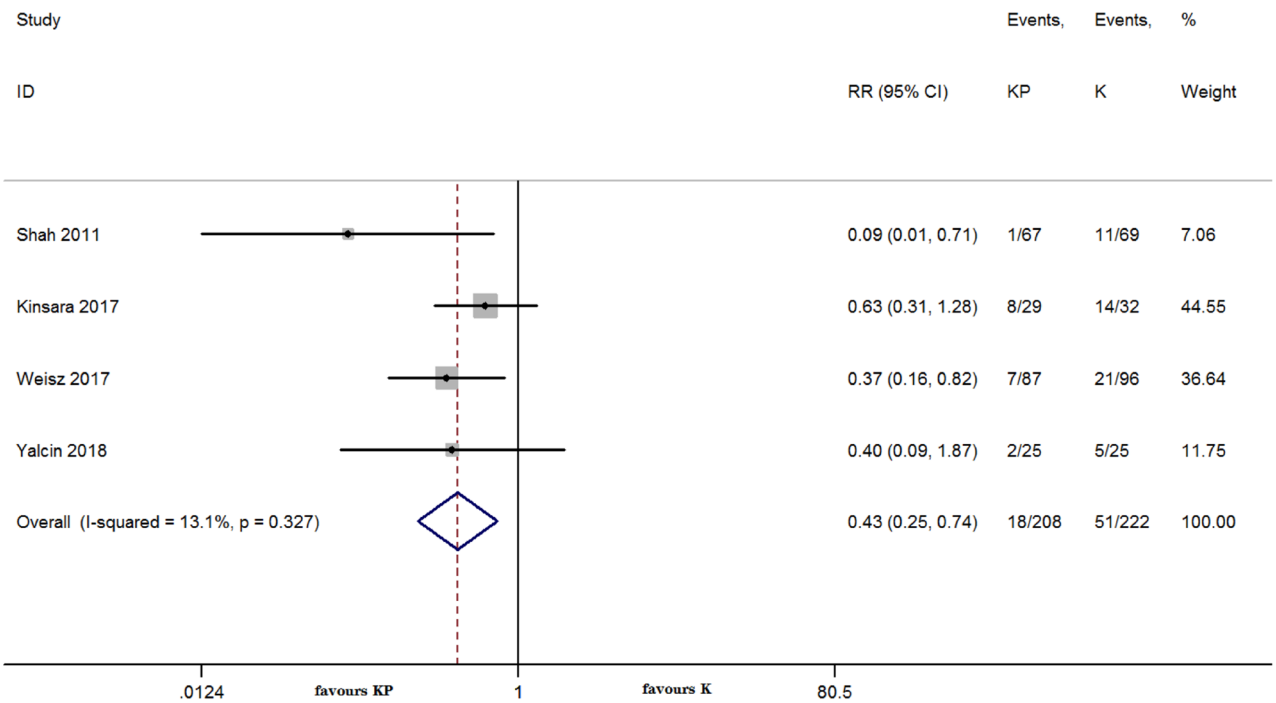

Fig. 5 Forest plot of studies comparing ketamine–propofol with ketamine in nausea and vomiting

Maybe ketamine–propofol is a better alternative for physicians to administrate PSA compared to ketamine alone, but as a sedative agent, it causes adverse events. In addition, some researchers pay attention to nondrug therapy for PSA. They have found that nitrous oxide may be a tool to be used in the treatment of chronic pain. The doses of analgesic drugs can be reduced after the use of nitrous oxide during dental treatment with conscious sedation. The mechanism of nitrous oxide sedation seems to be its role as an antagonist at the *N*-methyl-D-aspartate receptor, involved in pain chronification [16, 17]. Therefore, nondrug therapy for PSA also is a better alternative for physicians to administrate PSA.

Although included literatures in our study are high-quality randomized controlled trials, the results may be limited by the number of included literatures. There were only six studies comparing ketamine–propofol with ketamine for the treatment of PSA. The pooled studies counted altogether only 693 individuals, and presented their results using different standards. Therefore, our results should be viewed cautiously, and this field should be further studied. In addition, data of time endpoints are very heterogeneous, and we could not pool these outcomes to demonstrate differences in efficacious sedation between ketamine–propofol and ketamine.

Conclusion

In summary, the results from this meta-analysis showed ketamine–propofol produced lower frequency of cardiovascular and psychomimetic adverse events compared to ketamine, as well as lower incidence of nausea and vomiting. Therefore, the combination of ketamine and propofol has a very good security for PSA in children.

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Compliance with ethical standards

Conflict of interests None declared.

Statement of human and animal rights All procedures performed in this study are in accordance with ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent For this study, informed consent was not required.

References

1. Chawla N, Boateng A, Deshpande R (2017) Procedural sedation in the ICU and emergency department. Curr Opin Anesthesio 30(4):507–512
2. Johnson OG, Taylor DMD, Lee M et al (2017) Patient satisfaction with procedural sedation in the emergency department. Emerg Med Australas 29(3):303–309
3. Miner JR, Driver BE, Moore JC et al (2017) Randomized clinical trial of propofol versus alfentanil for moderate procedural sedation in the emergency department. Am J Emerg Med 35(10):1451–1456
4. Weisz K, Bajaj L, Deakyne SJ et al (2017) Adverse events during a randomized trial of ketamine versus co-administration of ketamine and propofol for procedural sedation in a pediatric emergency department. J Emerg Med 53(1):1–9
5. Lameijer H, Sikkema YT, Pol A et al (2017) Propofol versus midazolam for procedural sedation in the emergency department: A study on efficacy and safety. Am J Emerg Med 35(5):692–696
6. Costi D, Ellwood J, Wallace A et al (2015) Transition to propofol after sevoflurane anesthesia to prevent emergence agitation: a randomized controlled trial. Pediatr Anaesth 25(5):517–523
7. Kidd LR, Lyons SC, Lloyd G (2016) Paediatric procedural sedation using ketamine in a UK emergency department: a 7 year review of practice. Brit J Anaesth 116(4):518–523
8. Hopper AB, Vilke GM, Castillo EM et al (2015) Ketamine use for acute agitation in the emergency department. J Emerg Med 48(6):712–719
9. Shah A, Mosdossy G, McLeod S et al (2011) A blinded, randomized controlled trial to evaluate ketamine/propofol versus ketamine alone for procedural sedation in children. Ann Emerg Med 57(5):425–433
10. Canpolat DG, Yildirim MD, Aksu R et al (2016) Intravenous ketamine, propofol and propofol-ketamine combination used for pediatric dental sedation: a randomized clinical study. Pak J Med Sci 32(3):682–687
11. Kinsara AF, Almehmadi AAM, Abdulmajid TJ et al (2017) A study to evaluate KM/propofol versus KM alone for procedural sedation in children. Egypt J Hosp Med 69(8):2981–2985
12. Stevic M, Ristic N, Budic I et al (2017) Comparison of ketamine and ketofol for deep sedation and analgesia in children undergoing laser procedure. Laser Med Sci 32(7):1525–1533
13. Yalçın G, Öztaş N, Kip G (2018) Evaluation of clinical effectiveness of three different sedation protocols (intravenous propofol vs. ketamine vs. ketofol) in anxious children. Anaesth Pain Intens Care 22(1): 16–25.
14. Sherlin K, Wiedmar J, Shoff H et al (2018) Hemodynamic changes during procedural sedation with ketofol in the emergency department. Crit Care Med 46(1):436–438
15. Sanri E, Karacabey S, Akoglu H et al (2017) Comparison of ketamine/propofol (ketofol) and etomidate/fentanyl (etofen) combinations for procedural sedation and analgesia in the emergency department: an observational study. Turk J Emerg Med 17(3):89–94
16. Júnior M, Moreira F, Mattos RV et al (2015) Chronic pain relief after the exposure of nitrous oxide during dental treatment: longitudinal retrospective study. Arq Neuro-psiquiat 73(7):578–581
17. Roth JV (2018) Chronic pain and the opioid epidemic: are we ignoring the potential benefits of nitrous oxide? Anesth Analg 126(4):1423–1424