

Ketamine-propofol (Ketofol) on Procedural Sedation and Analgesia in Children: A Systematic Review and Meta-Analysis

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Abstract

ABSTRACT Objectives This review is to evaluate the efficacy and side effects of ketofol in comparison to other anaesthetic agents during procedural sedation and analgesia. **Method** The Cochrane Central Register of Controlled Trials and MEDLINE were searched, including the reference list of related randomized control trials and reviewed articles in order to find unpublished trials or trials not identified by electronic searches. Included criteria specifically comparing recovery time, clinician satisfaction and adverse effect of ketofol. **Results** Eleven trials that met our criteria were included in the analysis with total 1274 patients. Five trials compared with single agent, six trials compared with combined agents. For comparison between ketofol and single agent (ketamine or propofol), ketofol shows significant effect on recovery time (MD -9.88, 95% CI: -14.30 to -5.46; $P=0.0003$; $I^2 = 92\%$) but no difference when compared to combined agents (RR 0.75, 95% CI: -6.24 to 7.74; $P<0.001$; $I^2 = 98\%$). In single agent comparison, ketofol show no differences in clinician satisfaction (RR 2.86, 95% CI: 0.64 to 12.69; $P=0.001$; $I^2 = 90\%$), airway obstruction (RR 0.72, 95% CI: 0.35 to 11.48; $P=0.81$; $I^2 = 0\%$), apnea (RR 0.9, 95% CI: 0.33 to 2.44; $P=0.88$; $I^2 = 0\%$), desaturation (RR 1.11, 95% CI: 0.64 to 1.94; $P=0.28$; $I^2 = 21\%$), nausea (RR 0.52, 95% CI: 0.91 to 1.41; $P=0.2$; $I^2 = 38\%$) and vomiting (RR 0.63, 95% CI: 0.25 to 1.61; $P=0.18$; $I^2 = 42\%$). For comparison between ketofol and combined agents, ketofol is effective in reducing hypotension (RR 4.2, 95% CI: 0.2 to 0.85; $P=0.76$; $I^2 = 0\%$) but no differences in bradycardia (RR 0.70, 95% CI: 0.14 to 03.63; $P=0.09$; $I^2 = 53\%$), desaturation (RR 1.9, 95% CI: 0.15 to 23.6; $P=0.11$; $I^2 = 61\%$) and respiratory depression (RR 1.98, 95% CI: 0.18 to 21.94; $P=0.12$; $I^2 = 59\%$). **Conclusions** There is low certainty evidence that ketofol improve the recovery time and reduce the frequency of hypotension with moderate certainty of evidence. No difference in other adverse effect when compared to either single or combined agents.

Background

Procedural sedation and analgesia (PSA) is a treatment strategy for the administration of agent with sedative, analgesic or dissociative properties to suppress a patient's level of consciousness to a varying degree. It facilitates the completion of painful procedures, ensuring the safety and comfort of the patient without compromising airway patentability.¹ The demand of PSA outside of the operation theater (OT) has grown exponentially for both diagnostic and therapeutic purposes especially in emergency department (ED) and intensive care unit (ICU)² as clinician developed confidence in managing the sedated patient especially in children population.³ Various types of unpleasant procedures required optimal sedation and analgesia in order to increase the procedure success rate, clinician satisfaction and to reduce discomfort and anxiety of patients especially in children population. The American College of Emergency Physicians recommend proactive treatment of anxiety and pain associated with such procedures as a standard of care.¹ In a climate of increased emphasis on maintaining quality and minimizing costs, PSA outside the OT always offers significant advantages in delivering timely and cost-effective care to the patient.⁴

Appropriate agent for PSA should have predictable effects on sedation, analgesia, amnesia and motor control. Moreover, agent with rapid onset, steady maintenance, brief recovery time and tolerable drug-related complications are desirable. Unfortunately, no any single agent has showed superiority to the others despite various anesthetic agents available for use in clinical practice. Thus, combine different sedative, analgesic or dissociative agent have been considered in order to optimize the desired effect and minimize the adverse effect.⁵ However, PSA in pediatric population remain challenging as sedation risk is higher in children.³ The differences between pediatric airway anatomically and physiologically compared to adults are potentially difficult and complicated to manage. Medical problems affecting the airway, breathing, circulation and neurological function play a role in increasing the risk of PSA. The Pediatric Sedation Research Consortium (<http://www.pedsedation.org>) in the United States of America (USA) is a multi-centre registry involving over 30 centres that perform PSA⁶. It reported that there were a total of 1020 adverse events over 30000 PSA events undertook outside OT with no death, one cardiac arrest and required cardiopulmonary resuscitation. Less serious events were more common with desaturation, occurring 157 times per 10 000 sedation. Unexpected apnea, excessive secretions, and vomiting had frequencies of 24.0, 41.6, and 47.2 per 10 000 encounters, respectively.⁷

A large number of ED in USA have adopted this combination as their primary sedation regime.⁸ Both drugs exhibit synergistic reaction to each other and theoretically off set each other's dose dependent adverse effect. Combination of the drugs allow smaller dose of each, thus potentially improving the quality, safety and duration of recovery time.⁹ Recent study had shown that ketofol reduce complications in PSA in adults compare to propofol alone.⁵ But the superiority and safety of ketofol in pediatric population are still debatable. If it is proven to be a safe and effective anaesthetic agent in PSA in children, it should be considered as a primary choice. This study will clarify the efficacy and role of ketofol in comparison to other anaesthetic agents in PSA in paediatric.

Method

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (2015 to Feb 2019) and Medical Literature Analysis and Retrieval System Online (MEDLINE) (1966 to Feb 2019). We used the search strategy in Appendix 1 to search in CENTRAL and MEDLINE. We restricted the publication to English language. We checked the reference list of identified RCTs and review articles in order to find unpublished trials or trials not identified by electronic searches. We searched for ongoing trials through the World Health Organization International Clinical Trials Registry Platform (ICTRP) <http://www.who.int/ictcp/en/> and www.clinicaltrials.gov.

All the randomized control trials (RCTs) or clinical control trials comparing ketofol with other anaesthetic agents were included in the study. We included blinded and open-labelled studies with all patients below 18 years old who undergo procedural sedation. The primary outcomes were recovery time and satisfaction of clinician. Secondary outcome included adverse events (for example nausea, vomiting, airway obstruction, apnea, desaturation, respiratory depression, hypotension and bradycardia) and hemodynamic parameters (heart rate, respiratory rate, blood pressure).

We screened the titles and abstracts from the searches and obtained full-text articles when they appeared to meet the eligibility criteria, or when there is insufficient information to assess the eligibility. We assessed the eligibility of the trials independently and document the reasons for exclusion. We resolved any disagreements between the review authors by discussion. We contacted the authors if clarification is needed. Using data extraction form, from each of the selected trials we extracted data on: study setting, participant characteristics (age, sex, ethnicity), methodology (number of participants randomised and analysed), type and dosage of anaesthetic agent, recovery time, clinicians' and parents' satisfaction, occurrence of related adverse events and hemodynamic parameters.

We assessed the risk of bias based on random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, completeness of outcome data, selectivity of outcome reporting and other bias¹⁰. We resolved any disagreements by discussion. We assessed the quality of evidence for primary and secondary outcomes according to Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology¹¹ for risk of bias, inconsistency, indirectness, imprecision, and publication bias; classified as very low, low, moderate, or high.

We measured the treatment effect for dichotomous outcomes using risk ratios (RRs) and absolute risk reduction, and for continuous outcomes we will use mean differences (MDs); both with 95% confidence intervals (CIs). We checked included trials for unit of analysis errors. Unit of analysis errors can occur when trials randomize participants to intervention or control groups in clusters, but analyse the results using the total number of individual participants. We adjusted results from trials showing unit of analysis errors based on the mean cluster size and intracluster correlation coefficient, if any¹⁰. We planned to contact the original trial authors to request missing or inadequately reported data. We performed analyses on the available data in the event that missing data are not available.

We undertook meta-analyses using Review Manager (RevMan) version 5.3.5 (Nordic Cochrane Centre, Cochrane Collaboration). We assessed the presence of heterogeneity in two steps. First, we assessed obvious heterogeneity at face value by comparing populations, settings, interventions and outcomes. Second, we assessed statistical heterogeneity by means of the I^2 statistic. We used the guide to interpretation of heterogeneity as outlined: 0–40% might not be important; 30–60% may represent moderate heterogeneity; 50–90% may represent substantial heterogeneity; and 75–100% would be considerable heterogeneity¹⁰. If there were sufficient studies, we intended to use funnel plot to assess the possibility of reporting biases or small study biases, or both. We performed a sensitivity analysis to investigate the impact of risk of bias for sequence generation and allocation concealment of included studies.

Result

We retrieved 33 potentially relevant records from the search of the electronic databases. After eliminating duplicate records and those that did not meet eligibility criteria, we reviewed 12 full-text articles. One study was excluded due to non RCT¹². Finally, 11 RCTs met the review eligibility criteria^{13–23} (Fig. 1).

We included 11 trials with total 1274 patients. All trials were single centre study. Four trials included 121 to 351 patients.^{13,15,17,18}, seven trials included 46 to 92 patients^{14,16,19–23}. The age ranged from one month to 16 years old. The trials involved three orthopedic and one surgical procedures^{14,17–19}, five invasive procedures^{13,16,20–22}, one elective imaging study¹⁵ and one dental procedure²³. Table 1 summarizes the characteristic of included trials.

In 11 trials, five trials compared with single agent ^{13,15,17,18,23} and six trials compared with combination of agents. ^{14,16,19-22}. For single agent comparison, three trials compared with propofol ^{13,15,23}, three trials compare with ketamine ^{17,18,23}. For combination agents, two trials compare with ketamine-dexmedetomidine ^{19,20}, two trials compare with propofol-dexmedetomidine ^{21,22}, two trials compare with propofol-fentanyl ^{14,16}. Five trials gave bolus sedation without maintenance infusion ^{13,16-19}, six trials gave bolus sedation with maintenance infusion ^{14,15,20-23}.

Regarding the ratio between ketamine and propofol combination, 6 trials used 1:1 ratio ^{17-20,22,23}, two trials used 1:2 ratio ^{14,21}, one trial used 2:1 ratio ¹⁵, one trial used 1:4 ratio ¹³, and one trial used 1:6 ratio ¹⁶.

The assessment of risk of bias is shown in Fig. 2 and Fig. 3. Figure 2 shows the proportion of studies as low, high or unclear risk of bias for each risk of bias domain. Figure 3 shows the risk of bias summary for individual studies. All trials described the method of randomization used. Five trials randomized the participants by closed envelope method ^{14,16,20,22,23}; four trials randomized the participants by computer generated method ^{13,17,18,21}; one trial used the coin toss method ¹⁹; one trials used 1:1 block randomization with different strata based on age and type of magnetic resonance imaging (MRI) ¹⁵. Blinding of participants and personnel were not described in four trials ^{13,19,22,23}. Six trials analyzed all the samples without any withdrawal ^{16,19-23}. Five trials carried intention to treat analysis in which the participants were analyzed according to the group that they were initially assigned ^{13-15,17,18}. All trials reported the outcomes as specified in their method section. We detected no other potential source of bias

Table 1
Characteristic of included trials

| study | Intervention | Dose of ketofol | Dose of control | n | Age | Procedure | Outcome |
|----------------|-------------------------------------|--|--|-----|---|---|--|
| Canpolat 2012 | Ketofol vs Ketamine-dexmedetomidine | <ul style="list-style-type: none"> • 2 ml ketamine (50 mg/ml) + 8 ml NS • Propofol 1 mg/kg follow by ketamine 1 mg/kg • Additional propofol 1 mg/kg if needed | <ul style="list-style-type: none"> • 2 ml ketamine (50 mg/ml) + 8 ml NS • 0.5 ml dexmedetomidine (50 µg) + 9.5 ml NS • Dexmedetomidine 0.5 µg/kg follow by ketamine 1 mg/kg • Additional dexmedetomidine 0.5 µg/kg if needed | 60 | 8 months to 5 years | Burn injury dressing | <ol style="list-style-type: none"> 1. Surgeon satisfaction 2. Adverse effect 3. Hemodynamic parameter |
| Chiaretti 2011 | Ketofol vs propofol | <ul style="list-style-type: none"> • Ketamine 0.5 mg/kg before propofol injection • Propofol 2 mg/kg over 2 min • 0.5-1 mg/kg additional dose if required | <ul style="list-style-type: none"> • Bolus 2 mg/kg over 2 min • 0.5-1 mg/kg additional dose if needed | 121 | Ketofol: mean (SD): 6.9 (5.4) years Propofol: mean (SD): 7.3 (5.2) years | Lumbar puncture or bone marrow aspiration | <ol style="list-style-type: none"> 1. Adverse effect 2. Hemodynamic parameter |
| Joshi 2017 | Ketofol vs Dexmedetomidine-ketamine | <ul style="list-style-type: none"> • Propofol 1 mg/kg, ketamine 1 mg/kg • Maintenance IV infusion 100 µg/kg/min of propofol and 1 mg/kg/h of ketamine • Additional ketamine 0.5 mg/kg if needed | <ul style="list-style-type: none"> • Dexmedetomidine IV infusion 1 µg/kg over 1 min + ketamine 1 mg/kg IV bolus • Maintenance IV infusion of 0.5 µg/kg/h of dexmedetomidine and 1 mg/kg/h of ketamine • Additional ketamine 0.5 mg/kg if needed | 60 | 1 months to 6 years | Cardiac catheterization procedure | <ol style="list-style-type: none"> 1. Recovery time 2. Hemodynamic parameter |
| Khutia 2012 | Ketofol vs propofol-fentanyl | <ul style="list-style-type: none"> • Ratio 1:2 mixing 1 ml ketamine (50 mg/ml) with 10 ml propofol 1% (10 mg/ml) • Each ml contains 9 mg propofol:4.5 mg ketamine • Bolus: 1 mg/kg propofol: 0.5 mg/kg ketamine • Infusion 0.5 µg/kg/min | <ul style="list-style-type: none"> • 10 ml propofol 1% mixed with 1 ml NS (9 mg/ml) • Fentanyl 1.5 µg/kg diluted to 2 ml of NS • Bolus: propofol 1 mg/kg • Infusion: 50 µg/kg/min | 92 | 3–14 years | Reduction of fracture, I&D abscess, wound debridement | <ol style="list-style-type: none"> 1. Recovery time 2. Adverse effect 3. Hemodynamic parameter |

| study | Intervention | Dose of ketofol | Dose of control | n | Age | Procedure | Outcome |
|--------------|-------------------------------------|---|--|-----|-----------------------------|---|---|
| Shah 2011 | Ketofol vs ketamine | <ul style="list-style-type: none"> • Ketamine 0.5 mg/kg + propofol 0.5 mg/kg • Additional 0.5 mg/kg propofol if needed | <ul style="list-style-type: none"> • Ketamine 1 mg/kg + intralipid placebo • Additional 0.25 mg/kg ketamine if needed | 140 | Median(IQR): 11(7–14) years | Closed manual reduction | <ol style="list-style-type: none"> 1. Recovery time 2. Adverse event 3. Satisfaction 4. Hemodynamic parameter |
| Schmitz 2018 | Ketofol vs propofol | <ul style="list-style-type: none"> • 1 mg/kg ketamine 5% + propofol 1% 0.5 mg/kg + 0.03 ml/kg NS • propofol infusion 5 mg/kg/h | <ul style="list-style-type: none"> • Propofol 1% bolus 1 mg/kg • Propofol infusion 10 mg/kg/h | 351 | 3 months to 10 years | Elective MRI | <ol style="list-style-type: none"> 1. Recovery time 2. Satisfaction 3. Adverse event 4. Hemodynamic parameter |
| Tewari 2018 | Ketofol vs Dexmedetomidine-propofol | <ul style="list-style-type: none"> • Bolus ketamine 1 mg/kg + propofol 2 mg/kg over 10 min • Infusion ketamine 0.5 mg/kg/h and propofol infusion 4–6 mg/kg/h | <ul style="list-style-type: none"> • Bolus dexmedetomidine 1 µg/kg and propofol 2 mg/kg over 10 min • Infusion dexmedetomidine 0.25–0.75 µg/kg/h and propofol 4–6 mg/kg/h | 56 | 7–16 years | Congenital acyanotic heart disease considered amenable for device closure | <ol style="list-style-type: none"> 1. Recovery time 2. Adverse effect |
| Tosun 2007 | Ketofol vs propofol-fentanyl | <ul style="list-style-type: none"> • Ketamine 0.2 mg/kg + propofol 1.2 mg/kg • Additional propofol 0.5–1 mg/kg if needed | <ul style="list-style-type: none"> • Fentanyl 0.2 µg/kg + propofol 1.2 mg/kg • Additional propofol 0.5–1 mg/kg if needed | 90 | 1–16 years | Upper gastrointestinal endoscope | <ol style="list-style-type: none"> 1. Recovery time 2. Adverse effect 3. Hemodynamic parameter |
| Ulgey 2014 | Ketofol vs demedetomidine-propofol | <ul style="list-style-type: none"> • Ketamine 1 mg/kg + propofol 1 mg/kg • Maintenance ketamine 1 mg/kg/h and propofol 100 µg/kg/min • Additional propofol 0.5 mg/kg if needed | <ul style="list-style-type: none"> • Dexmedetomidine 1 µg/kg for 5 min, propofol 1 mg/kg • Maintenance dexmedetomidine 0.5 µg/kg/h and propofol 100 µg/kg/min • Additional propofol 0.5 mg/kg if needed | 46 | 3–14 years | Atrial septal defect for transcatheter closure | <ol style="list-style-type: none"> 1. Recovery time 2. Adverse effect 3. Hemodynamic parameter |

| study | Intervention | Dose of ketofol | Dose of control | n | Age | Procedure | Outcome |
|-------------|---------------------------------|--|--|-----|---|-----------------------------------|--|
| Weisz 2017 | Ketofol vs ketamine | <ul style="list-style-type: none"> • Ketamine 0.5 mg/kg and propofol 0.5 mg/kg • 3 maximum additional dose 0.25 mg/kg ketamine and 0.25 mg/kg propofol if needed | <ul style="list-style-type: none"> • Ketamine 1 mg/kg • 3 maximum additional dose of 0.5 mg/kg ketamine | 183 | Ketofol: mean(SD): 9.3(5) Ketamine: mean(SD): 8.3(6) | Fracture of dislocation reduction | 1. Recovery time 2. Satisfaction 3. Adverse effect |
| Yalcin 2018 | Ketofol vs ketamine vs propofol | <ul style="list-style-type: none"> • Ratio 1:1, 200 mg propofol (20 ml) + 200 mg ketamine (4 ml) • 0.6 mg/kg bolus followed by 40–60 µg/kg/min | <ul style="list-style-type: none"> • Ketamine 4 ml dilute with NS to 20 ml, 1 mg/kg bolus followed by 50–60 µg/kg/min • Propofol 2 mg/kg bolus followed by 70–90 µg/kg/min | 75 | 6–12 years | Dental treatment | 1. Recovery time 2. Adverse effect 3. Hemodynamic parameters |

A total of 11 trials measured the primary outcome i.e. recovery time^{13–23}. One study defined recovery time as time in minutes required for the patient to be conscious and responding to verbal stimuli, airway recovery with return of gag reflex or cough and motor recovery as purposeful movement of limbs²¹; another study defined recovery time as period needed by the patient to spontaneously return to baseline consciousness¹³; four studies used Steward Recovery Score to define the recovery time but with different cut off point: two studies used score of 6^{20,22} while another two studies used score of 7^{16,19}; one study defined time from discontinuation of infusion of study and achievement of Ramsey Sedation Score of 3 as recovery time¹⁴; another study used Modified Vancouver Sedation Recovery Scale to determine the recovery time²³.

Three trials measured satisfaction of clinician^{17,19,23}. Nine trials measured the secondary outcome i.e. adverse effects^{13–19, 21,23}.

The protocol intended to report hemodynamic parameters as a secondary outcome. There were not analyzed because there were either compared in different unit or non-comparable group.^{13–15, 23}. Four trials were not included in hemodynamic status data because they were demonstrated in graph.^{16,19,20,22}.

Comparison ketofol vs single agent control

Five trials with single agent of control group were analyzed^{13,15,17,18,23}. Five trials measured recovery time, but three trials reported the results in median and interquartile range (IQR)^{15,17,18}. Ketofol shows significant effect on recovery time compared to control (MD -9.88, 95% CI: -14.30 to -5.46; P = 0.0003; I² = 92%; 2 trials, 171 participants; low certainty evidence)^{13,23} (Fig. 4) (Table 2). However, ketofol shows no different on clinician satisfaction compared to control (RR 2.86, 95% CI: 0.64 to 12.69; P = 0.001; I² = 90%; 2 trials, 125 participants; low certainty evidence)^{17,23} (Fig. 5) (Table 2); airway obstruction compared to control (RR 0.72, 95% CI: 0.35 to 11.48; P = 0.81; I² = 0%; 2 trials, 467 participants; high certainty evidence)^{15,17} (Fig. 6) (Table 2); apnea compared to control (RR 0.9, 95% CI: 0.33 to 2.44; P = 0.88; I² = 0%; 2 trials, 514 participants; high certainty evidence)^{15,18} (Fig. 7) (Table 2); desaturation compared to control (RR 1.11, 95% CI: 0.64 to 1.94; P = 0.28; I² = 21%; 4 trials, 771 participants; high certainty evidence)^{13,15,17,18} (Fig. 8) (Table 2); nausea compared to control (RR 0.52, 95% CI: 0.91 to 1.41; P = 0.2; I² = 38%; 3 trials, 642 participants; high certainty evidence) (Fig. 9) (Table 2); vomiting compared to control (RR 0.63, 95% CI: 0.25 to 1.61; P = 0.18; I² = 42%; 3 trials, 642 participants; high certainty evidence) (Fig. 10) (Table 2)

Table 2
Summary of Finding for Comparison Between Ketofol and Single Agent

| Ketofol compared to single agent for procedural sedation and analgesia | | | | | |
|---|---|---|---------------------------------|-------------------------------------|--|
| Patient or population: Procedural sedation and analgesia | | | | | |
| Intervention: Ketofol | | | | | |
| Comparison: single agent | | | | | |
| Outcomes | Anticipated absolute effects* (95% CI) | | Relative effect (95% CI) | Nº of participants (studies) | Certainty of the evidence (GRADE) |
| | Risk with single agent | Risk with Ketofol | | | |
| Recovery time | The mean recovery time was 0 | MD 9.88 lower (14.3 lower to 5.46 lower) | - | 171 (2 RCTs) | ⊕⊕⊕⊕ LOW ^{1 2} |
| Satisfaction Clinician | Study population 457 per 1,000 | 1000 per 1,000 (293 to 1,000) | RR 2.86 (0.64 to 12.69) | 186 (2 RCTs) | ⊕⊕⊕⊕ LOW ^{2 3} |
| Airway Obstruction | Study population 72 per 1,000 | 52 per 1,000 (25 to 107) | RR 0.72 (0.35 to 1.48) | 467 (2 RCTs) | ⊕⊕⊕⊕ HIGH |
| Apnea | Study population 30 per 1,000 | 27 per 1,000 (10 to 74) | RR 0.90 (0.33 to 2.44) | 514 (2 RCTs) | ⊕⊕⊕⊕ HIGH |
| Desaturation | Study population 94 per 1,000 | 104 per 1,000 (60 to 182) | RR 1.11 (0.64 to 1.94) | 771 (4 RCTs) | ⊕⊕⊕⊕ HIGH |
| Nausea | Study population 85 per 1,000 | 44 per 1,000 (16 to 120) | RR 0.52 (0.19 to 1.41) | 642 (3 RCTs) | ⊕⊕⊕⊕ HIGH |
| Vomiting | Study population 104 per 1,000 | 65 per 1,000 (26 to 167) | RR 0.63 (0.25 to 1.61) | 642 (3 RCTs) | ⊕⊕⊕⊕ HIGH |
| *The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). | | | | | |
| CI: Confidence interval; RR: Risk ratio; OR: Odds ratio; | | | | | |
| GRADE Working Group grades of evidence | | | | | |
| High certainty: We are very confident that the true effect lies close to that of the estimate of the effect | | | | | |
| Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different | | | | | |
| Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect | | | | | |
| Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect | | | | | |

Footnote:

¹ Duration of treatment varies following different procedures, thus required different dose of intervention

² Small sample size

³ Subjective outcome with different type of population

Comparison Ketofol vs Combined Agent Control

Six trials with combined agent of control group were analyzed ^{14,16,19-22}. Ketofol shows no effect on recovery time compared to control (RR 0.75, 95% CI: -6.24 to 7.74; $P < 0.001$; $I^2 = 98\%$; 6 trials, 404 participants; moderate certainty evidence) ^{14,16,19-22} (Fig. 11) (Table 3). Different RCTs had different ratio of mixture between ketamine and propofol. Thus, we included three studies which had 1:1 ratio of mixture ^{19,20,22} and two studies which had ratio of mixture 1:2 ^{14,21} in subgroup analysis. With dosage ratio of 1:1, Ketofol shows no effect on recovery time compared to control (RR -7.95, 95% CI: -21.86 to 5.96; $P < 0.001$; $I^2 = 97\%$; 3 trials, 166 participants; low certainty evidence) (Fig. 11) (Table 3). With dosage ratio of 1:2, Ketofol also shows no effect on recovery time compared to control (RR 14.62, 95% CI: -11.09 to 40.33; $P < 0.001$; $I^2 = 98\%$; 2 trials, 148 participants; low certainty evidence) (Fig. 11) (Table 3). For adverse event, ketofol shows no effect on desaturation compared to control (RR 1.9, 95% CI: 0.15 to 23.6; $P = 0.11$; $I^2 = 61\%$; 2 trials, 150 participants; low certainty evidence) ^{16,19} (Fig. 12) (Table 3); respiratory depression compared to control (RR 1.98, 95% CI: 0.18 to 21.94; $P = 0.12$; $I^2 = 59\%$; 2 trials, 116 participants; low certainty evidence) (Fig. 13) (Table 3). However, ketofol shows significant effect on hypotension compared to control (RR 4.2, 95% CI: 0.2 to 0.85; $P = 0.76$; $I^2 = 0\%$; 3 trials, 208 participants; moderate certainty evidence) ^{14,19,21} (Fig. 14) (Table 3) but no difference in bradycardia compared to control (RR 0.70, 95% CI: 0.14 to 03.63; $P = 0.09$; $I^2 = 53\%$; 4 trials, 298 participants; low certainty evidence) ^{14,16,19,21} (Fig. 15) (Table 3)

Table 3
Summary of Finding Table for Comparison between Ketofol and Combined Agents

| Ketofol compared to combined agent for procedural sedation and analgesia | | | | | |
|---|---|--|---------------------------------|-------------------------------------|--|
| Patient or population: Procedural Sedation and Analgesia | | | | | |
| Intervention: Ketofol | | | | | |
| Comparison: Combined agent | | | | | |
| Outcomes | Anticipated absolute effects* (95% CI) | | Relative effect (95% CI) | Nº of participants (studies) | Certainty of the evidence (GRADE) |
| | Risk with combined agent | Risk with Ketofol | | | |
| Recovery time | The mean recovery time was 0 | MD 0.75 higher (6.24 lower to 7.74 higher) | - | 404 (6 RCTs) | ⊕⊕⊕⊕ MODERATE ¹ |
| Recovery time - Dosage ratio 1:1 | The mean recovery time - Dosage ratio 1:1 was 0 | MD 7.95 lower (21.86 lower to 5.96 higher) | - | 166 (3 RCTs) | ⊕⊕⊕⊕ LOW ^{2,3} |
| Recovery time - Dosage ratio 1:2 | The mean recovery time - Dosage ratio 1:2 was 0 | MD 14.62 higher (11.09 lower to 40.33 higher) | - | 148 (2 RCTs) | ⊕⊕⊕⊕ LOW ^{2,3} |
| Desaturation | Study population | | RR 1.90 (0.15 to 23.60) | 150 (2 RCTs) | ⊕⊕⊕⊕ LOW ^{1,3} |
| | 54 per 1,000 | 103 per 1,000 (8 to 1,000) | | | |
| Respiratory depression | Study population | | RR 1.98 (0.18 to 21.94) | 116 (2 RCTs) | ⊕⊕⊕⊕ LOW ^{1,3} |
| | 68 per 1,000 | 134 per 1,000 (12 to 1,000) | | | |
| Hypotension | Study population | | RR 0.42 (0.20 to 0.85) | 208 (3 RCTs) | ⊕⊕⊕⊕ MODERATE ³ |
| | 194 per 1,000 | 82 per 1,000 (39 to 165) | | | |
| Bradycardia | Study population | | RR 0.70 (0.14 to 3.63) | 298 (4 RCTs) | ⊕⊕⊕⊕ LOW ^{1,3} |
| | 109 per 1,000 | 76 per 1,000 (15 to 395) | | | |
| *The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). | | | | | |
| CI: Confidence interval; RR: Risk ratio; OR: Odds ratio; | | | | | |
| GRADE Working Group grades of evidence | | | | | |
| High certainty: We are very confident that the true effect lies close to that of the estimate of the effect | | | | | |
| Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different | | | | | |
| Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect | | | | | |
| Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect | | | | | |

Footnote:

¹ Result show large heterogeneity can be due to the following: 1) different population: some procedure required longer duration of treatment, thus larger dose required. 2) different ratio of mixture and dose of combination

² Results show large heterogeneity can be due to different population and duration of procedure determine the required dose of intervention

³ Small sample size

Discussion

The combination of ketamine with propofol concept is based on the synergistic effect and the benefits they provide with the compensation of side effects. This review was designed to include all RCTs addressing the effectiveness of ketofol in PSA in pediatric population compare to other analgesic agents. Ketofol showed significant effect in recovery time compared to single agent but showed no differences when compare to combined agent. The subgroup analyses (different ratio of dosage) showed no differences. However, the small samples sizes in single agent analysis with three studies were not included in our analysis due to non-usable format that discouraged generation of appropriate and meaningful conclusion.

Ketofol showed no effect on clinician satisfaction and respiratory adverse event (airway obstruction, apnea, desaturation, respiratory depression) in both comparisons to single and combined agent. In cardiovascular adverse event, ketofol reduced the frequency of hypotension but showed no effect on bradycardia. There was no significant difference between ketofol and control group in gastrointestinal adverse event (nausea and vomiting).

The quality of trial evidence was variable. Generally, there was a low or unclear risk of bias for most trials in most domains. For recovery time in single agent comparison, the certainty of evidence was low. We downgraded for inconsistency and imprecision as we noted substantial statistical heterogeneity and small sample size. For recovery time in combined agent comparison, the certainty of evidence was moderate. We downgraded because of apparent inconsistencies. The quality of the evidence for both subgroup analysis for dosage ratio 1:1 and ratio 1:2 were downgraded two levels due to heterogeneity and small sample size. A low quality rating was assigned to the pooled estimates of effect for outcome of clinician satisfaction due to small sample size and large heterogeneity.

For the outcome of adverse event for nausea, vomiting, airway obstruction, apnea and desaturation in single agent comparison, the overall quality of the evidence was judged to be high. However, in combined agent comparison, the quality of the evidence for respiratory depression, desaturation and bradycardia were judged to be low. The evidence for these outcomes were from small sample size and our certainty in the evidences were reduced because of imprecision. We also noted unexplained difference between study data, thus we downgraded for inconsistency. Evidence for hypotension was from few studies and few participants, therefore the evidence was imprecise and this reduced our certainty in the evidence to moderate. (Table 3)

Clinical heterogeneity was anticipated; therefore we explored statistical heterogeneity through subgroup analysis. Specifically, we analysed based on the different ratio of dosage mixture where it was best reflecting the interventions present in analysed data.

Prior to our meta-analysis, there are lack of comprehensive review regarding ketofol in PSA in pediatric population. We found a systematic review and meta-analysis compared ketofol to propofol alone in adult and children, which included six RCTs with total of 932 patients ²⁴. In the review, two RCTs were peer-reviewed abstract selected for presentation at international conferences, one of these RCTs included pediatric patient aged 3 to 18 years old, which was excluded in our study ²⁵ due to absent of full text article. The study only included ED patients undergoing PSA for any non-elective painful procedures; whereas, the current review included both emergency and elective procedures. They concluded that adverse respiratory events were significant compared to propofol where in our study showed no different compared to control group. Their result regarding recovery time was inconclusive as the included RCTs were presented with non-usable data.

Another systematic review and meta-analysis compared ketofol to propofol included all RCTs regardless of patient's age, sex, location, publication year and language ⁵. The review reported outcomes of adverse event but did not describe about recovery time. The outcome of respiratory complication requiring intervention, bradycardia was significant compared to control group, which was contradicted to our finding. Otherwise, other outcome of hypotension, nausea and vomiting showed similar results to the current review.

Limitation

This meta-analysis has several limitations. First, our study demonstrates significant heterogeneity for outcome of recovery time due to multiple factors, including variety of patient population, type and duration of procedures, different dosage of bolus and maintenance with varying method of mixture. Most of the studies did not use standardized and quantifiable endpoints to define recovery time. However, exploration of an effect in subgroup analyses found no difference between them. Second, hemodynamic parameters which play an important role in monitoring patient who undergo PSA were not analyzed due to lack of presentable data with different unit of measurement. Additionally, small samples size range from 46 to 351 participants discourage us to generate appropriate and meaningful analyses. Lastly, we conducted a thorough search and used two review authors to assess study eligibility, extract data and assess risk of bias in the included studies, thereby reducing potential bias in the review process. Although the search strategy used to identify potentially relevant studies was extensive, only English language articles were included in this review. It is possible that some studies have been skipped if they were conducted in other languages.

Conclusion

There is low certainty evidence that ketofol improve the recovery time compared to single agent and reduce the frequency of hypotension with moderate certainty of evidence during PSA in pediatric population. There is no difference in other adverse effect; neither between ketofol and single agent nor between ketofol and combined agent. Larger sample size would increase the certainty of these evidences. It is useful to practitioners in making decision the choice of agent in PSA.

Futures studies addressing this research question would benefit from focusing on some of the limitations we encountered with current evidence. Firstly, in order to increase the certainty in the effect for most outcomes in this review, a larger sample size is required. More research in this field would also enable a more precise exploration of subgroups. In particular, the favourable dosage of bolus and maintenance, ratio and method of mixture for combination of ketamine and propofol has an important influence on their effect such as recovery time, sedation level and hemodynamic adaptation. Secondly, there is currently a paucity of data regarding hemodynamical parameter, which play significant role in monitoring patient. The subtle change of hemodynamical parameter may help to prevent complication during PSA and it plays an important role in the choices for PSA by physician. Finally, future studies should clearly defined recovery time with standardized scoring system as well as for the sedation level.

List Of Abbreviations

CENTRAL Cochrane Central Register of Controlled Trials

CI confidence interval

ED emergency department

GRADE grading of recommendations assessment, development and evaluation

I&D incision and drainage

I² I square

ICTRP international clinical trial registry platform

ICU intensive care unit

IQR interquartile range

IV intravenous

Ketofol ketamine-propofol

Kg kilogram

MD mean differences

MEDLINE Medical Literature Analysis and Retrieval System Online

Mg miligram

Min minute

MRI magnetic resonance imaging

NS Normal saline

OR Odds ratio

OT operation theater

P P-value

PROSPERO International Prospective Register of Systematic Reviews

PSA procedural sedation and analgesia

RCTs randomised control trials

RevMan review manager

RR risk ratio

SD standard deviation

USA United States of America

µg microgram

Declarations

1. Ethics approval and consent to participate –

Not applicable

2. Consent for publication –

Not applicable

3. Availability of data and materials -

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

4. Competing interests –

The authors declare that they have no competing interests

5. Funding –

Not applicable

6. Authors' contributions –

(all authors have read and approved the manuscript)

Designing the reviews: TYF, NMN, MBY

Co-ordinating the reviews: TYF, NMN, MBY

Literature search: TYF, MBY

Quality assessment: TYF, NMN, MBY

Entering data into RevMan: TYF

Data analysis: TYF, NMN, MBY

Data interpretation: TYF, NMN, MBY

Writing the review: TYF, NMN, MBY, MHF, SFAW, MZA

7. Acknowledgements –

Not applicable

Appendix 1

Search Strategy

1. (child):ti,ab,kw OR (pediatric): ti,ab,kw
2. (ketofol):ti,ab,kw OR (ketamine-propofol): ti,ab,kw
3. (procedural sedation and analgesia): ti,ab,kw
4. #1 AND #2 AND #3

References

1. Godwin SA, Burton JH, Gerardo CJ, et al. Clinical Policy: Procedural Sedation and Analgesia in the Emergency Department. *Annals of Emergency Medicine*. 2014;63(2):247-258.e218.
2. Chawla N, Boateng A, Deshpande R. Procedural sedation in the ICU and emergency department. *Current opinion in anaesthesiology*. 2017;30(4):507-512.
3. Krieser D, Kochar A. Paediatric procedural sedation within the emergency department. *Journal of paediatrics and child health*. 2016;52(2):197-203.
4. Ebersson CP, Hsu RY, Borenstein TR. Procedural sedation in the emergency department. *The Journal of the American Academy of Orthopaedic Surgeons*. 2015;23(4):233-242.
5. Jalili M, Bahreini M, Doosti-Irani A, Masoomi R, Arbab M, Mirfazaelian H. Ketamine-propofol combination (ketofol) vs propofol for procedural sedation and analgesia: systematic review and meta-analysis. *The American journal of emergency medicine*. 2016;34(3):558-569.
6. Sedation Sfp. Pediatric Sedation Research Consortium. 2019; <http://www.pedsedation.org>.
7. Cravero JP, Blike GT, Beach M, et al. Incidence and nature of adverse events during pediatric sedation/anesthesia for procedures outside the operating room: report from the Pediatric Sedation Research Consortium. *Pediatrics*. 2006;118(3):1087-1096.
8. Green SM, Andolfatto G, Krauss B. Ketofol for procedural sedation? Pro and con. *Ann Emerg Med*. 2011;57(5):444-448.
9. Roback MG, Carlson DW, Babl FE, Kennedy RM. Update on pharmacological management of procedural sedation for children. *Current opinion in anaesthesiology*. 2016;29 Suppl 1:S21-35.
10. Higgins JPT, Green S. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. *The Cochrane Collaboration*. 2011.
11. Guyatt GH, Oxman AD, Kunz R, Vist GE, Falck-Ytter Y, Schunemann HJ. What is "quality of evidence" and why is it important to clinicians? *BMJ (Clinical research ed)*. 2008;336(7651):995-998.

12. Ahmed SS, Hicks SR, Slaven JE, Nitu ME. Deep Sedation for Pediatric Dental Procedures: Is this a Safe and Effective Option? *The Journal of clinical pediatric dentistry*. 2016;40(2):156-160.
13. Chiaretti A, Ruggiero A, Barbi E, et al. Comparison of propofol versus propofol-ketamine combination in pediatric oncologic procedures performed by non-anesthesiologists. *Pediatric blood & cancer*. 2011;57(7):1163-1167.
14. Khutia SK, Mandal MC, Das S, Basu SR. Intravenous infusion of ketamine-propofol can be an alternative to intravenous infusion of fentanyl-propofol for deep sedation and analgesia in paediatric patients undergoing emergency short surgical procedures. *Indian journal of anaesthesia*. 2012;56(2):145-150.
15. Schmitz A, Weiss M, Kellenberger C, et al. Sedation for magnetic resonance imaging using propofol with or without ketamine at induction in pediatrics-A prospective randomized double-blinded study. *Paediatric anaesthesia*. 2018;(no pagination).
16. Tosun Z, Aksu R, Guler G, et al. Propofol-ketamine vs propofol-fentanyl for sedation during pediatric upper gastrointestinal endoscopy. *Paediatr Anaesth*. 2007;17(10):983-988.
17. Shah A, Mosdosy G, McLeod S, Lehnhardt K, Peddle M, Rieder M. A blinded, randomized controlled trial to evaluate ketamine/propofol versus ketamine alone for procedural sedation in children. *Annals of emergency medicine*. 2011;57(5):425-433.e422.
18. Weisz K, Bajaj L, Deakynne SJ, et al. Adverse Events During a Randomized Trial of Ketamine Versus Co-Administration of Ketamine and Propofol for Procedural Sedation in a Pediatric Emergency Department. *The Journal of emergency medicine*. 2017;53(1):1-9.
19. Canpolat DG, Esmoğlu A, Tosun Z, Akn A, Boyacı A, Coruh A. Ketamine-propofol vs ketamine-dexmedetomidine combinations in pediatric patients undergoing burn dressing changes. *Journal of burn care & research*. 2012;33(6):718-722.
20. Joshi VS, Kollu SS, Sharma RM. Comparison of dexmedetomidine and ketamine versus propofol and ketamine for procedural sedation in children undergoing minor cardiac procedures in cardiac catheterization laboratory. *Annals of cardiac anaesthesia*. 2017;20(4):422-426.
21. Tewari K, Tewari VV, Datta SK. Dexmedetomidine-propofol vs ketamine-propofol anaesthesia in paediatric and young adult patients undergoing device closure procedures in cardiac catheterisation laboratory: an open label randomised trial. *Indian journal of anaesthesia*. 2018;62(7):531-537.
22. Ülgey A, Bayram A, Güneş I, et al. Sedation for paediatric transcatheter atrial septal defect closure: comparison of two sedation protocols. *Cardiology in the young*. 2014;24(5):880-885.
23. Yalcin G, Oztas N, Kip G. Evaluation of clinical effectiveness of three different sedation protocols (intravenous propofol vs. ketamine vs. ketofol) in anxious children. *Anaesthesia, pain and intensive care*. 2018;22(1):16-25.
24. Yan JW, McLeod SL, Iansavitchene A. Ketamine-Propofol Versus Propofol Alone for Procedural Sedation in the Emergency Department: A Systematic Review and Meta-analysis. *Academic emergency medicine : official journal of the Society for Academic Emergency Medicine*. 2015;22(9):1003-1013.
25. Del Pizzo J, Agha BS, Downes K, Mularoni PP. Efficiency in sedation for forearm fracture reduction in children: propofol vs. Ketamine-propofol vs. Ketofol. *Pediatric emergency care*. 2011;27(10):999.

Figures

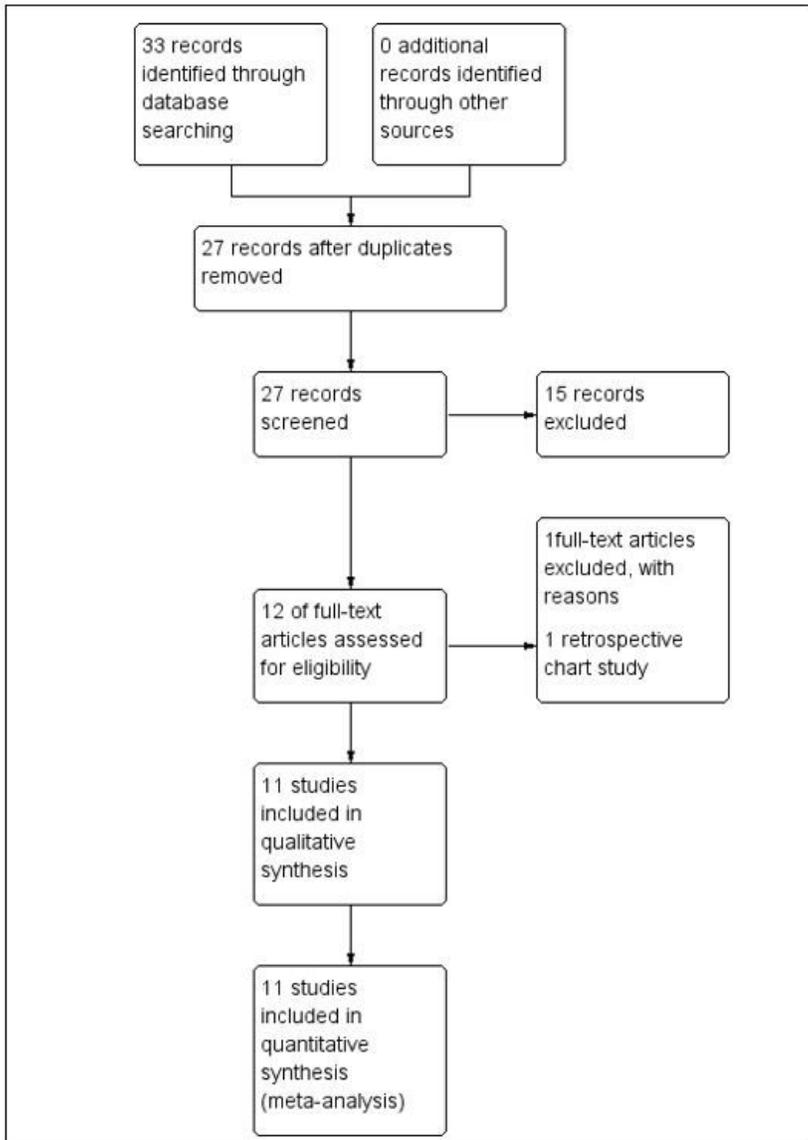


Figure 1

PRISMA flow chart

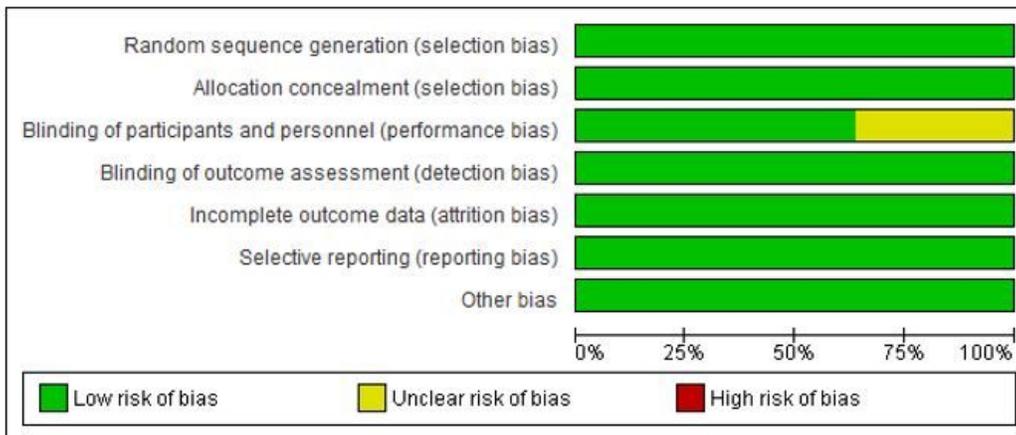


Figure 2

Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies

| | 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 |
|----------------|---|---|---|---|--|--------------------------------------|------------|
| Canpolat 2012 | + | + | ? | + | + | + | + |
| Chiaretti 2011 | + | + | ? | + | + | + | + |
| Joshi 2017 | + | + | + | + | + | + | + |
| Khutia 2012 | + | + | + | + | + | + | + |
| Schmitz 2018 | + | + | + | + | + | + | + |
| Shah 2011 | + | + | + | + | + | + | + |
| Tewari 2018 | + | + | + | + | + | + | + |
| Tosun 2007 | + | + | + | + | + | + | + |
| Ulgey 2014 | + | + | ? | + | + | + | + |
| Weisz 2017 | + | + | + | + | + | + | + |
| Yalcin 2018 | + | + | ? | + | + | + | + |

Figure 3

Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

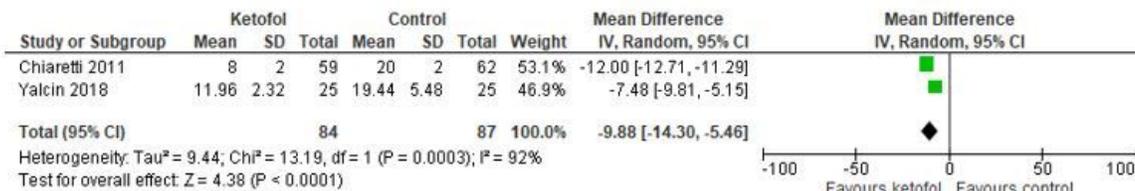


Figure 4

Comparison ketofol vs single agent control for outcome recovery time.

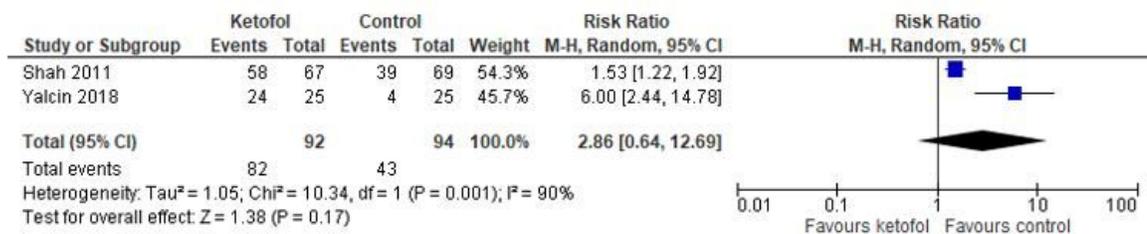


Figure 5

Comparison ketofol vs single agent control for outcome clinician satisfaction.

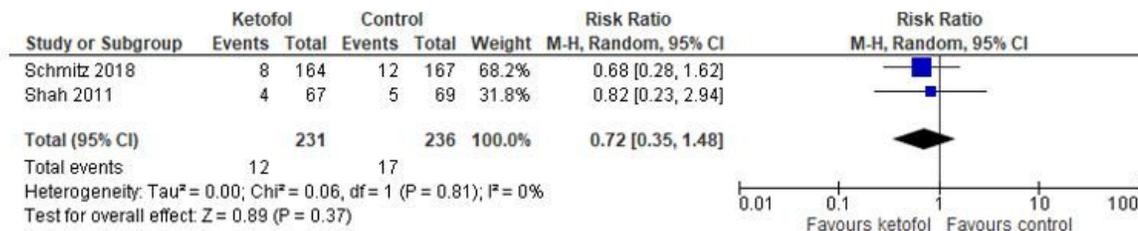


Figure 6

Comparison ketofol vs single agent control for outcome airway obstruction.

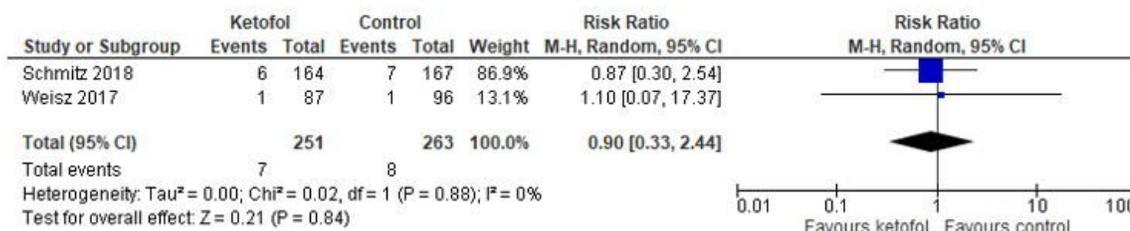


Figure 7

Comparison ketofol vs single agent control for outcome apnea.

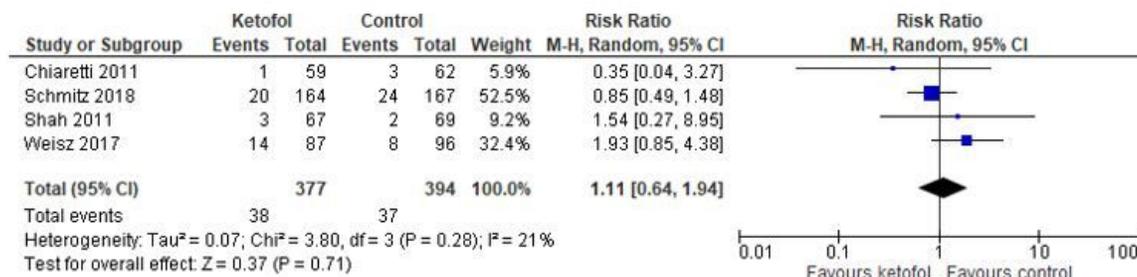


Figure 8

Comparison ketofol vs single agent control for outcome apnea.

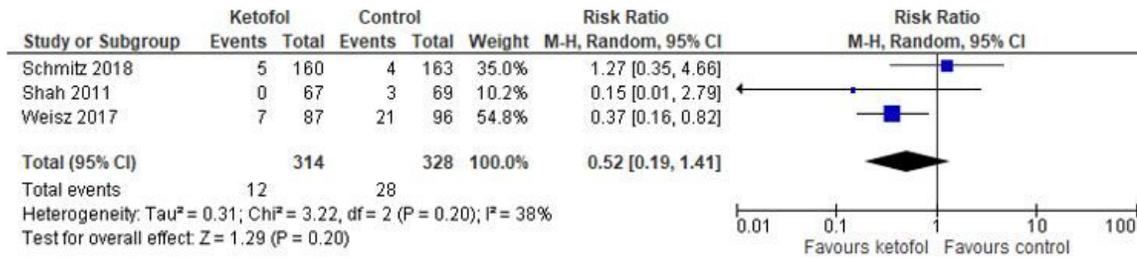


Figure 9

Comparison ketofol vs single agent control for outcome nausea.

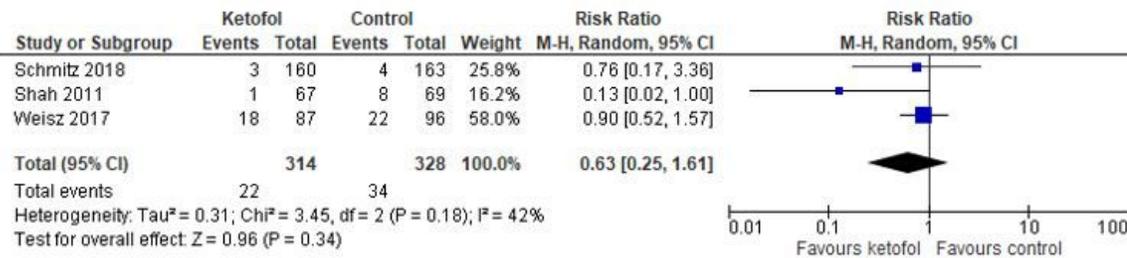


Figure 10

Comparison ketofol vs single agent control for outcome vomiting.

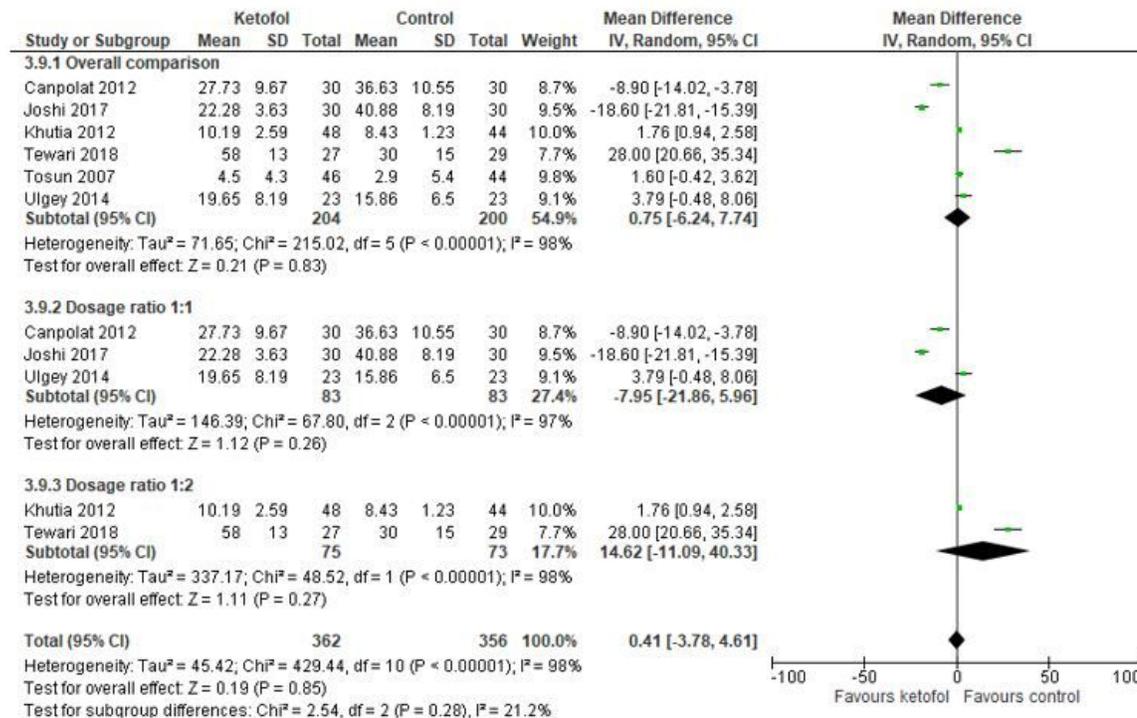


Figure 11

Comparison ketofol vs combined agents control for outcome recovery time

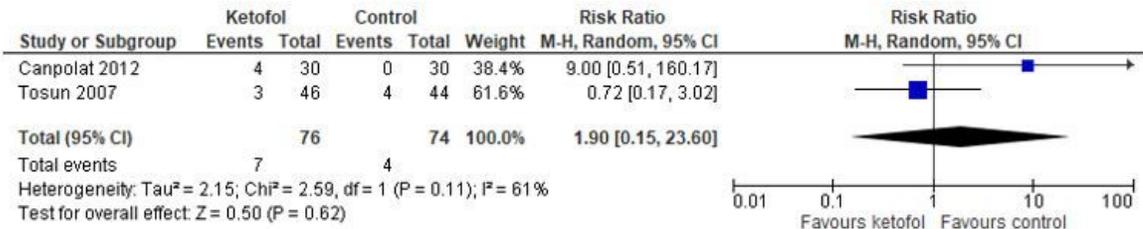


Figure 12

Comparison ketofol vs combined agents control for outcome desaturation

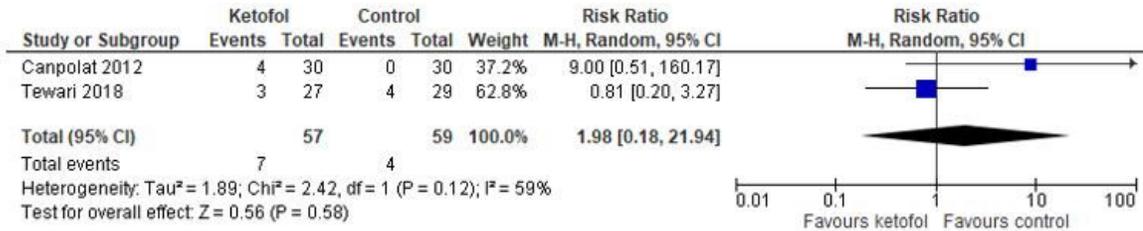


Figure 13

Comparison ketofol vs combined agents control for outcome respiratory depression

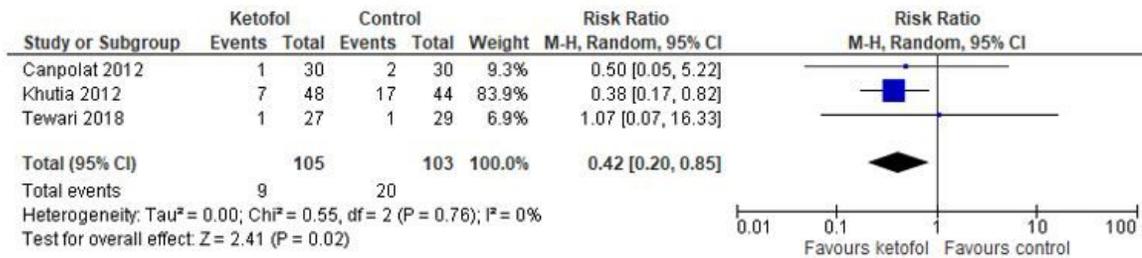


Figure 14

Comparison ketofol vs combined agents control for outcome hypotension

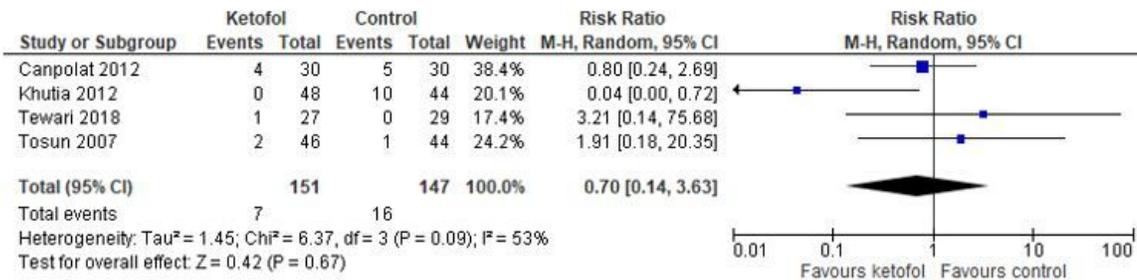


Figure 15

Comparison ketofol vs combined agents control for outcome bradycardia

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

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- [PRISMA2009checklist.doc](#)