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Ketamine-propofol (ketofol) in procedural sedation: a narrative review

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Sedation methods for dental treatment are increasingly explored. Recently, ketofol, which is a combination of ketamine and propofol, has been increasingly used because the advantages and disadvantages of propofol and ketamine complement each other and increase their effectiveness. In this review, we discuss the pharmacology of ketamine and propofol, use of ketofol in various clinical situations, and differences in efficacy between ketofol and other sedatives.

Keywords: Dentistry; Ketamine; Ketofol; Procedural Sedation; Propofol.

INTRODUCTION

In dentistry, sedation is conducted when patients are reluctant to receive dental treatment due to fear and anxiety or when performing invasive dental procedures. Sedation methods include different routes of administration, including oral, intramuscular, inhalation, intranasal, and intravenous routes [1]. Among the various sedation methods, intravenous sedation has advantages of fast action, easy initiation, continuous and repetitive administration, and high quality of sedation; therefore, it is currently widely applied for dental procedures [2].

Propofol is the most commonly used intravenous anesthetic that is currently used in various procedural sedations, including dental sedation. Its use is preferred owing to advantages of rapid onset of action, short duration of action, and easy titration. However, despite these advantages, it carries risks of respiratory depression and hemodynamic instability; therefore, dentists are not skilled in airway management or response to emergency situations [3,4].

Ketamine is an anesthetic preferred owing to its analgesic effect and the maintenance effect on airway reflex [5]. Nevertheless, its clinical use is controversial because of disadvantages of dissociative anesthesia, postoperative hallucinations, sympathomimetic effects, and stimulations of saliva and secretions [6].

Recently, the use of a combination of ketamine and propofol (ketofol) as a sedative has been attracting attention in various clinical fields. Theoretically, the combination of ketamine and propofol can reduce the dose of each drug and compensate for the disadvantages of the other through the antagonistic characteristics of both drugs, resulting in beneficial results for successful sedation. In this review, we summarize the pharmacology

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of ketamine and propofol, the use of ketofol in various clinical dental situations, including pediatric patients, and the comparison of ketofol with other sedatives for sedation.

PHARMACOLOGY OF KETAMINE AND PROPOFOL

1. Ketamine

Ketamine, a phencyclidine derivative, is widely used for sedation, analgesia, and induction of general anesthesia and produces hypnotic, amnestic, and analgesic effects. It induces dissociative anesthesia through electrophysiological dissociation between the cortical and limbic systems. Owing to these characteristics, when used in sedation, the patients are unaware of the environment but open their eyes, appear awake, and may produce involuntary movements [7]. Ketamine is water- and lipid-soluble; therefore, it can be administered via intravenous, intramuscular, oral, rectal, intranasal routes [8]. The onset of action and peak plasma concentration are reached approximately 1, 5, and 30 min after intravenous, intramuscular, and oral administration, respectively. The distribution half-life is 10–15 min, and elimination half-life is 2–3 h. By structure, 12% of ketamine is bound to proteins and rapidly crosses the blood–brain barrier. The duration of sedation is usually 30–45 min, with a half-life of 10–15 min and dose dependence [7,9]. Ketamine acts on several receptors, such as N-methyl-D-aspartate (NMDA), non-NMDA glutamate, nicotinic, muscarinic, cholinergic, monoaminergic, and opioid receptors. It produces analgesic and sympathomimetic effects and preserves airway reflexes by acting on NMDA receptors [8]. Maintaining spontaneous respiration and airway reflexes is an advantage of using ketamine as a sedative. However, ketamine can cause laryngospasm by increasing saliva secretion, tracheobronchial secretion, and vomiting [10,11]. Another adverse effect of ketamine is emergence. This phenomenon shows clinical symptoms, such as vivid dreams, a floating sensation, hallucinations, and delirium [12]. The intravenous dose of ketamine for sedation is 0.25–0.5 mg/kg, and ketamine is used for sedation in combination with other sedatives in general [13]. Ketamine can be infused at a dose of 0.8–5.0 μg/kg/min (0.05–0.3 mg/kg/h) to a maximum of 15 μg/kg/min (0.9 mg/kg/h) after a loading dose of 0.1–0.5 mg/kg [14].

2. Propofol

Propofol (2, 6-diisopropylphenol), a derivative of alkylphenols, is a short-acting intravenous anesthetic used for the sedation, induction, and maintenance of general anesthesia. It activates inhibitory aminobutyric acid receptors and leads to central nervous system depression, resulting in sedation and anesthesia [15]. It is administered intravenously and has a rapid onset of action, with peak effects occurring within 90–100 s after administration. It is rapidly metabolized in the liver and excreted in urine. Its elimination half-life short, ranging from 4 to 7 h, depending on the dose and patient factors. The context-sensitive half-life for infusions of up to 8 h is < 40 min; therefore, recovery is rapid even if it is continuously infused for a long time [16]. It inhibits sympathetic activity and the baroreceptor reflex, leading to hemodynamic compromise, such as hypotension and bradycardia [17]. It also increases NO production, leading to vasodilation [18]. Its administration frequently causes respiratory depression. Therefore, caution should be exercised when increasing its dose because it has a relatively narrow safety margin [4]. It produces no analgesic effects; therefore, opioids and other agents are often required for pain control. This can cause vascular pain during injection, which can be prevented by slow injection and prior administration of lidocaine. A pre-injection of ketamine reduces vascular pain caused by propofol injections [19]. For procedural sedation, an initial dose of propofol of 0.5–1.0 mg/kg is administered slowly via an intravenous injection, and the dose can be titrated up in small increments with 0.5 mg/kg every 3–5 min, until the desired level of sedation is achieved [20]. For infusion, 25–75 μg/kg/min of propofol is administered [21].

CLINICAL USE AND STUDIES OF KETAMINE AND PROPOFOL MIXTURE (KETOFOL) FOR DENTAL TREATMENT

In dental clinics, sedation is required for the dental treatment of children and adults with poor cooperation or dental phobia and to provide patient comfort during invasive dental treatment accompanied by pain. Several drugs can be used for dental sedation, depending on the level of sedation required and the patient's medical history. Several studies have investigated the use of ketofol for dental sedation.

A recent study examined the effects of adding low-dose ketamine to propofol during dental procedures for patients with intellectual disability. Deep sedation is performed using propofol alone (loading dose, 1.2 mg/kg; infusion, 5–8 mg/kg/h) or in combination with ketamine (0.2 or 0.4 mg/kg). Prior addition of low-dose ketamine (0.4 mg/kg) suppresses patient movement and vascular pain with no side effects [22].

Cillo et al. [23] compared the effect of three mixtures of propofol and ketamine with that of propofol and saline solutions during outpatient dentoalveolar surgery. They divided the experimental group in four subgroups: A, propofol and saline solution (propofol 9.7 mg/mL); B, a ketamine/propofol ratio of 1:10 (ketamine, 0.97 mg/mL; propofol, 9.7 mg/mL); C, a ketamine/propofol ratio of 1:5 (ketamine, 1.94 mg/mL; propofol, 9.7 mg/mL); and D, a ketamine/propofol ratio of 1:3 (ketamine, 2.9 mg/mL; propofol, 9.7 mg/mL). For an adequate sedation depth, boluses of 0.3 mg/kg were administered. They showed the benefit of infusion of ketamine 0.55 mg/kg/h and propofol 5.5 mg/kg/h (ketamine/propofol ratio of 1:10) over other doses of both drugs (1:5, 1:3) and propofol alone.

Canpolat et al. [24] reported that a bolus injection of propofol 0.5 mg/kg and ketamine 0.5 mg/kg results in high satisfaction levels of surgeons during tooth extraction in noncooperative pediatric patients compared to a bolus injection of propofol 1 mg/kg alone and ketamine 1 mg/kg alone. However, the recovery time and postoperative nausea and vomiting are significantly lower with propofol alone than with propofol and ketamine.

Yalcin et al. [25] evaluated the clinical effectiveness of propofol (bolus dose of 2 mg/kg, followed by continuous infusion of 4.2–5.4 mg/kg/h) and ketamine (bolus dose of 1 mg/kg, followed by continuous infusion of 3.0–3.6 mg/kg/h of ketofol in pediatric patients with anxiety scheduled for dental sedation. They showed that ketofol was associated with a higher satisfaction rate and lower complication rate. They administered ketofol (1:1, 20 mL of 200 mg propofol and 4 mL of 200 mg ketamine) at a priming dose of 0.6 mg/kg, followed by a continuous infusion dose of 2.4–3.6 mg/kg/h.

CLINICAL USE AND STUDIES OF KETOFOL FOR VARIOUS PROCEDURAL SEDATIONS

1. Procedural sedation

Mortero et al. [26] reported that co-administration of propofol and small-dose ketamine (mixture of propofol 9.8 mg/mL and ketamine 0.98 mg/mL) provided adequate sedation and ventilation during monitored anesthesia care for surgery, including laparoscopic bilateral tubal occlusion, cervical conization, and superficial surgeries, compared to propofol alone (10 mg/mL). In addition, this combination provides immediate-to-early recovery of cognitive function and prolonged pain relief.

In a previous study on ketofol dosing simulations for procedural sedation, ketamine and propofol were mixed in a ratio ranging from 1:1 to 1:10, and the optimal ketofol dosing regimen during procedural sedation was explored. A ratio of 1:3 (ketamine:propofol) was found to be optimal for intermittent bolus dosing. The optimal ketofol (ketamine 3.23 mg/mL, propofol 9.68 mg/mL) dose for children was 0.1 mL/kg initially, and an additional 0.05 mL/kg was administered at 2 min, followed by 0.025 mL/kg for subsequent doses. The adults were injected with 0.05 mL/kg of ketofol initially, followed by an additional dose of 0.025 mL/kg. A short ketofol infusion

at a ratio of 1:4 (ketamine 2.4 mg/mL, propofol 9.8 mg/mL) is a suitable alternative to intermittent boluses. The loading dose was 0.1 mL/kg for children and 0.05 mL/kg for adults. The infusion dose was 0.8 mL/kg/h (ketamine 1.95 mg/kg/h, propofol 7.80 mg/kg/h) for all ages [27].

Endoscopic retrograde cholangiopancreatography (ERCP) is a diagnostic and therapeutic procedure used for biliary tract diseases. During ERCP, certain procedures, including stone removal, visualization of the pancreatobiliary tract, sphincterotomy, laser lithotripsy, severe pain, deep sedation, and analgesia, are required. A previous study compared ketofol (0.5 mg/kg ketamine and 0.5 mg/kg propofol) and midazolam (2.5 mg) with meperidine (0.5 mg/kg) for sedation during ERCP in patients over 85 years of age. Ketofol (1:1) was mixed with 2 mL of ketamine (50 mg/mL), 10 mL of propofol (10 mg/mL), and 8 mL of normal saline, and a solution containing 5 mg of ketamine and 5 mg of propofol per mL was prepared. Ketofol provided adequate sedation, more stable vital signs, fewer complications (bradycardia and apnea), and a shorter recovery time than midazolam with meperidine during ERCP [28].

2. Emergency department

Procedural sedation is required in the emergency department to perform various painful procedures, such as orthopedic reduction, incision and drainage of abscesses, cardioversion, chest tube placement, hernia reduction, and suturing. Various clinical studies have compared the combination of ketamine, propofol, and propofol alone for sedation in emergency departments, and several systematic reviews have been published.

In a previous double-blinded randomized controlled trial (RCT), the use of ketofol alone and propofol alone for sedation in the emergency department resulted in a similar incidence of adverse effects on respiration and high patient satisfaction. The incidence of hypotension was higher in the propofol group than in the ketofol group. Ketofol (1:1) contains ketamine (100 mg in 10 mL), propofol (100 mg in 10 mL or 200 mg in 20 mL). The initial bolus dose was 0.05 mL/kg (0.25 mg/kg of ketamine and propofol or 0.5 mg/kg of propofol), and half of the initial dose was administered to the patient for an adequate sedation depth [29].

Andolfatto et al. [30] compared the effects of ketofol (0.375 mg/kg ketamine and propofol) and propofol alone (0.75 mg/kg) on procedural sedation in the emergency department. During the course of the study, 1 min after the initial dose and every minute thereafter, half of the initial dose of ketofol or propofol was additionally administered when the Ramsay sedation scale score (Table 1) was < 5 points. This study showed that the sedation depth remained consistent with the use of ketofol and that the incidence of agitation during the procedure was lower in the ketofol group. However, the use of ketofol did not decrease the incidence of adverse respiratory events compared to propofol.

David et al. [31] performed an RCT of the combination of ketamine and propofol (0.5 mg/kg of ketamine and 1 mg/kg of propofol) in comparison with propofol alone (1 mg/kg) for emergency procedural sedation. They injected 0.5 or 1.0 μg/kg of fentanyl to all patients, followed by ketamine 0.5 mg/kg or placebo at random. Immediately, propofol (1 mg/kg) was administered, and additional propofol 0.5 mg/kg was repeatedly administered to reach or maintain an appropriate sedation level. This RCT showed that the combination of ketamine and propofol resulted in higher physician and nurse satisfactions, a lower total dose of propofol, and better sedation quality compared to propofol alone. However, the incidence of respiratory depression was similar between groups.

CLINICAL USE AND STUDIES OF KETOFOL FOR INTENSIVE CARE UNIT (ICU) SEDATION

In the ICU, sedation is required to relieve anxiety, promote synchrony with the ventilator during mechanical ventilation, and reduce various stimuli that can cause pain, such as postoperative pain, endotracheal intubation,

invasive monitoring, and frequent venipuncture [32]. The ideal sedative conditions for patients with critical illness should be economical, exert mild hemodynamic effects and respiratory depression, cause no drug interactions, produce fewer active metabolites, and have a metabolic mechanism unrelated to multi-organ function [33].

In a case series, Hamimy et al. [34] evaluated the safety and efficacy of ketofol for short-term sedation for patients with critical illness who had been mechanically ventilated in the ICU. Ketofol (1:1) was mixed with 40 mL of 1% propofol (10 mg/mL), 8 mL of ketamine (50 mg/mL), and 2 mL of 5% dextrose (8 mg/mL propofol and ketamine). The initial bolus of 0.5 mg/kg was administered intravenously, followed by an initial maintenance infusion at 0.6 mg/kg/h and the infusion dose adjusted in 0.3-mg/kg/h increments to achieve a Ramsay sedation scale score of 4, with a maximum infusion time of 24 h. This study concluded that continuous infusion of ketofol may provide adequate and safe short-term sedation (< 24 h) for patients with critical illness in the ICU. No major complications, including respiratory depression, agitation, hypotension, or bradycardia, occurred.

Mahmoud and Rashwan [35] compared the efficacies of dexmedetomidine and ketofol for postoperative sedation in patients on mechanical ventilation with obstructive sleep apnea. The dexmedetomidine group received a dexmedetomidine loading dose of 1 μg/kg over 10 min, followed by infusion of a maintenance dose 0.2–0.7 μg/kg/h. The ketofol group received a ketofol (1:1) loading dose of 0.5 mg/kg, followed by infusion of a maintenance dose of 0.3–0.6 mg/kg/h. Ramsay sedation and behavioral pain scale scores were similar between the two groups. In addition, dexmedetomidine and ketofol provided hemodynamic stability with no pulmonary complications.

Previous studies have compared the effects of propofol and ketofol on ICU sedation during coronary artery bypass grafting surgery. The propofol group received propofol at a dose of 0.9 mg/kg/h, and the ketofol group received propofol at a dose of 0.9 mg/kg/h with an additional dose of ketamine 0.18 mg/kg/h (with ratio of 1:5). The sedation scale scores were significantly lower in the propofol group, and the mean arterial blood pressure was significantly higher in the ketofol group 4 and 5 h after ICU admission. The mean pain intensity did not differ significantly between the two groups. The prevalence of delirium was 6.7% in the ketofol group and 0% in the propofol group; however, this difference was not statistically significant [36].

Table 1. Ramsay sedation scale

Score	Description
1	Awake, agitated or restless or both
2	Awake, cooperative, oriented, and tranquil
3	Awake, but responds to commands only
4	Asleep, brisk response to light glabellar tap or loud auditory stimulus
5	Asleep, sluggish response to light glabellar tap or loud auditory stimulus
6	Asleep, no response to glabellar tap or loud auditory stimulus

CLINICAL USE AND STUDIES OF KETOFOL IN PEDIATRIC PATIENTS

For pediatric patients with poor cooperation due to dental phobia, various sedation methods, such as oral drugs, NO inhalation, and intravenous sedation, are applied for dental treatment with behavioral management. In addition to dental sedation, procedural sedation is used to perform various medical procedures that lead to pain in pediatric patients. However, the incidence of complications related to sedation are higher in children than in adults. The most common complications are vomiting, agitation, apnea, and hypoxia [37].

Clinical trials have compared ketofol with other sedatives. Some trials compared the efficacy of ketofol with that of a single sedative, including propofol and ketamine, during procedural sedation in pediatric patients. The procedures included closed manual reduction, elective magnetic resonance imaging, and dental treatment. In these clinical trials, ketofol showed a significant decrease in recovery time compared to other

Table 2. Characteristics of included trials

Study	Procedure	Bolus or Infusion	Dose of ketofol	Dose of control	Outcome
Hirayama, et al (2019) [22]	Dental treatment in intellectually disabled patients	Infusion	• 1.2 mg/kg propofol bolus followed by 5-8 mg/kg/h infusion and ketamine 0.2 or 0.4 mg/kg	• 1.2 mg/kg propofol bolus followed by 5-8 mg/kg/h infusion	• Movement • Vascular pain • Side effect
Cillo, et al (2012) [23]	Outpatient dentoalveolar surgery	Infusion	• 1:10 mix, ketamine 0.97 mg/mL and propofol 9.7 mg/mL • 2 mg midazolam and infusion of ketamine 0.55 mg/kg/h and propofol 5.5 mg/kg/h • Additional bolus 0.03 mg/kg ketamine and 0.3 mg/kg propofol	• 2 mg midazolam and infusion of 6 mg/kg/h propofol infusion • Additional bolus with 0.3 mg/kg propofol	• Bispectral index • Hemodynamic parameters • Number of boluses • Recovery time
Canpolat, et al (2016) [24]	Tooth extraction in noncooperative pediatric patients	Bolus	• 1:1, 0.5 mg/kg ketamine and propofol	• 1 mg/kg propofol alone • 1 mg/kg ketamine alone	• Surgeon satisfaction • Hemodynamic parameters • Recovery time • Complications
Yalcin, et al (2018) [25]	Dental treatment in pediatric patients	Infusion	• 1:1 mix, 200 mg ketamine (4 mL) + 200 mg propofol (20 mL) • 0.6 mg/kg bolus followed by 2.4–3.6 mg/kg/h infusion	• 4 mL ketamine diluted with normal saline to 20 mL, 1 mg/kg bolus followed by 3–3.6 mg/kg/h • 2 mg/kg propofol bolus followed by 4.2–5.4 mg/kg/h infusion	• Recovery time • Adverse effect • Hemodynamic parameters
Mortero, et al (2001) [26]	Laparoscopic bilateral tubal occlusion, cervical conization, and superficial surgeries	Infusion	• 1:10 mix, ketamine 0.98 mg/mL and propofol 9.8 mg/mL • 1-3 mg midazolam and ketofol solution 1-3 mL bolus followed by ketamine 0.2 ± 0.1 mg/kg/h propofol 2.0 ± 0.8 mg/kg/h infusion	• 10 mg/mL propofol alone • 1-3 mL bolus followed by propofol 2.3 ± 1.4 mg/kg/h infusion	• End-tidal PCO_2 • Mood, state • Recovery of cognition • Pain after discharge
Coulter, et al (2014) [27]	Procedural sedation	Bolus and infusion	• Bolus; 1:3, ketamine 3.23 mg/mL, propofol 9.68 mg/mL, 0.1 mL/kg at initially and additional 0.05 mL/kg for children, 0.05 mL/kg at initially and additional 0.025 mL/kg for adults • Infusion; 1:4, ketamine 2.4 mg/mL, propofol 9.8 mg/mL, loading dose with 0.1 mL/kg for children and 0.05 mL/kg for adults and the infusion of 0.8 mL/kg/h (ketamine 1.95 mg/kg/h, propofol 7.80 mg/kg/h)	none	• Optimal ketofol dosing regimen
Ebru, et al (2019) [28]	Endoscopic retrograde cholangiopancreatography	Bolus	• 1:1 mix, 100 mg ketamine (2 mL) + 100 mg propofol (10 mL) + 8 mL of normal saline • 0.5 mg/kg ketamine and propofol	• 2.5 mg propofol and 0.5 mg/kg meperidine	• Sedation depth • Vital sign • Complication • Recovery time
Ferguson, et al (2016) [29]	Sedation for emergency department	Bolus	• 1:1, ketamine 100 mg (10 mL) + propofol 100 mg (10 mL) • Initial dose of 0.25 mg/kg propofol and ketamine • Additional dose with a half of initial dose	• Initial dose of 0.5 mg/kg propofol alone • Additional dose with a half of initial dose	• Respiratory adverse event • Hypotension • Patient satisfaction
Andolfatto, et al (2012) [30]	Sedation for emergency department	Bolus	• 1:1 mix, initial dose of 0.375 mg/kg ketamine and propofol • Additional dose with a half of initial dose, 1 min after initial dose	• Initial dose of 0.75 mg/kg propofol alone • Additional dose with a half of initial dose, 1 min after initial dose	• Sedation consistency, efficacy • Induction time • Adverse events • Recovery time
David, et al (2011) [31]	Sedation for emergency department	Bolus	• 1:2, 0.5 mg/kg ketamine and 1 mg/kg propofol • Additional dose with 0.5 mg/kg propofol	• Placebo and 1 mg/kg propofol alone • Additional dose with 0.5 mg/kg propofol	• Sedation quality • Satisfaction • Total propofol use • Adverse respiratory event

(continued)

Study	Procedure	Bolus or Infusion	Dose of ketofol	Dose of control	Outcome
Hamimy, et al (2012) [34]	Sedation for critically ill patients who were mechanically ventilated in the ICU	Infusion	• 1:1 mix, 400 mg ketamine (8 mL) + 400 mg propofol (40 mL) + 2 mL of dextrose 5% • 0.5 mg/kg bolus followed by 0.6 mg/kg/h infusion	None	• Median bolus and infusion dose of ketofol • Median infusion period • Complications
Elmoutaz Mahmoud H (2018) [35]	Postoperative sedation of mechanically ventilated patients with obstructive sleep apnea	Infusion	• 1:1 mix, loading dose of 0.5 mg/kg ketamine and propofol • maintenance dose 0.3-0.6 mg/kg/h infusion	• Dexmedetomidine loading dose 1 μg/kg over 10 min and followed by infusion of maintenance dose 0.2-0.7 μg/kg/h.	• Duration of mechanical ventilation • Time for extubation • Ramsay sedation score and behavioral pain scale • Vital sign • Complications
Moshtaghion, et al (2018) [36]	Sedation in ICU with Coronary Artery Bypass Grafting surgery	Infusion	• 1:5, ketamine 0.18 mg/kg/h and propofol 0.9 mg/kg/h infusion	• Propofol 0.9 mg/kg/h infusion	• Sedation scale scores • Mean of arterial blood pressure • Pain intensity • Prevalence of delirium
Schmitz, et al (2018) [38]	Elective MRI in pediatric patients	Infusion	• 1 mg/kg ketamine + 0.5 mg/kg propofol + 0.03 mL/kg normal saline bolus and followed by 5 mg/kg/h propofol infusion	• 1 mg/kg propofol bolus and followed by 10 mg/kg/h propofol infusion	• Recovery time • Satisfaction • Adverse events • Hemodynamic parameters
Weisz, et al (2017) [39]	Fracture of dislocation reduction in pediatric patients	Bolus	• 1:1, 0.5 mg/kg ketamine and propofol • 3 maximum additional doses of 0.25 mg/kg ketamine and propofol, if needed	• 1 mg/kg ketamine • 3 maximum additional doses of 0.5 mg/kg ketamine	• Recovery time • Satisfaction • Adverse effects
Khutia, et al (2012) [40]	Reduction of fracture, Incision and drainage of abscess, wound debridement in pediatric patients	Infusion	• 1:2 mix, 50 mg ketamine (1 mL) and 100 mg propofol (10 mL) • 0.5 mg/kg ketamine and 1 mg/kg propofol bolus and followed by of 3 mg/kg/h infusion	• 100 mg propofol (10 mL) and 1 mL normal saline (9 mg/ mL) • 1.5 μg/kg fentanyl diluted to 2 mL of normal saline • 1 mg/kg propofol, 1.5 μg/kg fentanyl bolus and followed by 3 mg/kg/h infusion	• Recovery time • Adverse effects • Hemodynamic parameters
Joshi, et al (2017) [41]	Cardiac catheterisation procedure in pediatric patients	Infusion	• 1:1, 1 mg/kg ketamine and propofol bolus • Maintenance infusion of ketamine 1 mg/kg/h and propofol 6 mg/kg/h • Additional 0.5 mg/kg ketamine, if needed	• 1 μg/kg dexmedetomidine infusion over 1 min and 1 mg/kg ketamine bolus • Maintenance infusion of dexmedetomidine 0.5 μg/kg/h and ketamine 1 mg/kg/h • Additional 0.5 mg/kg ketamine, if needed	• Recovery time • Hemodynamic parameters
Tewari, et al (2018) [42]	Congenital acyanotic heart disease considered amenable for device closure	Infusion	• 1:2, 1 mg/kg ketamine and 2 mg/kg propofol bolus and followed by ketamine 0.5 mg/kg/h and propofol 4–6 mg/kg/h infusion	• 1 μg/kg dexmedetomidine and 2 mg/kg propofol bolus and followed by dexmedetomidine 0.25–0.75 μg/ kg/h and propofol 4–6 mg/kg/h infusion	• Recovery time • Adverse effects

ICU, intensive care unit; MRI, magnetic resonance imaging; pCO2, partial pressure of carbon dioxide.

drugs, with no difference in clinical satisfaction, airway obstruction, desaturation, nausea, or vomiting [25,38,39]. Several trials have compared the efficacy of ketofol and combined sedatives, including ketamine and dexmedetomidine, propofol and fentanyl, and propofol and dexmedetomidine. In these clinical trials, pediatric sedation was performed to reduce fractures, for cardiac catheterization, incision and drainage, and wound debridement. The recovery time, desaturation, or respiratory depression was not affected by ketofol (1:1

or 1:2) in comparison with other combined drugs. However, ketofol significantly reduced hypotension in these trials [40–42]. Therefore, the use of ketofol for pediatric sedation has no clear advantages. In addition, the American Academy of Pediatrics suggested that pediatric patients under the age of 6 years could be vulnerable to respiratory drive and patent airway reflex due to sedatives [43].

STRATEGY OF KETOFOL USE FOR DENTAL SEDATION

Table 2 presents the characteristics of the included studies. Ketamine and propofol can be administered using a syringe or mixed with one syringe at various ketamine/propofol ratios. Additionally, ketofol can be administered as an intermittent bolus dose or continuous infusion. A 1:1 mixture of ketofol leads to lower respiratory depression and appropriate hemodynamic responses compared to mixtures with 1:2 and 1:3 ratios [44–46]. Generally, ketofol (1:1) can be prepared as a 5-mg/mL concentration of each component [25,28,29]. A regimen of intermittent bolus administration of ketofol is 0.5 mg/kg initially, with half of the initial dose administered at 1–2-min intervals for the adequate sedation level [24,27,29]. For ketofol infusion, 0.5 mg/kg of ketofol is administered as a loading dose, followed by continuous infusion at a dose of 2.4–3.6 mg/kg/h [25]. In the case of ketofol mixed at a 1:2 or 1:4 ratio instead of a 1:1 ratio and when low-dose ketamine is used, ketamine can be continuously administered at 0.5–2.0 mg/kg/h and propofol at 3–8 mg/kg/h [22,27,40–42]. However, since the propofol dose for sedation is 1.5–4.5 mg/kg/h, continuous infusion at a dose above this can cause respiratory depression. Therefore, caution should be exercised.

CONCLUSIONS

A comprehensive review of various studies showed that the combined administration of ketamine and propofol provided effective sedation during various clinical sedation procedures, improved hemodynamic stability, did not increase the risk of respiratory depression, and resulted in rapid onset and recovery and reduced pain after the procedure. Thus, ketofol can be used as a sedative for surgical procedures, including dental sedation, and is a promising alternative to other sedatives.

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