Ketofol for Procedural Sedation and Analgesia in the Pediatric Population

Ammarah U. Iqbal, MD, Megan E. Shuster, PharmD,* and Carl R. Baum, MD*†*

Abstract: The combination of ketamine and propofol, commonly referred to as ketofol, is sometimes used for procedural sedation and analgesia in the pediatric emergency department. This article reviews the pharmacology, dosing, and indications, as well as adverse effects and contraindications of ketamine, propofol, and ketofol.

Key Words: procedural sedation, ketamine, propofol, ketofol, sedation

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TARGET AUDIENCE

This continuing medical education activity is intended for pediatric practitioners who provide procedural sedation and analgesia in the pediatric emergency department and critical care settings.

LEARNING OBJECTIVES

After completion of this article, the reader should be better able to:

1. Explain the pharmacology, dosing, indications, and risks of using propofol or ketamine as agents for procedural sedation and analgesia (PSA);
2. Describe the benefits and risks of using ketamine and propofol in conjunction, commonly known as ketofol, for PSA;
3. Summarize the literature discussing the adverse event profile of using ketofol for PSA compared with alternative sedation regimens.

Procedural sedation and analgesia (PSA) is commonly used for patients in the pediatric emergency department (PED) to provide sedation, analgesia, and amnesia during specific procedures. The ideal drug for PSA is the one with the abovementioned properties along with rapid onset of action, short duration of action, short recovery time, and minimal associated adverse events. The purpose of PSA is to provide moderate to deep sedation as per the American Society of Anesthesiologists definitions.[1] Commonly used drugs include propofol, ketamine, remifentanil or fentanyl, midazolam, etomidate, nitrous oxide, and dexmedetomidine. Single-agent sedatives are thought to be safer than a combination of sedatives; however, combination agents may confer certain advantages.[2] This review highlights existing evidence for the use of ketamine and propofol, as well as these agents in conjunction, commonly known as ketofol, for PSA. It is important to understand each medication before using them in combination.

From the *Clinical Fellow, Pharmacist, Pediatric Emergency Department, Yale New Haven Hospital; and †Professor, Section of Pediatric Emergency Medicine, Yale University School of Medicine, New Haven, CT.

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Reprints: Ammarah U. Iqbal, MD, Suite 1D, 100 York Street, New Haven, CT 06511 (e-mail: ammarah.iqbal@yale.edu).

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KETAMINE: Pharmacology

Ketamine is a non-competitive *N*-methyl-D-aspartate (NMDA) receptor antagonist.[3] By blocking the binding of glutamate, ketamine provides sedation and analgesia, and induces amnesia or a sense of dissociation from the immediate environment. Ketamine is a favored anesthetic because of its safety profile and higher level of analgesia as compared with alternative regimens. It has a rapid onset of action for all routes of administration, but onset does vary based on route. If ketamine is given intravenously (IV), the onset of action is within 30 seconds; intramuscularly (IM), within 3 to 4 minutes; and intranasally (IN), within 10 minutes.[3] The duration of action also varies with route of administration: IV, 5 to 10 minutes (anesthetic time, 1–2 hours); IM, 15 to 30 minutes (anesthetic time, 3–4 hours); and IN, 45 to 60 minutes (anesthetic time, up to 1 hour).

KETAMINE: Dosing

It is important to note that dosing for ketamine is dependent on the route of administration and should be based on available access. For PSA, ketamine can be given IV, IM, or IN, and repeat doses can be administered as needed to prolong the desired sedation. The following dosing of ketamine is recommended for PSA as a single agent. Intravenous dosing is recommended to start at 1 to 2 mg/kg given as a push over 30 to 60 seconds, and if sedation is not adequate after 5 to 15 minutes, repeat doses of 0.5 to 1 mg/kg can be administered every 5 to 15 minutes. It is important to note that intravenous ketamine should be given over 30 to 60 seconds to avoid respiratory depression and neurological effects that can mimic tonic-clonic movements from enhanced skeletal muscle tone.

For intramuscular dosing, a patient can receive 3 to 5 mg/kg IM, and if sedation is not adequate after 5 to 10 minutes, a repeat dose of 2 to 5 mg/kg IM can be administered.[3]

KETAMINE: Indications and Benefits

Ketamine is an excellent agent for PSA not only because of its pharmacodynamic and pharmacokinetic properties but also because of its preservation of cardiac and respiratory function. It is a preferred agent in procedures that will be brief and painful, such as difficult laceration repairs or orthopedic procedures.

The advantages of ketamine are bronchodilation with preservation of airway reflexes, and preservation of, or increased, cardiac function. The preservation of cardiac function is due to an inhibition of catecholamine reuptake, which stimulates a sympathetic nervous system response and increases heart rate, blood pressure, and cardiac output. Blood pressure and heart rate should return to baseline within 15 minutes after administration of the ketamine, which may benefit patients with hypotension or hypovolemia. Adverse effects of ketamine include vomiting, sialorrhea, prolonged recovery period, and emergence reactions such as hallucinations, vivid dreams, and delirium.

KETAMINE: Risks, Adverse Events, and Contraindications

Ketamine is typically well tolerated by patients but has warnings and contraindications. Because of the stimulation in the sympathetic nervous system that leads to temporary elevations in heart rate, blood pressure, and cardiac output, ketamine is contraindicated in patients with significant hypertension. Given such effects, it is not a favored agent for those with ischemic heart disease. Another contraindication is a known allergy to the drug or its inactive ingredients.

As for the pediatric population, there is a warning of pediatric neurotoxicity. Some published studies show that after administration of anesthetic and sedatives that block NMDA receptors, there is an increase in neuronal apoptosis in the developing brain and can result in long-term cognitive deficits when it is used for an extended period, usually greater than 3 hours.[3]

Other warnings include respiratory and neurological effects. Although ketamine typically preserves airway reflexes, it can cause respiratory depression; therefore, resuscitation equipment should be readily available for use. Typically, a code cart should be stationed outside of the patient's room for each PSA. As for neurological effects, there can be an increase in skeletal muscle tone that can mimic tonic-clonic movements, usually related to the rate of ketamine infusion.

PROPOFOL: Pharmacology

Propofol was first approved by the Federal Drug and Administration (FDA) in 1989 as an intravenous anesthetic for multiple indications, including sedation and amnesia. Propofol is a short-acting, highly lipophilic, sedative-hypnotic agent with a mechanism of action that has not been well defined. It is presumed that propofol produces the anesthetic effects by γ-aminobutyric acid agonism. It is important to note that propofol provides only sedation and amnesia, but not analgesia. Therefore, it is best used in procedures that will be brief and painless. Propofol is an emulsion that is currently formulated with soybean oil, egg lecithin, disodium edetate, and glycerol,[4] so it is important to clarify allergies before administration. Because of its lipophilicity and large volume of distribution, it crosses the central nervous system membranes rapidly to produce central nervous system effects, including rapid sedation.

The onset of action is typically within 40 to 60 seconds, with a duration of only 10 to 15 minutes depending on the dose[4] and serum concentration of the drug. Propofol can be titrated for procedural sedation; however, it is important to space each bolus dose by 3 to 5 minutes to assess the clinical effects on the patient. As serum concentrations build, the risk of undesirable adverse effects, such as apnea and bradycardia, increases. This rapid onset of action and short duration of action is ideal for shorter procedures, but appropriate dosing intervals are necessary to avoid cardiorespiratory depression.

PROPOFOL: Dosing

Unlike ketamine, propofol is administered only by the intravenous route. For procedural sedation, propofol should be dosed by the repeat bolus method. Children typically require higher doses of propofol because of the larger volumes of distribution. The initial dose is 1 to 2 mg/kg IV with a typical maximum of 100 mg/dose, followed by repeat doses of 0.5 to 1 mg/kg IV every 3 to 5 minutes as needed for sedation.[4] Each dose should be infused over 30 seconds to 1 minute to reduce the risk of apnea.

PROPOFOL: Indications and Benefits

It is important to note that propofol does not provide analgesia. As noted above, it is best for procedures that will be brief and painless, unless used in conjunction with an analgesic agent. Propofol has the advantage of rapid CNS penetration, allowing for rapid sedation, and a brief recovery period.

PROPOFOL: Risks, Adverse Events, and Contraindications

The side effect profile of propofol is not as favorable as ketamine, as it has a higher risk of hypotension and apnea. The major cardiovascular effect of propofol is hypotension, which is more likely in patients who are hypovolemic or are receiving bolus doses.[4] The cardiac effect can cause as much as a 30% decrease in blood pressure with minimal change in heart rate. Given such effects, it is not a first-line agent in patients with hemodynamic instability, but may be advantageous in those with ischemic heart disease. As for the respiratory side effects, propofol is a sedative, so there is risk of apnea. It should be administered as a slow infusion or a slow bolus dose over 30 seconds to 1 minute.

Propofol is contraindicated in patients with a history of anaphylactic reaction to eggs, egg products, soybeans, or soy products, as the emulsion is formulated with these inactive ingredients.[4]

KETOFOL: Background

Ketamine and propofol have their own advantages for sedation; however, ketofol has been theorized as an improved anesthetic agent in short painful procedures because it mitigates the adverse effects of the individual agents.

KETOFOL: Pharmacology

Ketofol is intended to avoid respiratory depression and to improve hemodynamic stability as well as recovery and post-procedural analgesia.[5] Because it is presumed that the adverse effects of the single agents are dose-dependent, the risk of adverse events increases as serum levels increase. The use of ketofol reduces the serum concentrations of each drug, and therefore the risk of unwanted adverse effects. Propofol alone has rapid CNS penetration and provides rapid sedation with a short recovery period, but does have the increased risk of respiratory depression and hypotension.[6] The addition of ketamine minimizes the risks of respiratory depression and hemodynamic changes. Ketamine also provides analgesic properties to supplement the anesthetic properties. The combination of the 2 medications allows lower doses of each, which leads to respiratory and hemodynamic stability while preserving the anesthetic or analgesic properties that each drug has to offer.

KETOFOL: Dosing

Dosing for ketofol is usually based on a 1:1 ratio of ketamine to propofol. For pediatrics, a weight-based dose of 0.5 mg/kg of ketamine and 0.5 mg/kg of propofol is administered every 2 to 5 minutes as needed for sedation.[7] There are numerous studies that evaluated different ketamine-to-propofol ratios to optimize adequate sedation with the shortest recovery time. The ratios studied range from 1:1 to 1:10, but several studies suggest a ratio of 1:1 to 1:3. For a 1:3 ratio, the dosing is 0.25 mg/kg of ketamine and 0.75 mg/kg of propofol.

Aside from the benefits, it is likely that the rate of adverse events is similar in either ratio of medication regimens. One retrospective case-series analysis reported a similar rate of adverse events in the 1:1 ratio group compared with ratios greater than 1:1.[8] This study demonstrated that it is safe and practical to use

TABLE 1. Trials Comparing Ketofol With Ketamine or Propofol Alone

Study/Size	Patients/Setting	Ketofol Dosing (KTF)	Control Dosing	Respiratory Events	CV Events	Emesis/ Nausea	Agitation/ Emergence	Recovery Time Duration
Chiaretti et al[20] 2011; n = 121	Ages 1–12 y with ALL; setting, clinic (LP or BM aspirations)	*KTF* = K: 0.5 mg/kg + P: 2 mg/kg, maintenance: P: 0.5–1.0 mg/kg prn	*P*= P: 2 mg/kg, maintenance: P: 0.5–1.0 mg/kg prn	*P > KTF*	*P > KTF*	—	—	*P > KTF*
Canpolat et al[21] 2016; n = 60	Ages 3–9 y; setting, dental clinic	*KTF*= K: 0.5 mg/kg + P: 0.5 mg/kg, maintenance: K: 0.25 mg/kg + P: 0.25 mg/kg prn	*K* = 1 mg/kg K, maintenance 05 mg/kg K prn *P* = 1 mg/kg P, maintenance 05 mg/kg P prn	No difference	P/KTF > K (⇓ MAP)	No difference	—	*KTF > P*
Kinsara et al[22] 2017; n = 61	Ages 3–21 y; setting, PED	*KTF*= K: 0.5 mg/kg + P: 0.5 mg/kg, maintenance: K 0.25 mg/kg + P 0.25 mg/kg prn × 3	*K* = 1 mg/kg, maintenance: K 0.5 mg/kg prn × 3	No difference	No difference	*K > KTF*	—	No difference
Gozde et al[23] 2018; n = 75	6–12 y w anxiety; setting, dental clinic	*KTF* = 0.6 mg/kg ketofol (1:1), maintenance; ketofol infusion 40–60 μg/kg/min	*K* = 1 mg/kg, maintenance K: infusion 50–60 μg/kg/min *P* = 2 mg/kg, maintenance P: infusion 70–90 μg/kg/min	*K > P* *K > KTF* (⇑ cough)	*P* > K (⇓ SAP/ DAP) KTF > K (⇓ SAP/DAP *P* > KTF (⇓ SAP/DAP) *P* > K (⇓ HR)	*K > P*	*K > P* *K > KTF*	*K > P* *K > KTF*
Shah et al[11] 2011; n = 136	Ages 2–17 y; setting, PED (ortho)	*KTF:* 1 mg/kg ketofol (1:1), maintenance P 0.5 mg/kg prn	*K* = K: 1 mg/kg, maintenance K: 0.25 mg/kg prn	—	—	K > KTF		K > KTF
Mittal et al,[13] 2013; n = 40	Ages 2–6 y with anxiety; setting, dental clinic	KTF= P: 1–1.5 mg/kg + K: 0.25 mg/kg, maintenance 1–1.5 mg/kg + K: 0.25 mg/kg prn	*P* = P: 1–1.5 mg/kg, maintenance P infusion 25–75 μg/kg/min	*KTF > P*	No difference	—	—	No difference
Rabie Soliman,[12] 2017; *n* = 60	Ages 12 15 y; setting, OR (pulmonary valve implantation)	KTF = Ketofol (1:1)1–2 mg/kg, maintenance infusion 20–60 μg/kg/min. Additional med: Fentanyl 1 μg/kg/dose prn	*P* = P: 1–2 mg/kg, maintenance P infusion of 50–100 μg/kg/min prn Additional med: Fentanyl 1 μg/kg/dose prn	No difference	No difference	*P* > KTF	—	*P* > KTF
Schmitz et al[14] 2018; n = 347	Ages 3 mo to10 y; setting, radiology (MRI)	*KTF* = Either P: 0.5 mg/kg + K: 1 m/kg OR inhalation + K: 1 mg/kg, maintenance P infusion rate of 5 mg/kg/hr	*P* = P: 1 mg/kg, maintenance P: infusion rate of 10 mg/kg/hr	No difference	No difference	No difference	No difference	*P > KFT*
Stevic et al[24] 2017; n = 203	Ages 1 mo to 12 y; setting, OR (plastic surgery laser)	*KTF*: Ketofol 1 m/kg (1:1) + fentanyl 1 μg/kg IV, maintenance Ketofol 0.5 m/kg (1:1) + fentanyl 0.5 μg/kg IV	*K* = K: 1 mg/kg + fentanyl 1 μg/kg IV, maintenance K 0.5 mg/kg + fentanyl 0.5 μg/kg IV	KTF > K	No difference	No difference	*K > KTF*	*K > KTF*
Jalili et al[25] 2019; n = 87	Ages 3 to 12 y; setting, ENT OR (tonsillectomy)	*KTF* = K: 25 μg/kg/min + P75 μg/kg/min (1:4)	*P* = P: 100 μg/kg/min	No difference	No difference	—	No difference	No difference
Weisz et al[15] 2015; n = 183	Ages 3–21 y; setting, PED	*KTF* = K: 0.5 mg/kg + P: 0.5 mg/kg, maintenance K 0.25 mg/kg/dose + P: 0.25 mg/kg/dose prn × 3	*K* = K: 1 mg/kg, maintenance K: 0.5 mg/kg/dose prn × 3	No difference	No difference	No difference	No difference	No difference

K indicates ketamine; P, propofol; KTF, ketofol.

TABLE 2. Trials Comparing Ketofol With Alternative Sedation Regimens

Study/Size	Patients/Setting	Ketofol Dosing	Control Dosing	Respiratory Events	CV Events	Emesis/Nausea	Agitation/ Emergence Rx	Recovery Time
Canpolat et al[26] 2012; n = 60	Ages 8–60 mo; setting, burn care	*KTF* = K: 1 mg/kg + P: 1 mg/kg, maintenance P: 1 mg/kg prn	*KD* = K: 1 mg/kg + D: 0.5 μg/kg, maintenance D 0.5 mg/kg prn	*KTF* > *KD*	—	—	—	*KD* > *KTF*
Canpolat et al[27] *2017*; n = 60	Ages 2–8 y; setting, dental clinic	KTF = Ketofol: 1 mg/kg Maintenance P: 0.5 mg/kg	KD = K 1 mg/kg + D: 0.5 μg/kg, Maintenance D 0.25 μg/kg	No difference	No difference	*KD* > *KTF*	—	No difference
Chandar et al[19] *2015*; n = 95	Ages 3–12 y; setting, EGD	KTF = K 0.5 mg/kg + P: 1 mg/kg, maintenance P: 0.5 mg/kg prn	PF = Fentanyl 1 μg/kg + P: 1 mg/k, maintenance P: 0.5 mg/kg prn	No difference	No difference	—	—	No difference
Joshi et al[18] *2017*; n = 60	Ages 1 mo to 10 y; setting, cardiac catheterization	KTF = P: 1 mg/kg + K: 1 mg/kg/h, maintenance P 100 μg/kg/h + K 1 mg/kg/h	KD: K 1 mg/kg + D: infusion 1 μg/kg over 10 min, maintenance D infusion 0.5 μg/kg/hr + K:1 mg/kg/hr.	No difference	No difference	—	—	KD > KTF
Khutia et al[28] *2012*; n = 100	Ages 3–14 y; setting, ED	KTF: Ketofol (1:2) 1 mg/kg, maintenance infusion 50 μg/kg/mi	PF = F: 1.5 μg/kg iv + P: 1 mg/kg, maintenance infusion 50 μg/kg/mi	PF > KTF (apnea)	PF > KTF	KTF > PF	KTF > PF	—
Seol et al[17] *2015*; n = 50	Ages 12–36 mo; setting, burn care	KTF = P: 2 mg/kg + K: 1 mg/kg, maintenance K: 0.5–1 mg/kg prn	PR = P 2 mg/kg + remifentanil 0.1 μg/kg, maintenance remifentanil 0.05 μg/kg/min + remifentanil 0.05–0.1 μg/kg/dose prn	No difference	No difference	No difference	—	KTF > PR
Ülgey et al[16] *2013*; n = 46	Ages 4–11 y; setting, angiography	KTF = K 1 mg/kg + P1 mg/kg, maintenance K 1 mg/kg + P 100 μg/kg/mi	DP = D 1 μg/kg + P1 mg/kg, maintenance D 0.5 μg/kg/hr + P 100 μg/kg/mi	No difference	DP > KTF (⇓MAP)	No difference	No difference	No difference
Ustun et al[29] *2017*; n = 120	Ages 1 mo to 12 y; setting, radiology (MRI)	KTF = ketofol (1:1) 0.5 mg/kg, maintenance ketofol (1:1) 0.5 mg/kg Q1min prn	T = T 3 mg/kg, maintenance T 1 mg/kg	No difference	No difference	No difference	KTF > T	KTF > T

D indicates dexmedetomidine; T, thiopental.

different ratios of ketamine to propofol and that there is not one favored dosing regimen.

Ketamine and propofol may be given simultaneously in the same syringe, because they are compatible medications, or may be administered separately as intravenous bolus doses. Although most studies have evaluated the use of ketamine and propofol given simultaneously, there is some suggestion that independent dosing may mitigate adverse events, given ketamine's longer duration of effect; similarly, an additional dose of propofol would be preferable to a dose of ketofol near the end of a sedation.[9] In addition, small doses of propofol may be superior to small incremental doses of ketamine, given the latter's dichotomous manner of providing dissociation.[9]

KETOFOL: Indications and Benefits

As mentioned previously, ketofol is intended to optimize the benefits of both medications, leading to improved hemodynamic stability with improved recovery and postprocedural analgesia.[5]

Many studies have shown ketofol to be effective in achieving and maintaining adequate sedation when compared with propofol or ketamine in isolation,[10–15] or to other combination agents,[16–19] but the evidence regarding adverse events is inconclusive.

Table 1 summarizes the literature to date comparing ketofol for PSA compared with either propofol or ketamine. Table 2 summarizes the literature to date comparing ketofol to alternative combination PSA regimens.

Most studies have shown no increase in respiratory events when comparing ketofol to either ketamine or propofol alone (Table 1) or when comparing ketofol to alternative regimens such as propofol-fentanyl.[28] Only 1 small study showed a slight increase in respiratory events when comparing ketofol with propofol-dexmedetomidine in a pediatric population.[26] Similarly, large adult studies have suggested a lower incidence of adverse respiratory events in those patients receiving ketofol compared with those receiving propofol in isolation.[30,31]

Most studies of ketofol in pediatric patients also show no increased risk of cardiovascular events (Table 1). In addition, when comparing ketofol with ketamine and/or other anesthetic agents, a recent meta-analysis by Foo et al[32] found ketofol to have a lower incidence of hypotension, but otherwise no difference in adverse events. Ketofol may have an advantage in terms of a lower incidence of nausea or vomiting compared with either medication in isolation.[7,11,12]

Although literature on the effect of ketofol on agitation or emergence reactions is scant, some smaller studies suggest ketofol to have an improved profile compared with ketamine alone,[11,23,24] whereas others show no difference.[14,15,25] No studies show an increased risk of agitation or emergence reaction with ketofol. Adult studies echo this finding and have shown that the use of ketofol is effective in minimizing emergence reactions compared with ketamine and propofol in isolation.[33]

Recovery time has also been shown in some cases to be significantly shorter with the use of ketofol compared with ketamine[11,25] or propofol alone,[12,14] whereas others suggest that the use of higher doses of ketamine may prolong recovery time.[7] There is some suggestion that the onset of sedation may be more rapid in those receiving ketofol over propofol[12] and better tolerated.[14] In regimens with lower ratios of ketamine-to-propofol (1:4 compared with 1:1), there is some evidence of improved nausea/vomiting and emergence reactions and of shortened recovery.[34]

Furthermore, provider and patient satisfaction with ketofol is often better than that of propofol or ketamine alone.[10,11,31,35] One study of adults and children evaluated the satisfaction of the provider in using ketofol versus propofol for PSA in the emergency room, and found that the satisfaction with ketofol was higher (95% vs 65%) as compared with propofol alone.[35] Similarly, satisfaction outside of the ED setting has been shown in other contexts, such as in hematology patients requiring bone marrow biopsy with minimal adverse events, dental procedures among children with anxiety, and orthopedic procedures in rural mission trips.[10,36,37]

KETOFOL: Risks, Adverse Events, and Contraindications

However, there is still risk for respiratory depression, hypotension, bradycardia, and all of the above-mentioned adverse events in the use of ketofol that are associated with use of ketamine and propofol as single agents. The idea of ketamine and propofol in combination is to balance the adverse effects, using lower dosing of each medication to potentially avoid those adverse events. Unfortunately, some risk of those adverse events remains.

Although pediatric studies have showed no significant and consistent disadvantage of ketofol (Table 1), 1 larger adult study did find some higher rates of hypotension in the propofol arm versus the ketofol arm, but with questionable clinical significance.[31]

CONCLUSIONS

Ketamine and propofol are 2 agents that are commonly used for PSA. Ketamine has benefits of preservation of cardiac and respiratory function, and also provides analgesic support. Propofol has a shorter onset of action and shorter duration of action, which decreases time to recovery, but lacks any analgesic properties. In addition, propofol has been shown to have a higher risk of apnea and cardiovascular depression. Ketofol is an alternative for PSA that seeks to maximize the benefits of each individual drug while minimizing adverse events. Although literature remains inconclusive for the use of ketofol, most literature to date suggests that ketofol is a safe, efficacious, and well-tolerated combination, with risks that are comparable to the individual components.

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