

# Ketofol: A Combination of Ketamine and Propofol

## Abstract

Ketofol is a combination of ketamine and propofol. To date, there is significant interest in ketofol as an agent for procedural sedation and analgesia. The combination of propofol and ketamine has several benefits in the terms of hemodynamic stability, absence of respiratory depression, post-operative analgesia and recovery. This combination can be mixed in the same syringe or administered independently in the two separate syringes. It can be administered as a bolus or as a continuous infusion for longer procedures. Ketamine-propofol combinations in the different ratios have been studied before. The optimal mixture and dosing of ketamine and propofol has yet to be determined. This short review will highlight recent clinical supports the therapeutic utility of the combination of ketamine and Propofol.

**Keywords:** ketofol; ketamine; propofol; efficacy; safety

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## Introduction

Sedative and analgesic agents are frequently used for procedural sedation. Titration of anesthetic doses should be done cautiously and the patients should be continuously monitored. So far, an ideal intravenous anesthetic agent is none<sup>1,2</sup>. A combination of ketamine and propofol has several ideal anesthetic properties. Several clinical studies of the use of ketofol have been evaluated. To date, there is significant interest in ketofol as an agent for procedural sedation. This report highlights on the combination of ketamine and propofol (Ketofol).

## Ketofol

Ketofol is the combination of ketamine and propofol in various concentrations. It commonly used for several procedures. Ketamine, a neuroleptic anesthetic agent, works on thalamocortical and limbic N-methyl-D-aspartate (NMDA) receptors.<sup>1,2</sup> It can be given through intravenous or intramuscular routes. Ketamine stimulates the cardiorespiratory system. A direct effect increases cardiac output, arterial blood pressure, heart rate and central venous pressures. Therefore, it is a valuable agent for hypotensive or hypovolemic patients, but a less desirable agent in patients with ischemic heart disease or raised pulmonary vascular pressure. However, ketamine induces psychomimetic activity and emergence reactions in up to 30% of patients. In contrast, propofol, a sedative, hypnotic and anesthetic agent, is also an antagonist at N-methyl-D-aspartate receptors.<sup>1,2</sup> However, propofol has a narrow therapeutic range and risks of cardiovascular depression.<sup>3</sup> It is legally used by anesthetic personnel in many countries. The use of propofol by nonanesthesiologists is controversial.<sup>4,5</sup> However, propofol-based sedation is safe and highly effective. Mild respiratory adverse events occur frequently and major complications may happen rarely. Additionally, the adverse events do not occur more frequently compared to other sedation regimens.<sup>6-8</sup> As a result, the combination of these two drugs has several advantages.

## Ketofol mixtures

The Propofol-ketamine mixtures have been used for procedural sedation. Several studies had been published. The study of Wang and colleagues investigated the propofol-ketamine mixtures in the ratios of 2:1, 3:1 and 4:1 compared with the combination of propofol and fentanyl as well as the Propofol alone. The study demonstrated that ketofol was safe and effective as the combination of propofol and fentanyl combination. The ratios of 2:1, 3:1 and 4:1 were very effective for the procedure. The efficacy of sedation, recovery

and discharge time in the ratios of 3:1 and 4:1 mixtures of ketofol presented comparable. Additionally, the incidence of respiratory depression and postprocedural dizziness in the ratio of 4:1 (40 mg of ketamine and 160 mg of propofol in a 20 mL syringe) was a relatively lower than in the other ratios of ketofol. Additional doses of propofol in the propofol only group were also significantly higher.<sup>9</sup>

Dal et al.,<sup>10</sup> compared the effectiveness and safety of the ketofol and the combination of ketamine and midazolam for procedural sedation in the endobronchial ultrasound-guided needle aspiration. The 60 adult patients were randomized into the two groups. Group KP was given 0.125 mg/kg i.v. ketamine and propofol mixture (ketofol) and injection of 0.25 mg/kg each. Group KM was given 0.25 mg/kg i.v. ketamine and 0.05 mg/kg i.v. midazolam. Procedural sedation was maintained with additional doses of ketofol 0.125 mg/kg and ketamine 0.25 mg/kg in Group KP and Group KM, respectively. The result of their study demonstrated that HR in the 10<sup>th</sup> min and Ramsay Sedation Score (RSS) in the 35<sup>th</sup> min in group KP were significantly lower than in group KM. Additionally, the recovery time in group KP was significantly shorter than group KM. However, there were no significant differences in the consumption of the agents, oxygen saturation, respiratory rate, RSS value and the severity of cough as well as the satisfaction of physician and the patients between the two groups. The authors concluded that ketofol was effective and safe for sedation in the endobronchial ultrasound-guided needle aspiration procedure. No serious adverse events were observed.

Phillips et al.,<sup>11</sup> compared ketamine and propofol with propofol alone in 28 patients underwent procedural sedation in the emergency department. The intravenous ketamine doses ranged from 0.5 to 1 mg/kg, with propofol 0.75 mg/kg. The comparator intravenous propofol doses ranged from 0.5 to 1.5 mg/kg. The primary outcome was adequacy of sedation measured using the bispectral index scale (BIS). The propofol-ketamine group presented less of a difference in BIS between baseline and goal sedation. The authors recommended that adequate sedation with the combination of propofol and ketamine was completed without the need for deep sedation compared with the propofol alone. Safety outcomes revealed significantly less reduction in blood pressure in the propofol-ketamine group. Neither group experienced respiratory depression or a significant difference in length of sedation.

Another previous study also compared the quality of sedation and side effects of two different ratios of ketofol in 60 pediatric patients under lumbar puncture or bone marrow aspiration. They divided the

patients into the 1:2 and the 1:3 ratios of ketofol. The results confirmed that the 1:3 ratio of ketofol had lower psychological side effects and shorter recovery time than the 1:2 ratio of ketofol. However, the quality of sedation, the total dose of drug and respiratory and hemodynamic parameters were comparable in both groups.<sup>12</sup>

A randomized, double-blind, placebo-controlled trial compared the frequency of respiratory depression in 98 adults and 93 children receiving a propofol-ketamine combination and propofol alone for procedural sedation in the emergency department.<sup>13</sup> All patients received an intravenous dose of fentanyl 0.5-1.0 mcg/kg 5 min before sedation. Patients were given either ketamine 0.5 mg/kg or placebo over 1 min, followed by a dose of propofol 1 mg/kg over 2 min. Bolus doses of propofol 0.5 mg/kg were given as needed to maintain a Colorado Behavioral Numerical Pain Scale of 0 (restful, no facial expression). The depth of sedation level in both groups was similar. There was no significant difference in respiratory depression between the two groups. However, there was a significant difference in the overall satisfaction of the quality of the sedation, with 95% of physicians being satisfied with propofol-ketamine compared to 65% satisfied with propofol alone. There were no reported occurrences of emergence reactions or other adverse drug events.

Coulter et al.,<sup>14</sup> evaluated the Ketofol in the different ratios for general anesthesia in the pediatric patients. The drug concentration and the anesthesia profiles of ketofol were also studied. The authors concluded that infusion of ketofol would prolong recovery period if the infusion rate was not decreased. They suggested an optimal ratio of ketamine to propofol of 1:5 for a 30 min-anesthesia, and 1:6.7 for a 90 min-anesthesia. The same authors evaluated the ketofol in the different ratios for procedural sedation in the healthy pediatric patients. They suggested that a 1:3 ratio of ketamine and propofol was the best combination for the intermittent dosing. An optimal dose of ketofol for pediatric patients was 0.1 mL/kg in the beginning followed by 0.05 mL/kg at 2 min and then 0.025 mL/kg for the subsequent doses. Consequently, an optimal dose of ketofol for adult patients was 0.05 mL/kg followed by 0.025 mL/kg for the subsequent doses. Furthermore, the mixing ratio greater than 1:3 resulted in prolong of recovery.<sup>15</sup>

Another prospective case series was conducted the use of propofol-ketamine in the emergency department.<sup>16</sup> The propofol-ketamine was administered in a 1:1 ratio mixed in the same syringe (median dose 0.75 mg/kg). All patients could receive opioids before the procedure at the discretion of the physician. Of the 114 procedures attempted, 96% required no adjunct medications to complete the procedure. The median recovery time for propofol-ketamine was 15 min. Apnea occurred in three patients? The bag-valve-mask ventilation was required for one, while two patients required repositioning, stimulation and supplemental oxygen. A fourth patient experienced recovery agitation and required midazolam.

Recently, Nalini et al.,<sup>17</sup> studied 60 patients, ASA physical status I who underwent puerperal sterilization. All patients were randomized into ketamine-propofol infusion in a concentration of 8 mg/ml each (group PK) and fentanyl 2 mcg/kg followed by a continuous infusion of 8 mg/ml propofol (group PF). In both groups, the infusion was started at 300 mL/h till the patient lost consciousness. After that, the rate was set at 0.75 mL/kg/h for group PK and at 1.5 mL/kg/h for group PF, and was reduced to 0.5 mL/kg/h for group PK and 1 mL/kg/h for group PF after 10 min. The results demonstrated that the reduction of systolic and diastolic blood pressure as well as oxygen saturation in group PK was significantly lower than in group PF. The patients in group PK had also better surgical and recovery conditions.

The authors concluded that this combination technique (ketofol) is safe and may be an alternative regimen to the combination of propofol and fentanyl.

A Ketofol is also frequently used to achieve sedation and analgesia during endoscopic procedures. The author compared and evaluated the clinical efficacy of the ketofol and propofol alone when each regimen is used as sedative agents for colonoscopy. The 194 patients were randomized into two groups. The 97 patients in group PK received propofol and ketamine and 97 patients in group P received propofol and normal saline for sedation. All patients were premedicated with 0.02-0.03 mg/kg of midazolam. All endoscopic procedures were completely successful. The mean total dose of propofol in group PK and P were 6.98±2.90 mg/kg/h and 7.73±3.45 mg/kg/h, respectively. Mean total dose of ketamine in group PK was 1.49±0.61 mg/kg/h. There were no significant differences in patient tolerance, discomfort during insertion, patient and endoscopist satisfaction, hemodynamic responses, procedural pain, recovery time and recovery score. Overall, cardiovascular and respiratory adverse events were not significantly different between the two groups. These adverse events were transient and easily treated with no sequelae.<sup>18</sup>

Interestingly, Ketofol can be used for electroconvulsive therapy. Kayhan and colleagues evaluated the effect of a ketamine-propofol combination (ketofol) for electroconvulsive therapy (ECT) on seizure activity, hemodynamic response and recovery parameters. The 24 patients underwent a total of 144 ECT procedures were randomized into 1 mg/kg ketofol (0.5 mg/kg propofol and 0.5 mg/kg ketamine) and 1 mg/kg propofol 1% for anesthesia induction. Seizure duration and quality, hemodynamic data, recovery parameters and side effects were analyzed between the two groups. The seizure durations in both groups were similar. Post-ictal suppression index in the propofol group was lower than in the ketofol group. The heart rate and mean arterial pressure in the propofol group were also lower than in the ketofol group. Time to obeying commands was longer in the ketofol group. The undesirable psychological reactions were none in the ketofol group. The authors concluded that ketofol could be an optional technique for electroconvulsive therapy.<sup>19</sup>

## Conclusion

Ketofol is a combination of ketamine and propofol. It is an agent of choice for various procedures. The combination of propofol and ketamine has several benefits because of hemodynamic stability, lack of respiratory depression, good recovery and potent post-procedural analgesia. The safety and efficacy of ketofol as a sedoanalgesic agent are depended on the dose and the ratio of the mixture. Therefore, ketofol should be an ideal combination drug for procedural sedation.

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## Conflicts of interest

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