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Research Article

The application of a new regimen for short term sedation in the ICU (ketofol) – Case series

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KEYWORDS

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Abstract *Objective:* Sedation is an effective component of care in ICU patients. The aim of this study was to evaluate the safety and efficacy of ketamine/propofol combination in short term sedation for the critically ill patients in ICU.
Design: Prospective case series study.
Setting: Intensive care unit (ICU) in a tertiary hospital (Kasr Al Aini).
Methods: Fourteen critically ill patients who were mechanically ventilated and were in need for sedation were included in this case series. An initial bolus dose (500 μg/kg) of ketamine/propofol 1:1 (ketamine 8 mg/ml and propofol 8 mg/ml) was given to all patients followed by a maintenance dose of 10 μg/kg/min and the infusion dose adjusted (in 5 μg/kg/min increments) to achieve Ramsay Sedation Scale of 4. Recorded parameters included heart rate, systolic blood pressure, Ramsay score, the need for use of noradrenalin and the recovery time from discontinuation of sedation.
Results: The mean and standard deviation of the age of the patients was 60 ± 14.5 y and their APACHEII score ranged from 18 to 35. The median initial bolus dose of ketofol administered was 5 ml of aliquot with median infusion rate 6 ml/h (range: 4.8–7.5 ml/h) only three patients (21.4%) needed the infusion rate to be increased to achieve Ramsay score 4. Only one patient experienced hypotension due to hypovolemia secondary to internal hemorrhage.
Conclusion: Continuous intravenous infusion of ketofol may provide adequate and safe short term sedation (less than 24 h) for critically ill patients in the intensive care units, with rapid recovery and no clinically significant complications. Further studies with larger number of patients are required to evaluate and validate these findings.

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1. Introduction

Critically ill patients in an intensive care unit (ICU) are subjected to a variety of noxious stimuli including pain after surgery, frequent venipuncture, invasive monitoring and endotracheal intubation [1]. So Sedation is considered as an essential component of care in these patients.

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The aim of using sedation is to reduce stress, and to provide anxiolysis, analgesia and amnesia without compromizing the cardiovascular and respiratory system. Systolic blood pressure (SBP) and heart rate (HR) were recorded before starting sedation (T0), then after 15 min (T1), 30 min (T2), 1 h (T3), 3 h (T4), 6 h (T5) and 12 h (T6) after starting sedation.

The ideal sedative should be effective, short-acting and non-cumulative, free of adverse effects, having rapid onset and offset, with no effect on the metabolism of other drugs and lastly should have known pharmacokinetics and pharmacodynamics in organ failure. The drugs commonly used for sedation in the ICU include benzodiazepines, antipsychotics and propofol, none of which meets all these criteria.

Multiple studies evaluated the safety of intravenous ketamine/propofol combination (''ketofol'') in the same syringe [2–4].

Propofol is a short-acting intravenously administered sedative and hypnotic agent that can be used for the induction and maintenance of general anesthesia, sedation for intubated, mechanically ventilated patients in the ICU, and in procedures such as colonoscopy. It does not have analgesic properties [5]. The adverse effects related to the use of propofol include dose-dependent hypotension and respiratory depression [6–8].

Ketamine is classified as an NMDA receptor antagonist and has also been found to bind to opioid receptors and sigma receptors. It induces a state referred to as ''dissociative anesthesia'' [9]. It provides amnesia, analgesia and anesthesia while maintaining protective airway reflexes and spontaneous respiration [10,11]. Its significant adverse effects include its propensity to cause vivid and frightening emergent reactions [12], sympathomimetic effects and vomiting when administered in sedating doses [13].

Ketamine and propofol are physically compatible for 1 h at 23 °C with no increase in particle content at Y site injection [14]. Ketofol (ketamine/propofol combination) was used for procedural sedation and analgesia (PSA). Ketamine and propofol administered in combination have offered effective sedation for spinal anesthesia and for gynecologic, ophthalmologic, and cardiovascular procedures in all age groups [15]. Also it has been used as an infusion for sedation in awake craniotomy cases safely with minimal hemodynamic and respiratory events and with rapid smooth recovery profile [16]. The opposing hemodynamic and respiratory effects of each drug may enhance the utility of this drug combination, increasing both safety and efficacy while minimizing their respective adverse effects. This is due partly to the fact that many of the potential side effects are dose-dependent, and when administrating this combination the doses of each drug can be reduced [17]. There is a significant amount of literature describing the use of ketofol in infusion form.

Because ketofol is considered a relatively new idea for most practitioners, there is very little or nearly no data available in scientific literature for its use as a sedative in ICUs. Propofol is recommended as one of the preferred agents for the short-term (< 24 h) treatment of anxiety in the critically ill adults [18] and continuous infusion doses of ketamine have been also described for 24 h [19], so ketofol is expected to be given safely as a continuous infusion for 24 h (short-term sedation).

The aim of this study was to evaluate safety and efficacy of using ketofol for short term sedation for critically ill patients in the intensive care unit.

2. Patients and methods

After approval of this case series prospective study by the local Ethics Committee, critically ill patients (who were defined as those patients requiring intensive monitoring and may potentially need immediate intervention) who were mechanically ventilated and in need for sedation were included excluding patients less than 18 years old, head trauma patients or those with increased intracranial tension, epileptic patients and patients with known allergies to the studied drugs.

Ketofol (propofol/ketamine admixture) was prepared by an assistant who was not involved in the clinical management of the study patients. a ketofol (1:1): propofol 8 mg/ml, ketamine 8 mg/ml by mixing 40 ml propofol 1% (10 mg/ml) with 8 ml ketamine (50 mg/ml) and 2 ml dextrose 5% (each ml of aliquot contained 8 mg propofol and 8 mg ketamine).

Both bolus and maintenance doses will be given using syringe pump (B/Braun). Set up for delivery of ketofol as an initial bolus of 500 μg/kg IV of aliquot, followed by an initial maintenance infusion at 10 μg/kg/min and the infusion dose adjusted (in 5 μg/kg/min increments) to achieve Ramsay Sedation Scale of 4, maximum infusion time was 24 h.

The Ramsay score (target and actual) was recorded hourly for the first 24 h, and patients were continuously monitored for ECG, blood pressure, oxygen saturation, doses of vasoconstrictor agents (noradrenaline) were recorded before and during infusion, development of side effects, recovery time and APACHEII score will be recorded.

Systolic blood pressure (SBP) and heart rate (HR) were recorded before starting sedation (T0), then after 15 min (T1), 30 min (T2), 1 h (T3), 3 h (T4), 6 h (T5) and 12 h (T6) after starting sedation.

Complications including hypotension which is defined as systolic blood pressure less than 90 (Table 1), hypertension which is defined as systolic blood pressure more than 170, respiratory depression which is defined as apnea more than 20 s were recorded. Any change in the rate of infusion of vasoconstrictor agent (noradrenaline) if present was recorded.

Recovery time was defined as the time required for the patient to regain the baseline conscious level (conscious level before starting sedation) after discontinuing sedation.

Table 1 Ramsay Sedation Scale [20].

Sedation level	Description
1	Patient is anxious and agitated or restless, or both
2	Patient is co-operative, oriented, and tranquil
3	Patient responds to commands only
4	Patient exhibits brisk response to light glabellar tap or loud auditory stimulus
5	Patient exhibits a sluggish response to light glabellar tap or loud auditory stimulus
6	Patient exhibits no response