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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

Table 2 Hemodynamic changes, data are presented as mean ± sd.

	T0	T1	T2	T3	T4	T5	T6
SBP	122.4 ± 16.2	119.2 ± 14.7	119.8 ± 15.4	128.9 ± 14.1	129.6 ± 11.9	138.2 ± 14.7	139.3 ± 14.5
HR	104.7 ± 19.3	101 ± 21.9	103 ± 19.2	97.5 ± 19.8	98.1 ± 22.8	95.5 ± 18.3	95.2 ± 18.5

SBP: Systolic blood pressure, HR: Heart rate; T0: time before starting sedation, T1: time after 15 min, T2: time after 30 min, T3: time after 1 h, T4: time after 3 h, T5: time after 6 h, T6: time after 12 h of starting sedation.

3. Statistical analysis

Continuous data were presented as mean ± standard deviation or median, categorical data were presented as number and percent. ANOVA was used to compare the recorded hemodynamic parameters where P values less than 0.05 was considered significant. SPSS 17.0 (Statistical Package for the Social Sciences) was used for statistical calculations.

4. Results

A total of 14 patients were enrolled for the study. Median patient age was 63 years (range 32–84 y), 57.1% were males and 42.9% were females, 10 patients (71.4%) were surgical and four patients (28.6%) were medical, APACHEII score (range18–35) all patients were mechanically ventilated and only three patients (21.4%) were receiving noradrenaline infusion.

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). The median infusion period was 16 h (range: 1–24 h).

There were no significant changes observed in pulse rate and blood pressure except one patient (7.1%) who became hypotensive due to hypotension secondary to internal hemorrhage (Table 2).

Median recovery time was 30 min (range 18–60 min).

Non-significant complications in the form of respiratory depression and agitation were detected.

5. Discussion

The main finding of the current study was that, infusion of a combination of ketamine–propofol in the same syringe was effective in maintaining Ramsay Sedation Scale 4 without hemodynamic instability.

Non-significant changes in the form of hypertension, hypotension were detected except one patient who experienced hypotension due to hemorrhagic shock that followed postoperative repair of hepatic injury for whom ketofol infusion was stopped after 1 h of continuous infusion. Three patients were receiving noradrenaline infusion before starting ketofol sedation for whom we did not need to increase infusion rate of noradrenaline after starting ketofol infusion.

In line with our results, several authors demonstrated the safety of using ketofol on hemodynamics. Willman and Andolfatto [21], reported that no patient became hypotensive or had evidence of poor perfusion when ketofol was administrated in a mean dose of (0.75 mg/kg of ketamine and 0.75 mg/kg of propofol) for PSA for mainly orthopedic procedures conducted in the emergency department (ED) setting where 114 patients were enrolled in this study. Andolfatto and Willman [22], demonstrated that only 1 patient out of 728 patients became hypotensive when ketofol was used for PSA for primarily orthopedic procedures. Also Loh and Dalen [23], studied the effect of ketofol in procedural sedation, they reported that fewer patients given the ketamine–propofol combination experienced significant hemodynamic compromise, need for active interventions, including fluid or vasopressor administration. They attributed their results to the contradictory effect of both ketamine and propofol on autonomic nervous system, ketamine being sympathomimetic while propofol lessens this effect.

No respiratory depression or agitation were reported in the cohort group. Similar to our findings Willman and Andolfatto [21] reported that 3 out of 114 had transient hypoxia who required bag-valve-mask ventilation, four patients required repositioning for airway malalignment, and three patients (2.6%; 95% CI 0.6–7.5%) had mild unpleasant emergence, of whom one received midazolam. Also Andolfatto and Willman [22] who tried to evaluate the effectiveness, recovery time, and adverse event profile of intravenous (IV) mixed 1:1 ketamine–propofol for adult procedural sedation and analgesia in the emergency department where ketofol PSA was used in 728 patients for primarily orthopedic procedures reported that bag-mask ventilation occurred in 15 patients (2.1%) and Recovery agitation occurred in 26 patients (3.6%) of whom 13 (1.8%) required treatment.

Median recovery time was 30 min (range 18–60 min) which is comparable with Andolfatto and Willman [22] who demonstrated that the median recovery time was 14 min (range 3–50 min). Erden et al. [24] who reported that the mean recovery times were 12.1 ± 1 min in the patient group underwent interventional radiological procedures under sedation who received propofol 0.5 mg kg^{-1} + ketamine 0.5 mg kg^{-1}. In our study the median recovery time seems to be longer may be due to the longer infusion period.

Limitations: The study group was small and so reporting of adverse events is limited also ketofol was not compared in a randomized, blinded fashion to other ICU sedation regimens.

In 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, rapid recovery and no clinically significant complications. Because of the small size of this case series further studies with larger number of patients are required to evaluate and validate these findings.

References

[1] Chamorro C, de Latorre FJ, Montero A, Sanchez JA, Jareno A, Moreno JA, et al. Comparative study of propofol versus midazolam in the sedation of critically ill patients: results of a prospective, randomized, multicenter trial. Crit Care Med 1996;24:932–9.

[2] Santiveri X, Moltò L, Rodríguez C, Sandín F, Vilaplana J, Castillo J. Sedation and analgesia with propofol plus low-dose

ketamine for retrobulbar block. Rev Esp Anestesiol Reanim 2006;53(9):545–9.
[3] Andolfatto G, Willman E. A prospective case series of pediatric procedural sedation and analgesia in the emergency department using single-syringe ketamine–propofol combination (ketofol). Acad Emerg Med 2010;17(2):194–201.
[4] Singh R, Batra YK, Bharti N, Panda NB. Comparison of propofol versus propofol–ketamine combination for sedation during spinal anesthesia in children: randomized clinical trial of efficacy and safety. Paediatr Anaesth 2010;20(5):439–44.
[5] Miner JR, Burton JH. Clinical practice advisory. Emergency department procedural sedation with propofol. Ann Emerg Med 2007;50(2):182–7.
[6] Short SM, Aun CS. Haemodynamic effects of propofol in children. Anaesthesia 1991;46:783–5.
[7] Bassett KE, Anderson JL, Pribble CG, Guenther E. Propofol for procedural sedation in children in the emergency department. Ann Emerg Med 2003;42:773–82.
[8] Hig Jr CC, McLeskey CH, Nahrwold ML, Roizen MF, Stanley TH, Thisted RA, et al. Hemodynamic effects of propofol: data from over 25,000 patients. Anesth Analg 1993;77:S21–9.
[9] Harrison N, Simmonds M. Quantitative studies on some antagonists of N-methyl D-aspartate in slices of rat cerebral cortex. Br J Pharmacol 1985;84(2):38191.
[10] Krauss B, Green SM. Procedural sedation and analgesia in children. Lancet 2006;367:766–80.
[11] Warncke T, Stubhaug A, Jørum E. Ketamine, an NMDA receptor antagonist, suppresses spatial and temporal properties of burn-induced secondary hyperalgesia in man: a double-blind, cross-over comparison with morphine or placebo. Pain 1997;72:99–106.
[12] Green SM, Rothrock SG, Lynch EL, Ho M, Harris T, Hestdalen R, et al. Intramuscular ketamine for pediatric sedation in the emergency department: safety profile in 1022 cases. Ann Emerg Med 1998;31:688–97.
[13] Roback MG, Wathen JE, Bajaj L, Bothner JP. Adverse events associated with procedural sedation and analgesia in a pediatric emergency department: a comparison of parenteral drugs. Acad Emerg Med 2005;12:508–13.
[14] Trissl LA, Gilbert DL, Martinez JF. Compatibility of propofol injectable emulsion with selected drugs during simulated Y-site administration. Am J Health Syst Pharm 1997;54:1287–92.
[15] Daabiss Mohamed, Elsherbiny Medhat, Alotibi Rashed. Assessment of different concentration of ketofol in procedural operation. BJMP 2009;2(1):27–31.
[16] Samar A, Hany A, Enas M, Ehab M. Preliminary evaluation of ketofol based sedation for awake craniotomy procedures. EgJA 2011;26(4):293–7.
[17] Camu F, Vanlersberghe C. Pharmacology of systemic analgesics. Best Pract Res Clin Anaesthesiol 2002;16:475–88.
[18] Shapiro BA, Warren J, Egol AB, Greenbaum DM, Jacobi J, Nasraway SA, et al. Practice parameters for intravenous analgesia and sedation for adult patients in the intensive care unit: an executive summary. Crit Care Med 1995;23:1596–600.
[19] Yamauchi M, Asano M, Wtanabe M, Iwasaki S, Furuse S, Namiki A. Continuous low-dose ketamine improves the analgesic effects of fentanyl patient-controlled analgesia after cervical spine surgery. Anesth Analg 2008;107:1041–4.
[20] Griffiths RD, Jones C. Recovery from intensive care. Brit Med J 1999;319:427–9.
[21] Willman EV, Andolfatto G. A prospective evaluation of "ketofol" (ketamine/propofol combination for procedural sedation and analgesia in the emergency department. Ann Emerg Med 2007;49:23–30.
[22] Andolfatto G, Willman EV. A prospective case series of single-syringe ketamine–propofol (ketofol) for emergency department procedural sedation and analgesia in adults. Acad Emerg Med 2011;3:237–45.
[23] Loh G, Dalen D. Low-dose ketamine in addition to propofol for procedural sedation and analgesia in the emergency department. Ann Pharmacother 2007;41(3):485–92.
[24] Erden IA, Pamuk AG, Akinci SB, Koseoqlu A, Ayper U. Comparison of two ketamine–propofol dosing regimens for sedation during interventional radiology procedures. Minerva Anestesiol 2010;4:260–5.