American Journal of Case Reports

ISSN 1941-5923
© Am J Case Rep, 2015; 16: 81-86
DOI: 10.12659/AJCR.892424

Received: 2014.09.08
Accepted: 2014.10.29
Published: 2015.02.13

Ketamine and Propofol Combination ("Ketofol") for Endotracheal Intubations in Critically Ill Patients: A Case Series

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABCDEFG 1 Alice Gallo de Moraes
ABCDEFG 1 Carlos J. Racedo Africano
ABCDEFG 1 Sumedh S. Hoskote
ADEF 1 Dereddi Raja S. Reddy
ABCDEFG 1 Rudy Tedja
ADEF 1 Lokendra Thakur
ABDE 1 Jasleen K. Pannu
ABDE 1 Elizabeth C. Hassebroek
ABCDEFG 2 Nathan J. Smischney

1 Department of Medicine, Division of Pulmonary and Critical Care Medicine, Mayo Clinic, Rochester, MN, U.S.A.
2 Department of Anesthesiology, Division of Critical Care Medicine and Multidisciplinary Epidemiology and Translational Research in Intensive Care (METRIC), Mayo Clinic, Rochester, MN, U.S.A.

Corresponding Author: Alice Gallo de Moraes, e-mail: gallodemoraes.alice@mayo.edu
Conflict of interest: None declared

Case series
Patient: Male, 77 • Male, 25 • Male, 63 • Male, 70 • Male, 70 • Female, 61
Final Diagnosis: —
Symptoms: Hypotension • respiratory failure
Medication: Ketamine • Propofol • Etomidate
Clinical Procedure: Endotracheal intubation
Specialty: Critical Care Medicine

Objective: Educational Purpose (only if useful for a systematic review or synthesis)

Background: Endotracheal intubation is a common procedure performed for critically ill patients that can have immediate life-threatening complications. Induction medications are routinely given to facilitate the procedure, but most of these medications are associated with hypotension. While etomidate is known for its neutral hemodynamic profile, it has been linked with increased mortality in septic patients and increased morbidity in trauma patients. Ketamine and propofol are effective anesthetics with counteracting cardiovascular profiles. No data are available about the use of this combination in critically ill patients undergoing endotracheal intubation.

Case Series: We describe 6 cases in which the combination of ketamine and propofol ("ketofol") was used as an induction agent for endotracheal intubation in critically ill patients with a focus on hemodynamic outcomes. All patients received a neuromuscular blocker and fentanyl, while 5 patients received midazolam. We recorded mean arterial pressure (MAP) 1 minute before induction and 15 minutes after intubation with the combination. Of the 6 patients, 5 maintained a MAP ≥65 mmHg 15 minutes after intubation. One patient was on norepinephrine infusion with a MAP of 64 mmHg, and did not require an increase in the dose of the vasopressor 15 minutes after intubation. No hemodynamic complications were reported after any of the intubations.

Conclusions: This case series describes the use of the "ketofol" combination as an induction agent for intubation in critically ill patients when hemodynamic stability is desired. Further research is needed to establish the safety of this combination and how it compares to other induction medications.

MeSH Keywords: Anesthetics, Combined • Critical Illness • Drug Combinations • Intubation, Intratracheal • Ketamine • Propofol

Full-text PDF: http://www.amjcaserep.com/abstract/index/idArt/892424

2189 2 — 29

Background

Endotracheal intubation is frequently performed as a lifesaving procedure in critically ill patients. However, endotracheal intubation may lead to increased morbidity and mortality if not conducted with care and vigilant selection of the right induction sedatives, anesthetics, analgesics, and paralytics [1,2]. Patients requiring endotracheal intubation are often elderly, debilitated, and have multiple co-morbidities, which predispose them to an increased risk of post-intubation hypotension [3–5]. A number of agents with varying hemodynamic profiles are available for procedural sedation during intubation. Etomidate was, until recently, a popular choice for induction during intubation. However, in recent years, studies have shown that the administration of etomidate is associated with increased mortality, especially in septic patients [6,7]. This association has been observed not only in the intensive care unit (ICU), but also in the operating room as reported by at least 1 study [8]. Additionally, in trauma patients, etomidate was related to increased morbidity and lower serum cortisol concentrations post-intubation [9]. Patients in the ICU are frequently admitted with sepsis or suspicion of sepsis, which could make etomidate an unsuitable choice for most critically ill patients.

Even though the literature on the combination of ketamine and propofol goes back 3 decades [10], more recent data have been published evaluating its potential benefits [11,12]. Perhaps the renewed interest in "ketofol" is due to the recent reports of adverse events associated with etomidate. This combination offers cardiovascular stability, presumably due to a neutral hemodynamic profile [13]. Most of the literature on "ketofol" has involved patients presenting to the emergency department or operating room for elective surgery [13–16]. However, there are no reports evaluating the use of "ketofol" in the general ICU population where its potential benefits may not yet be fully known. Therefore, we report on the efficacy and safety of the combination of ketamine and propofol when used for induction during endotracheal intubation in 6 critically ill patients.

Case Series

In this case series, we report on 6 critically ill patients who received a combination of ketamine and propofol as induction agents for endotracheal intubation in the ICU. Ketamine and propofol were given as an admixture, in the same syringe. All patients had previously provided research authorization for use of their medical records and were cared for directly by 1 or more of the authors. Through our Institution's Institution Review Board (IRB) Wizard tool we obtained an exemption, because this is a case series, and patients were cared for using standard medical practice. All data were obtained from the hospital's electronic database [17]. Data on demographics, Acute Physiologic and Chronic Health Evaluation (APACHE) III scores within 24 hours from ICU admission, comorbidities, and primary ICU diagnoses were collected. Data collected during endotracheal intubation included total dose for both ketamine and propofol, total crystalloid and colloid volume 24 hours pre- and post-intubation, documented intubation complications, and Confusion Assessment Method for the ICU (CAM-ICU) scores 24 hours pre- and post-drug administration. Hemodynamic data consisted of noninvasively measured systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), and heart rate (HR) during the initial 15 minutes after drug administration. All co-interventions (e.g., narcotics, paralytics, vasoactive agents, benzodiazepines) were recorded during the same time interval.

Table 1. Patient characteristics and hemodynamic data.

	APACHE III	CAM-ICU 24 hr prior/ 24 hr after	Vasopressor use	Colloid fluids (ml) 24 h prior/ 24 h after	Crystalloid fluids (ml) 24 h prior/ 24 h after	MAP (mmHg) 15' prior/ 15' after	Heart rate (beats/min) 15' prior/ 15' after
Patient 1	83	+/–	Yes	0/0	3180/2675	64/64	93/94
Patient 2	51	–/+	No	500/500	1000/3110	79/69	119/120
Patient 3	46	–/+	No	0/100	3960/750	87/85	124/123
Patient 4	56	–/+	No	0/0	925/645	77/65	142/116
Patient 5	60	–/–	No	0/0	1800/1630	103/123	133/129
Patient 6	46	+/+	No	0/500	1270/4393	94/97	93/91

APACHE (Acute Physiology and Chronic Health Evaluation) III in the first 24 hours of admission; MAP – mean arterial pressure; 15' – 15 minute vital signs after intubation. CAM ICU – confusion assessment method for the intensive care unit; "+" implies CAM-ICU positive and "–" implies CAM-ICU negative.

Table 2. Technique and medications used during intubation.

	Weight (kg)	Technique	Fentanyl (mcg)	Midazolam (mg)	Ketamine (mg/kg)	Propofol (mg/kg)	Paralytic	Phenylephrine (mcg)
Patient 1	58.2	DL	25	None	0.5	0.5	SCh 60 mg	0
Patient 2	42.8	DL	50	2	0.5	0.5	Roc 25 mg	0
Patient 3	83.3	DL	50	2	0.5	0.5	SCh 100 mg	200
Patient 4	97.8	VL	50	2	1.0*	1.0*	SCh 100 mg	0
Patient 5	72.4	VL	50	2	0.5	0.5	Roc 50 mg	0
Patient 6	81.2	VL	50	2	0.5	0.5	Roc 80 mg	0

DL – direct laryngoscopy; VL – video laryngoscopy; SCh – succinylcholine; Roc – rocuronium. * Two doses of 0.5 mg/kg were required due to two intubation attempts.

Patient characteristics and hemodynamic data are presented in Table 1, while details of intubation, including medication doses, are presented in Table 2.

Patient #1

A 77-year-old male with end-stage primary sclerosing cholangitis status post orthotopic liver transplant and Roux-en-Y choledochojejunostomy was transferred to our ICU for *Pseudomonas* bacteremia and septic shock. He received meropenem, gentamicin, fluconazole, and vancomycin, along with multiple crystalloid boluses and norepinephrine infusion. After a period of initial improvement, he developed hypoxemic respiratory failure, tachycardia, and hypotension, necessitating non-invasive positive pressure ventilation (NIPPV) and increasing vasopressor support. A transesophageal echocardiogram was planned and the patient was electively intubated for the procedure. Norepinephrine dose remained at 0.14 mcg/kg/min prior to, during, and 15 minutes after intubation with no change in MAP.

Patient #2

A 25-year-old male with Noonan syndrome, complex congenital heart disease treated with multiple surgical procedures, and mechanical mitral valve replacement (on chronic warfarin therapy) was admitted with pneumonia and severe sepsis. His blood pressure had stabilized after 5 liters of crystalloid were given prior to ICU admission. NIPPV was initiated for respiratory distress. He was soon noted to be bacteremic with *Streptococcus agalactiae* with a concern for prosthetic valve endocarditis. The patient was electively intubated prior to transesophageal echocardiogram (TEE).

Patient #3

A 63-year-old male with alcoholic cirrhosis was admitted with hematemesis and melena. He was started on octreotide and pantoprazole infusions. The patient was electively intubated prior to esophagogastroduodenoscopy (EGD). The patient received phenylephrine 200 mcg after an initial failed intubation attempt; however, the MAP was >65 mmHg when the dose was delivered.

Patient #4

A 70-year-old male with atrial fibrillation, hypertension, and chronic alcoholism was admitted to an outside hospital with hyponatremia (116 mmol/L) and atrial fibrillation with rapid ventricular rate. On the second day, he was suspected to have pneumonia and was started on levofloxacin. He developed hypoxemic respiratory failure requiring NIPPV and was subsequently transferred to our ICU. The patient required endotracheal intubation due to evolving respiratory failure. Two attempts were required to place the endotracheal tube owing to laryngeal edema and additional doses of ketamine and propofol were given prior to the second attempt.

Patient #5

A 70-year-old male with primary biliary cirrhosis was admitted with massive hematemesis. Due to tachycardia during EGD, the procedure was terminated. The patient was transferred to the ICU and the EGD was performed following elective intubation.

Patient #6

A 61-year-old female with morbid obesity, diabetes mellitus, liver cirrhosis, hepatic encephalopathy, and Mobitz type 2 heart block status after pacemaker placement was transferred to the ICU for aspiration pneumonitis and acute hypoxemic respiratory failure. After failing to respond to NIPPV, she was intubated for acute respiratory distress syndrome and placed on invasive mechanical ventilation.

Discussion

We describe a series of cases where we used a combination of induction agents for endotracheal intubation in critically ill patients. It was intended to generate the hypothesis that the combination of ketamine and propofol was safe and effective for pre-intubation sedation in critically ill patients. Since no prior study has used this combination in ICU patients, our case series fills a void in the existing knowledge on this subject. Our case series demonstrates that, in a wide spectrum of co-morbidities and primary disease processes encountered in ICU patients, the combination of ketamine and propofol was successful in providing adequate sedation for intubation with minimal adverse hemodynamic effects.

Choosing an appropriate and safe induction agent for endotracheal intubation is challenging due to the varying degree of adverse effects of the available medications. In 1 study, hemodynamic collapse occurred in 26% of cases and there was at least 1 severe complication in 27% of patients [1]. Due to its favorable hemodynamic profile, etomidate is an attractive option for providers. However, recent studies have shown that etomidate is associated with increased mortality and adrenal insufficiency in septic patients [6]. In addition, etomidate has been linked to worse 30-day outcomes when used for induction of anesthesia when compared to propofol [8].

Ketamine and propofol combinations are being increasingly used for sedation and analgesia, especially in the emergency department [18,19]. Ketamine has been associated with emergence hallucinations and emesis [20], and with prolonged recovery time when compared to propofol [21–23]. It is associated with increases in systemic vascular resistance (SVR) and HR due to sympathetic stimulation from inhibition of norepinephrine reuptake [13]. Propofol use is limited by respiratory depression and dose-dependent hypotension, presumably caused by decreased SVR and, infrequently, increase in HR from primarily arteriolar vasodilation [24,25]. The combination of ketamine and propofol is a beneficial option due to the counteracting cardiovascular effects of the individual drugs while maintaining adequate sedation.

Typically, hemodynamically unstable patients are given ketamine alone, which may increase the risk of emergence delirium, especially if used as a single agent (typical dose 1–2 mg/kg). Our case series provides proof-of-concept that a ketamine-propofol combination using 0.5 mg/kg of each agent reduces the ketamine-induced delirium as well as propofol-induced hypotension and may be a suitable alternative in these patients. This is evidenced by our findings, which showed that CAM-ICU scores did not worsen after receiving the ketamine-propofol combination. We propose that, by combining 0.5 mg/kg doses of ketamine and propofol, we can successfully limit their adverse effects while providing adequate sedation. Additionally, this combination has no known risk of causing adrenal suppression.

The use of "ketofol" has been studied in the emergency department for procedural sedation [26]. Recent studies demonstrate that the combination is satisfactory for sedation and analgesia, and is associated with less hemodynamic instability and adverse effects [16,26,27]. The combination of ketamine and propofol has also been studied during induction of general anesthesia in the operating room, where it was found to be associated with better hemodynamics when compared to propofol alone [13] or to the combination of propofol and fentanyl [10]. However, at the time of our literature review, no studies on the safety profile of the "ketofol" combination in the ICU setting had been published. The ICU population is significantly different from the operating room population, primarily due to the incidence of sepsis and suspected sepsis and associated reduced systemic vascular resistance, as well as increased circulation of inflammatory mediators. The diagnosis of sepsis has been described as a risk factor for intubation requirement [28], as the single culprit of hypotension in burn patients [29], and as a predictor of mortality if documented during the immediate period prior to intubation [5]. Given the association of sepsis and poor prognosis after orotracheal intubation, combined with the physiological knowledge that sepsis causes decreased SVR, we hypothesize that the combination of ketamine and propofol should be expanded from the ED and operating room to the ICU.

This case series reports on the presentation, events, and hemodynamic outcomes of 6 critically ill patients that received endotracheal intubation using the combination of ketamine and propofol as the induction agent. The patients had different primary diagnoses and circumstances under which intubation took place, but all patients received "ketofol." All patients except patients #3 and #4 were intubated in the first attempt. Of the 6 patients, 4 maintained MAP above 65 mmHg up to 15 minutes post-intubation without the need for vasoactive agents. Patient #4 received phenylephrine 200 mcg for SBP <90 mmHg, although the MAP was >65 mmHg. Patient #1 was on norepinephrine infusion for the management of septic shock before, during, and after intubation, and received the ketamine-propofol combination without requiring dose escalation of norepinephrine. Fluid resuscitation was no different in the 24 hours before and after intubation. On the other hand, only 2 patients received more volume in the 24 hours after intubation compared to the same period before intubation. Upon detailed chart review, we discovered that this volume was not administered for resuscitation due to acute hemodynamic instability in the post-intubation period. Patient #2 was taken to the operating room after intubation, and most of the volume was given during the operation. Patient #6 developed septic

shock several hours after intubation and received crystalloid and colloid resuscitation, and the heart rate was not affected by the use of "ketofol." There was no documentation of recovery agitation in our patients' records. These results are in agreement with the theoretical benefit of preserved hemodynamics and decreased dysphoric emergence phenomena when a combination of ketamine and propofol is used.

Our series is limited by the small number of patients reviewed and the lack of comparison with an alternative induction agent. Although it is standard practice in our ICU to have continuous cardiorespiratory monitoring, pulse oximetry, and blood pressure checks every 2–3 minutes in the peri-intubation period, these vital signs were pulled into the electronic medical record at varying frequencies. Some patients had vital signs pulled at 5-minute intervals, while others had pulls up to 15 minutes apart. We may have potentially missed short-lived hemodynamic changes due to the retrospective nature of the case series. However, any hemodynamically significant drops in blood pressure would have promptly been corrected with intermittent doses of phenylephrine, which we recorded. Additionally, "ketofol" is not used by all providers performing endotracheal intubations in the ICU at our institution, which may introduce selection bias in the patients in this series.

Our case series raises several questions: 1) Would the stable hemodynamics observed in our case series with the use of "ketofol" become apparent in a larger ICU population? 2) How would the ketamine-propofol combination compare with alternatives such as etomidate or ketamine alone? 3) Do these hemodynamic changes, or lack thereof, have any impact on patient outcomes?

Conclusions

We present the first case series to describe the use of ketamine and propofol in critically ill patients as an induction agent for endotracheal intubation. The combination was associated with adequate sedation along with hemodynamic stability for up to 15 minutes following intubation. Our report generates important proof-of-concept data to plan further research, including randomized controlled trials comparing "ketofol" with other induction agents in critically ill patients.

Financial support and disclosure

This work did not receive any funding.

References:

1. Jaber S, Amraoui J, Lefrant JY et al: Clinical practice and risk factors for immediate complications of endotracheal intubation in the intensive care unit: a prospective, multiple-center study. Crit Care Med, 2006; 34: 2355–61
2. Jaber S, Jung B, Corne P et al: An intervention to decrease complications related to endotracheal intubation in the intensive care unit: a prospective, multiple-center study. Intensive Care Med, 2010; 36: 248–55
3. Griesdale DE, Bosma TL, Kurth T et al: Complications of endotracheal intubation in the critically ill. Intensive Care Med, 2008; 34: 1835–42
4. Le Tacon S, Wolter P, Rusterholtz T et al: [Complications of difficult tracheal intubations in a critical care unit]. Ann Fr Anesth Reanim, 2000; 19(10): 719–24 [in French]
5. Schwartz DE, Matthay MA, Cohen NH: Death and other complications of emergency airway management in critically ill adults. A prospective investigation of 297 tracheal intubations. Anesthesiology, 1995; 82: 367–76
6. Chan CM, Mitchell AL, Shorr AF: Etomidate is associated with mortality and adrenal insufficiency in sepsis: a meta-analysis*. Crit Care Med, 2012;40: 2945–53
7. de la Grandville B, Arroyo D, Walder B: Etomidate for critically ill patients. Con: do you really want to weaken the frail? Eur J Anaesthesiol, 2012; 29: 511–14
8. Komatsu R, You J, Mascha EJ et al: Anesthetic induction with etomidate, rather than propofol, is associated with increased 30-day mortality and cardiovascular morbidity after noncardiac surgery. Anesth Analg, 2013; 117: 1329–37
9. Hildreth AN, Mejia VA, Maxwell RA et al: Adrenal suppression following a single dose of etomidate for rapid sequence induction: a prospective randomized study. J Trauma, 2008; 65: 573–79
10. Guit JB, Koning HM, Coster ML et al: Ketamine as analgesic for total intravenous anaesthesia with propofol. Anaesthesia, 1991; 46: 24–27
11. Andolfatto G, Willman E: A prospective case series of single-syringe ketamine-propofol (Ketofol) for emergency department procedural sedation and analgesia in adults. Acad Emerg Med, 2011; 18: 237–45
12. 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
13. Smischney NJ, Beach ML, Loftus RW et al: Ketamine/propofol admixture (ketofol) is associated with improved hemodynamics as an induction agent: a randomized, controlled trial. J Trauma Acute Care Surg, 2012; 73(1): 94–101
14. Goh PK, Chiu CL, Wang CY et al: Randomized double-blind comparison of ketamine-propofol, fentanyl-propofol and propofol-saline on haemodynamics and laryngeal mask airway insertion conditions. Anaesth Intensive Care, 2005; 33: 223–28
15. Miner JR, Gray R, Delavari P et al: Alfentanil for procedural sedation in the emergency department. Ann Emerg Med, 2011; 57: 117–21
16. Nejati A, Moharari RS, Ashraf H et al: Ketamine/propofol versus midazolam/fentanyl for procedural sedation and analgesia in the emergency department: a randomized, prospective, double-blind trial. Acad Emerg Med, 2011; 18: 800–6
17. Hinchcliff M, Just E, Podlusky S et al: Text data extraction for a prospective, research-focused data mart: implementation and validation. BMC Med Inform Decis Mak, 2012; 12: 106
18. Bahn EL, Holt KR: Procedural sedation and analgesia: a review and new concepts. Emerg Med Clin North Am, 2005; 23: 503–17
19. Baker SN, Weant KA: Procedural sedation and analgesia in the emergency department. J Pharm Pract, 2011; 24: 189–95
20. Newton A, Fitton L: Intravenous ketamine for adult procedural sedation in the emergency department: a prospective cohort study. Emerg Med J, 2008; 25: 498–501
21. Saby RC, Mardelle V, Gil C et al: [Ketamine: drug facts, uses in anesthesia, and new applications for analgesia]. Med Trop, 2006; 66: 125–29
22. Granry JC, Dube L, Turroques H, Conreux F: Ketamine: new uses for an old drug. Curr Opin Anaesthesiol, 2000; 13: 299–302
23. White PF, Way WL, Trevor AJ: Ketamine – its pharmacology and therapeutic uses. Anesthesiology, 1982; 56: 119–36
24. Claeys MA, Gepts E, Camu F: Haemodynamic changes during anaesthesia induced and maintained with propofol. Br J Anaesth, 1988; 60: 3–9

25. Hug CC Jr, McLeskey CH, Nahrwold ML et al: Hemodynamic effects of propofol: data from over 25,000 patients. Anesth Analg, 1993; 77: S21–29
26. Arora S: Combining ketamine and propofol ("ketofol") for emergency department procedural sedation and analgesia: a review. West J Emerg Med, 2008; 9: 20–23
27. Andolfatto G, Abu-Laban RB, Zed PJ et al: Ketamine-propofol combination (ketofol) versus propofol alone for emergency department procedural sedation and analgesia: a randomized double-blind trial. Ann Emerg Med, 2012; 59: 504–12.e1–2
28. Braune SA, Wichmann D, von Heinz MC et al: Clinical features of critically ill patients with Shiga toxin-induced hemolytic uremic syndrome. Crit Care Med, 2013; 41: 1702–10
29. Dennis CJ, Chung KK, Holland SR et al: Risk factors for hypotension in urgently intubated burn patients. Burns, 2012; 38: 1181–85