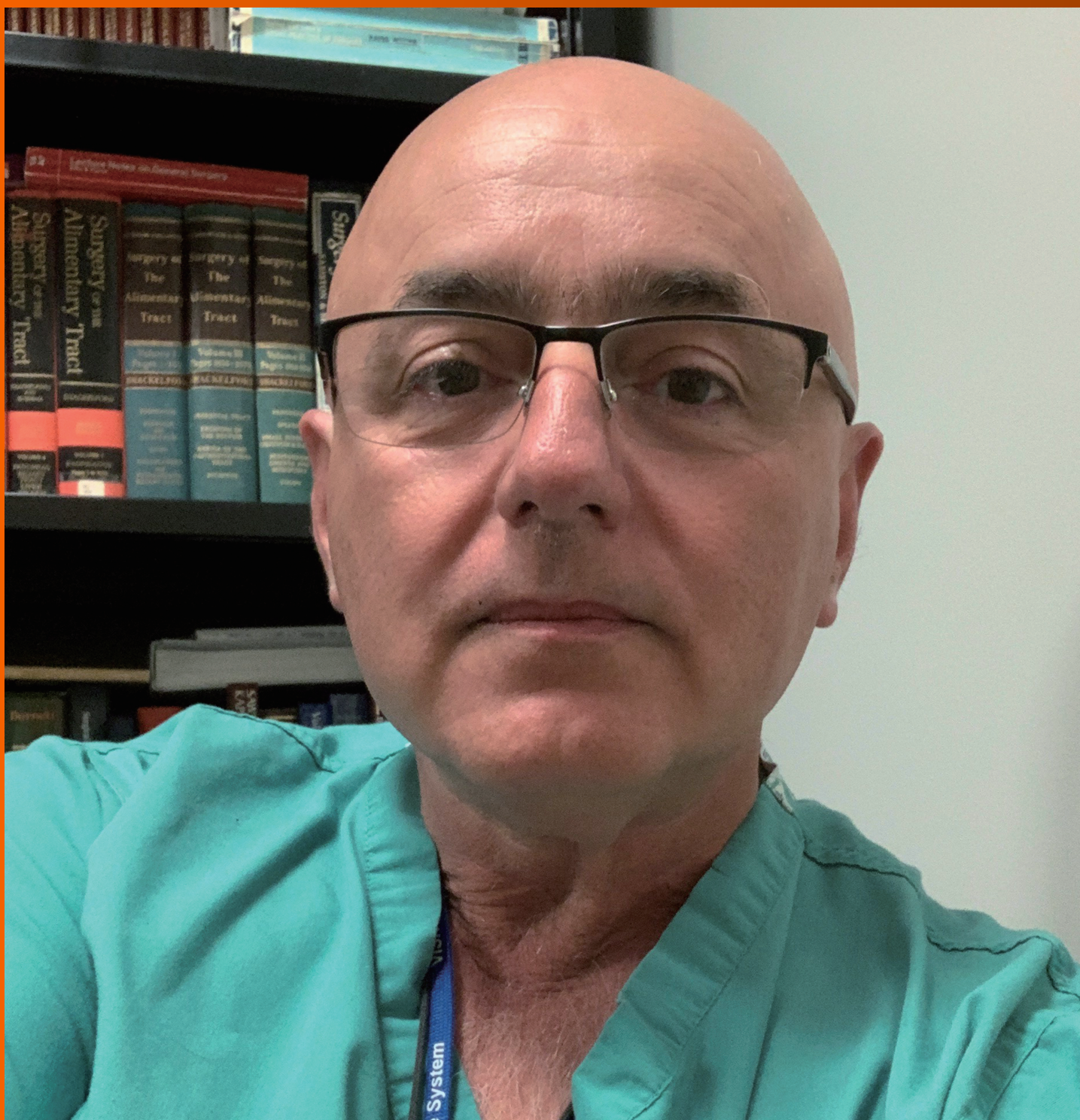


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# Endotracheal intubation sedation in the intensive care unit

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## Abstract

Endotracheal intubation is one of the most common, yet most dangerous procedure performed in the intensive care unit (ICU). Complications of ICU intubations include severe hypotension, hypoxemia, and cardiac arrest. Multiple observational studies have evaluated risk factors associated with these complications. Among the risk factors identified, the choice of sedative agents administered, a modifiable risk factor, has been reported to affect these complications (hypotension). Propofol, etomidate, and ketamine or in combination with benzodiazepines and opioids are commonly used sedative agents administered for endotracheal intubation. Propofol demonstrates rapid onset and offset, however, has drawbacks of profound vasodilation and associated cardiac depression. Etomidate is commonly used in the critically ill population. However, it is known to cause reversible inhibition of 11  $\beta$ -hydroxylase which suppresses the adrenal production of cortisol for at least 24 h. This added organ impairment with the use of etomidate has been a potential contributing factor for the associated increased morbidity and mortality observed with its use. Ketamine is known to provide analgesia with sedation and has minimal respiratory and cardiovascular effects. However, its use can lead to tachycardia and hypertension which may be deleterious in a patient with heart disease or cause unpleasant hallucinations. Moreover, unlike propofol or etomidate, ketamine requires organ dependent elimination by the liver and kidney which may be problematic in the critically ill. Lately, a combination of ketamine and propofol, "Ketofol", has been increasingly used as it provides a balancing effect on hemodynamics without any of the side effects known to be associated with the parent drugs. Furthermore, the doses of both drugs are reduced. In situations where a difficult airway is anticipated, awake intubation with the help of a fiberoptic scope or video laryngoscope is considered. Dexmedetomidine is a commonly used sedative agent for these procedures.

**Key Words:** Critically ill; Endotracheal intubation; Etomidate; Hypotension; Intensive care



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**Core Tip:** Intensive care unit endotracheal intubations are associated with a higher risk of complications such as hypotension, hypoxemia, and cardiac arrest when compared to non-intensive care unit endotracheal intubations. A necessity of endotracheal intubations, sedation, is a modifiable risk factor in the pathway to cardiovascular instability. The goal of this review is to present the pros and cons of each sedative agent used for endotracheal intubation while comparing the outcomes. This will help the reader to make an informed decision when choosing a sedative agent for endotracheal intubation in the intensive care unit.

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## INTRODUCTION

Endotracheal intubations are one of the most common, yet most dangerous procedures performed in the intensive care unit (ICU). Complications from ICU endotracheal intubations are seen in approximately 40%-45% of patients and include severe hypotension (10%-43%), severe hypoxemia (9%-25%), and cardiac arrest (2%-3%) [1]. Severe cardiovascular collapse is one of the most common complications after ICU endotracheal intubation [2]. Understandably, identification of risk factors for cardiovascular collapse surrounding endotracheal intubation becomes extremely imperative to mitigate or avoid this devastating complication. In a multicenter observational study, Perbet *et al* [2] identified patient risk factors for cardiovascular collapse which included advanced patient age, higher sequential organ failure assessment score, acute respiratory failure, brain injury, trauma, and chronic obstructive pulmonary disease. Procedural risk factors included multiple intubations, use of propofol for induction, and desaturation during intubation [2]. Recently, a multicenter observational prospective study derived and validated a hypotension prediction score for patients undergoing endotracheal intubation in the ICU. The investigators identified 11 variables (increasing illness severity; increasing age; sepsis diagnosis; endotracheal intubation in the setting of cardiac arrest, mean arterial pressure < 65 mmHg, and acute respiratory failure; diuretic use 24 h preceding endotracheal intubation; decreasing systolic blood pressure from 130 mmHg; catecholamine or phenylephrine use immediately prior to endotracheal intubation; and use of etomidate during endotracheal intubation) that were independently associated with peri-intubation hypotension with a C-statistic of 0.75 [95% confidence interval (CI): 0.72-0.78]. Of the 11 variables, the use of etomidate was found to protect against peri-intubation hypotension [3].

Incidence of adverse events like death or hypoxic brain damage are higher with intubations done in ICUs compared to those performed in the operating rooms [4]. In contrast to the ICU, endotracheal intubations in the operating room are frequently performed in a controlled fashion under non-emergent conditions. Although patients may have numerous comorbidities, personnel are specifically trained in airway management, and due to the elective nature of surgical procedures, preparations can be made for difficulties encountered [5,6].

Thus, based on the above evidence, preparation and planning for endotracheal intubations is paramount in critically ill patients to avoid life-threatening complications. An element of endotracheal intubation that is modifiable is the choice of sedative agents administered, which as the evidence suggests, may alter ICU complications, in particular, severe hypotension.

## ICU SEDATION AGENTS

### **Propofol**

Propofol is currently the most common anesthetic induction agent used worldwide. Its rapid onset and short duration of action is ideally suited to settings such as the ICU. Propofol's sedative effects are mediated through gamma aminobutyric acid receptors with some activity on N-methyl-D-aspartate receptors. Termination of action of propofol is by redistribution and is independent of organ elimination, thereby making it very useful in ICU patients who may have organ impairment. Standard induction doses of propofol in a healthy adult are 2-2.5mg/kg[7]. However, dosing in the ICU is dramatically different due to the nature of the patient population with patients usually requiring endotracheal intubation for acute respiratory failure or cardiovascular collapse as illustrated recently[1]. In fact, propofol has been shown to have increased potency in shock states indicating less is more[8]. This finding demonstrates the profound vasodilatory effects and associated cardiac depression of propofol[7]. For the healthy patient, this is well tolerated but in patients who are in septic or cardiogenic shock, this attribute can have a detrimental effect on patient hemodynamics. Hence, caution is warranted when using propofol in the critically ill population. A recent study evaluating intubation practices in critically ill patients from 29 countries showed that propofol is the most used sedative and was significantly associated with hemodynamic instability in 63.7% of patients who exhibited precarious hemodynamics, as compared to etomidate with only 49.5% of patients developing hemodynamic instability[1]. Another study performed at the Long Island Jewish Medical center looked at safety of propofol in urgent endotracheal intubations in the medical ICU[9]. Propofol was the sole sedative agent used in 87% of the patients, in 4% it was combined with other agents like benzodiazepines and in the remaining 9%, other sedative agents were used. Interestingly, only 4% of the patients in which propofol was used developed hypotension. This may be explained by the observation that patients were pre-emptively administered vasoactive agents along with propofol to maintain a targeted perfusion pressure. Despite the hemodynamic decompensation known to be associated with propofol, it remains an ideal induction agent in the ICU because of its rapid onset, short duration of action, minimal drug interactions, and organ independent elimination likely explaining its frequent use in the critically ill.

### **Ketamine**

Ketamine is an anesthetic agent which causes complete anesthesia while providing analgesia at the same time. In addition, it causes less respiratory depression and has hemodynamic effects that are opposite that of propofol[7]. This property makes it a desired drug in multiple settings. It is a phencyclidine derivative which acts on the N-methyl-D-aspartate receptor[10,11]. The standard induction dose of ketamine is 1-2 mg/kg. Ketamine's hemodynamic effects are mediated through central nervous system stimulation and inhibition of catecholamine reuptake. However, it is also a known direct myocardial depressant. Thus, in severely ill patients such as the patient in septic shock who is depleted of catecholamines, the direct myocardial depressant effects can be unmasked[7,12]. In addition, ketamine may cause increased intracranial pressure through increased cerebral perfusion thereby limiting its use in trauma patients[13]. Lastly, ketamine is known to induce salivation which can be problematic in airway management in the setting of difficult airways where visualization of the airway is paramount[7]. Although medications such as atropine or glycopyrrolate can be administered to help reduce this effect, these medications may alter the patient's hemodynamics which may not be desirable. When compared to etomidate in the setting of rapid sequence intubation for trauma patients, no significant difference was observed for peri-intubation outcomes such as first pass intubation success, need for rescue surgical airway, and peri-intubation cardiac arrest. However, ketamine was associated with lower odds of hospital acquired sepsis [adjusted odds ratio [OR] 0.72, 95%CI: 0.52-0.99] but higher number of days on vasopressor therapy (adjusted OR 0.74 95%CI: 0.58-0.95)[14]. Another trial which compared these two agents was the Ketased trial which failed to show any difference in immediate post-intubation complications, catecholamine free days at day 28, or 28-d mortality[15].

### **Etomidate**

Etomidate is an anesthetic induction agent commonly used because of its ability to maintain stable hemodynamics. Etomidate causes sedation by its agonistic action on gamma aminobutyric acid receptors and it is thought to maintain hemodynamics through simultaneous stimulation of  $\alpha$ -2b adrenoreceptors[16]. In addition to this,

etomidate also reversibly inhibits 11 $\beta$ -hydroxylase and therefore suppresses the adrenal production of cortisol for at least 24 h after a single induction dose[17]. This specific adverse effect is a major reason that causes many intensivists to shy away from using etomidate in the critically ill. Furthermore, the use of etomidate for endotracheal intubation in septic patients has been associated with increased mortality and poor outcomes[18-20]. Moreover, this trend has been seen in surgical patients[21]. For example, a study at Cleveland Clinic in non-cardiac surgery patients showed that patients who received etomidate had a 2.5 (98% CI: 1.9-3.4) higher odds of dying than those who received propofol anesthesia. In addition, patients who received etomidate had a prolonged hospital stay without a significant difference in intraoperative vasopressor requirements[21]. A recent meta-analysis that included 29 trials totaling 8584 patients comparing etomidate with other induction agents demonstrated that etomidate was associated with adrenal insufficiency [risk ratio (RR) = 1.54, 95% CI: 1.42, 1.67,  $P < 0.001$ ] and increased overall relative mortality rates (RR = 1.09, 95% CI: 1.04, 1.16,  $P = 0.001$ ). However, on meta-regression, the increased mortality was associated with increasing severity of disease[22]. Hence, the association between etomidate and increased mortality should be interpreted with caution. It is likely that etomidate does lead to additional organ dysfunction, through adrenal suppression, in the critically ill resulting in possibly increased morbidity and mortality.

In the past, high doses of benzodiazepines and opioids were used for sedation during endotracheal intubation. However, with the association of benzodiazepines and increased delirium combined with the awareness to maintain lighter sedation levels, these practices have decreased[23,24].

### ***Ketamine-Propofol Admixture (“Ketofol”)***

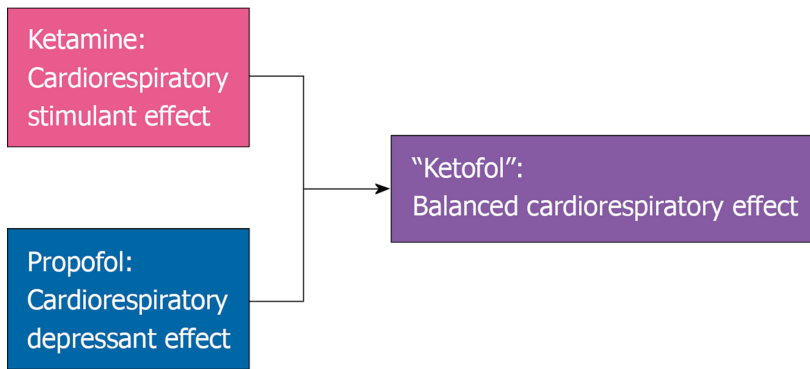
Lately, a combination of two sedatives, namely ketamine and propofol (“Ketofol”), has demonstrated efficacy in terms of hemodynamic preservation when sedating for airway management. This is supported by two randomized controlled trials in which “Ketofol” was compared to propofol only and to half-dose etomidate. In addition to the hemodynamic stability offered by “Ketofol”, both trials also suggested that “Ketofol” reduced opioid requirements as compared to the competitor[25,26]. In one trial, “Ketofol” was associated with reduced transfusion requirements as compared to etomidate due to cortisol’s role in maintaining vascular homeostasis (inhibited by etomidate)[26]. Other systemic reviews and meta-analyses have suggested that “Ketofol” is associated with less respiratory events than propofol alone[27,28]. Thus, this unique drug combination has the ability to cause less hemodynamic alterations than either parent compound while providing non-opioid pain control, which may translate into improved metrics such as reduction in post-intubation hypotension and therefore, morbidity and mortality.

### ***Clinical implications of “Ketofol”***

An ideal anesthetic is one that has a balanced effect on the cardiopulmonary system while providing hypnosis and analgesia[7]. The “Ketofol” admixture possesses these qualities and as such, its use is applicable to a variety of patient care settings. The rationale behind the drug combination is to provide an admixture that when used together, attenuates blood pressure swings and provides a smooth blood pressure profile during endotracheal intubation and beyond (Figure 1). Although this depends on dosing used for both individual medications, most of the evidence points to a stabilizing effect on blood pressure. This stabilization has the potential to translate into direct and indirect benefits to patients across multiple hospital settings (e.g., emergency room, ICU, operating room, procedural suites) throughout the world. For example, the admixture may offer neuroprotection *via* maintenance of cerebral perfusion through mean arterial pressure, which may reduce post-ICU psychological phenomena (e.g., cognitive dysfunction, depression, *etc.*) in long-term critical care survivors as well as delirium in surgical patients through reduction of benzodiazepines. Moreover, maintenance of hemodynamics in these settings has the potential to translate into reduced rates of adverse cardiac events, acute kidney injury, and mortality. This is of major significance as propofol is the most common anesthetic in use today[29]. Equally important is the ability to limit opioid medications with this admixture due to the properties of ketamine[7]. Every day, more than 130 people in the United States die after overdosing on opioids resulting in an economic burden of 78.5 billion dollar/year[30]. Thus, the admixture may result in reduced exposure to opioid medications by providing a non-opioid alternative to patients needing sedation in multiple locations (e.g., pre-hospital, emergency room, ICU, operating room). This initiative aligns with the United States Health Human Services’ opioid crisis strategy [30]. Thus, the “Ketofol” admixture offers the advantage of stable hemodynamics that



## Concept behind the drug mixture



**Figure 1 Ketofol concept.** In addition, this drug mixture provides hypnosis and analgesia (closest to an ideal anesthetic agent).

is similar to etomidate with non-opioid pain control and minimal, if any, ill effects on patients over ketamine, propofol, or etomidate.

### Muscle relaxants

Use of muscle relaxants also varies for endotracheal intubations in the ICU. An observational study comparing outcomes of intubation with or without the use of muscle relaxants failed to show any significant difference in post intubation complications, however, it did show that excellent intubation conditions were achieved in patients in which muscle relaxants were used[31]. Another observational study showed higher first attempt success rate when neuromuscular blockers were used (80.9% *vs* 69.6%,  $P = 0.003$ )[32].

### Special occasions

There are many unique occasions which affect the choice of sedatives in the ICU other than those mentioned above. Cardiac arrest is one such occasion. Typically, no drugs are administered during the intubation. For difficult airways, sedatives may be chosen that provide quick onset and offset or have specific reversal agents associated with their use. Burns, angioedema, and superior vena cava syndrome are some examples when awake fiberoptic intubation might be preferred over routine intubation. In addition, another setting in which sedatives are altered from the usual intubation practice include awake video laryngoscopy, which has been increasingly used to avoid a lost airway or spontaneous respirations[33]. Dexmedetomidine has been used during these situations, along with topical anesthesia, due to its anxiolytic effect with minimal adverse effects on spontaneous respirations[34].

## CONCLUSION

Endotracheal intubation is a common procedure, yet can be associated with devastating complications, namely hypoxemia and cardiovascular collapse, that increase when conducted outside a controlled setting such as the operating room. Sedation is frequently administered to facilitate this procedure. However, sedation can sometimes exacerbate these complications, especially relevant when endotracheal intubation is carried out in an urgent/emergent context (*e.g.*, ICU, emergency department, *etc.*). Several sedatives are available to facilitate airway management. Each has its own drawbacks as discussed above which the clinician needs to take into consideration when performing this procedure. As an alternative to the individual sedatives, a combination of sedatives may be needed to achieve the desired outcome such as “Ketofol” in which available evidence suggests a hemodynamic sparing effect with reduced opioid requirements.

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