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Editorial

Patient Safety Matters with Use of Propofol in Critically Ill Patients

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Received: 1 November 2025; Revised: 3 November 2025; Accepted: 13 November 2025; Available online: 19 November 2025

ABSTRACT: Despite its tendency to produce hypotension, propofol is used widely to induce general anesthesia and to facilitate endotracheal intubation in critically ill patients. Both dose reduction and routine co-administration of vasopressors have been used to offset this unfavorable hemodynamic effect in this subset of individuals. There are potential problems associated with each of these corrective measures, however, and criticism of other intravenous hypnotics used for this purpose—particularly etomidate—may be unwarranted. Choice of the appropriate pharmacology to induce anesthesia to assist with intubation should likely be based on individual clinical assessment, together with an understanding of the drug profile and realistic adverse effects.

Keywords: Patient safety; Intubation; Hypotension; Dose-reduced propofol; Etomidate

It is relatively common to intubate critically ill patients in the intensive care unit (ICU), the emergency room, and the operating room. The most common drug employed internationally to facilitate this intervention is propofol [1], despite having dose-related properties that can cause hypotension [2–5]. This intravenous hypnotic is also routinely used to induce anesthesia, often without intubation, for the performance of transesophageal echocardiography and/or cardioversion in patients with low cardiac output and borderline hemodynamics. Advocates of this technique point to the excellent intubating conditions provided by propofol alone (without muscle relaxation), to the drug's relative safety due to appropriate dose reduction and/or co-treatment with a vasopressor, to propofol's rapid onset of hypnosis, and to its widespread usage and reliability [6,7]. Furthermore, the argument runs, other drugs potentially useful for this purpose have adverse effects that make them poor choices [7]. Is this correct?

Peri-intubation cardiovascular (CV) instability represents an independent predictor of mortality in the critically ill population [8], and propofol reproducibly decreases cardiac output (CO) and systemic vascular resistance (SVR) and thereby produces hypotension [4]. Patients most susceptible to such hypotension are those with minimal CV reserve, often encountered in this setting [2,3], who may or may not already be on some degree of vasopressor support at the time of induction. Propofol dose reduction minimizes but does not eliminate these hemodynamic perturbations [2,3], and the adage that "a little bit of poison is still poison" probably applies. Indeed, co-administration of a vasopressor is a relatively common technique to reduce these adverse effects [7].

Recently, this practice of vasopressor co-delivery with propofol during intubation of critically ill patients has been criticized [7]. Specifically, these pharmacologic agents (including phenylephrine, ephedrine, norepinephrine, and epinephrine) have adverse physiologic effects that are unnecessary. Also, the degree of dose reduction of propofol with extremely frail patients is often inadequate [7] and pits incomplete hypnosis and potential recall against adverse hemodynamics. Indeed, this concern may explain why dose reduction of propofol is often less than needed to avoid hypotension and organ compromise. Interestingly, in a randomized prospective (unblinded) study of 100 patients with mixed cardiovascular reserve, use of processed electroencephalographic (EEG) monitoring during propofol induction decreased the likelihood of vasopressor administration, although dosing of propofol was not significantly different with EEG use—suggesting that providers who were not aware of EEG findings were more likely to administer preemptive vasopressors [9].

https://doi.org/10.70322/cvs.2025.10013

Propofol, however, has a clinically indispensable application due to its rapid onset and offset of action, as well as its smooth induction of general anesthesia, particularly in relatively healthy ASA I and II patients. Other intravenous hypnotic agents are available for critically ill patients that have little or no adverse hemodynamic effect under most circumstances when used in isolation, namely etomidate and ketamine. Like propofol, the onset (within one circulation time) and offset (a few minutes) of an intravenous sleep dose of etomidate are rapid, and termination of action is via redistribution out of the brain (also similar to propofol). However, etomidate has a consistently favorable hemodynamic profile in critically ill cardiac patients and therefore often represents the induction agent of choice in low CO states [10]. This profile most likely derives from the drug's stimulation of alpha-2B adrenergic receptors, resulting in an increase in SVR (unlike propofol), which combined with its minimal effects on myocardial contractility (also unlike propofol), preload, and heart rate, avoids hypotension with hypnosis [10]. Its effect on SVR makes etomidate particularly useful in patients with congestive heart failure who are dependent on elevated sympathetic tone and often receive angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers that make them prone to postinduction hypotension [10]. Etomidate is also an ideal induction agent for patients with significant aortic or mitral stenosis or hypertrophic cardiomyopathy, where maintenance of preload and preservation or even an increase in afterload is desired [10].

A number of studies (including randomized controlled trials) have compared etomidate and ketamine as induction agents in critically ill patients [11–13]. A review of seven of these endeavors concluded that the two drugs were associated with similar mortality at the longest available follow-up as well as statistically indistinguishable secondary outcomes [12]. On a Bayesian random-effects meta-analysis and based on a sensitivity analysis for mortality using a frequentist approach that also used a random-effects model, etomidate and ketamine appeared to be clinically equivalent. Although a recent analysis comparing the drug profiles of induction agents concluded that ketamine (rather than etomidate) may represent the preferred pharmacologic choice for patients with hemodynamic instability, this conclusion relates to data showing a transient reduction in adrenal function with long-term (days) of ICU use rather than any increased morbidity/mortality associated with its single dose administration in the setting of airway instrumentation [4,14,15]. Furthermore, ketamine has a direct negative ionotropic effect that may be unmasked when catecholamine stores are depleted in shock [16]. For example, this is true of patients presenting with severe cardiac tamponade who often have maximum levels of circulating catecholamines, and in these patients, ketamine induction may result in hypotension due to these direct effects [16,17]. In addition, a need to use an antisialagogue with its potential untoward anticholinergic effects, and emergence delirium represent other potential problems for ketamine in this context.

On the other hand, it is important to recall that most anesthesia and critical care providers have widespread experience with propofol, and this experience is undoubtedly beneficial when caring for critically ill patients. The choice of induction agents for the hemodynamically compromised patient may depend on individual circumstances and may not be arbitrarily defined [10]. For example, a mixture of propofol and ketamine ("ketofol") may minimize the hemodynamic instability associated with propofol, and a randomized trial comparing ketofol with etomidate for emergency tracheal intubation in 163 patients found no difference in postintubation outcomes [4,12].

Regardless, under many circumstances with critically ill patients, dose reduced propofol with or without a vasopressor is usually not the first choice to induce general anesthesia and/or facilitate endotracheal intubation. Etomidate or ketamine have pharmacologic and clinical characteristics that may make them superior selections for this purpose. In addition, the use of a hemodynamically more benign, dose-reduced quantity of propofol is complicated by a potential lack of adequate hypnosis and recall, and may necessitate the co-administration of amnestic agents and/or vasoactive support, which is often physiologically problematic. Even though propofol represents the most common induction agent, it often may not represent the best single agent for such intervention in a patient with significantly limited cardiovascular reserve, even in a dose reduced quantity. Etomidate or ketamine may represent pharmacodynamically better choices.

Author Contributions

B.S.: Conceptualization; Formal analysis; Project administration; Visualization; Writing—original draft; Writing—review and editing.

Ethics Statement

Not applicable.

Informed Consent Statement

Not applicable.

Data Availability Statement

Not applicable.

Funding

This research received no external funding.

Declaration of Competing Interest

The author declares that he has no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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