



Ketamine versus etomidate for rapid sequence induction: current data in emergency medicine and critical care

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Abstract

To evaluate current clinical evidence comparing ketamine and etomidate in rapid sequence induction (RSI) and critical care, focusing on survival, haemodynamic stability and endocrine complications. Etomidate provides immediate haemodynamic stability, but its use in critically ill patients is associated with systematic adrenal suppression and, in some cohorts, increased hospital mortality. Ketamine does not appear to increase the risk of post-intubation hypotension compared to etomidate when the shock index is taken into account and offers a protective advantage against long-term post-traumatic stress. In paediatrics, both agents have a comparable safety profile. Although intubation success rates are similar, ketamine is the agent of choice for sepsis and trauma due to its endocrine safety, while etomidate remains an option for neurosurgery subject to careful selection.

Keywords:

Ketamine, etomidate, anaesthesia, critical care, adrenal suppression, mortality, Haemodynamic instability.

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1. Introduction

Rapid sequence intubation (RSI) is a highly critical procedure in which the choice of induction agent directly impacts the patient's immediate and long-term prognosis [1]. Historically, etomidate has been preferred for its cardiovascular stability and neuroprotective effect [2, 3]. However, its inhibition of cortisol synthesis raises major concerns about the survival of the most fragile patients [4, 5].

At the same time, ketamine has emerged as a robust alternative, offering dissociative sedation and haemodynamic stability through its sympathomimetic effects [3, 6]. Recent data even suggest that ketamine may reduce post-traumatic stress symptoms at 12 months [7]. However, the debate continues: some studies report more marked haemodynamic instability with ketamine in trauma patients [8, 9], while others find no significant difference in post-induction hypotension compared to etomidate [10, 11].

The current issue is no longer just the technical success of the procedure, for which the two molecules are equivalent [12, 13], but the impact on overall mortality [14, 15]. While some meta-analyses show no difference in 28-day survival [16, 17], signs of excess mortality associated with etomidate in critical care necessitate a reassessment of practices [15]. This narrative review aims to synthesise data from recent sources to clarify the choice of agent according to clinical profile, from septic shock to paediatric and geriatric contexts.

2. Ketamine versus etomidate in emergency medicine and intensive care

The choice of induction agent for rapid sequence intubation (RSI) remains a major topic of debate, particularly in unstable patients. Etomidate and ketamine are the two most commonly used molecules due to their respective pharmacodynamic profiles.

2.1. Intubation performance and first-pass success

One of the key criteria during an ISR is the first-pass success rate in order to minimise hypoxic complications. According to a retrospective study conducted at a level 1 trauma centre in Korea, there is no significant difference between ketamine and etomidate in terms of first-pass success rate in trauma patients [8]. This observation is confirmed by a recent meta-analysis, which shows no superiority of either agent on this specific criterion [12].

2.2. Haemodynamic stability and cardiovascular profile

The haemodynamic response to induction is often the decisive factor in the choice of agent, although data sometimes differ depending on the clinical context. In the context of helicopter emergency medical services (HEMS), ketamine significantly improves systolic blood pressure in patients who are initially hypotensive [18]. Conversely, some data suggest that ketamine is associated with more marked haemodynamic instability than etomidate in trauma patients undergoing emergency intubation [8]. A meta-analysis also highlights that etomidate significantly reduces the risk of post-induction hypotension compared to ketamine [12]. However, in multicentre cohorts, although ketamine causes greater immediate haemodynamic instability after intubation, the long-term consequences differ [19]. A multicentre randomised trial also noted that ketamine is associated with a higher frequency of per-intubation cardiovascular collapse in critically ill adults [9].

However, the use of drug combinations appears to modulate these effects:

- ✓ The combination of ketamine, midazolam and sufentanil ensures better haemodynamic stability during and after laryngoscopy compared to the combination of etomidate and sufentanil [20].
- ✓ In patients aged 65 years and older, the combination of ketamine and propofol (Ketofol) provides better blood pressure and heart rate stability than etomidate alone [21].

2.3. Impact on mortality and clinical outcomes

The issue of long-term safety, particularly due to the adrenal suppression induced by etomidate, is a major concern. A study of critically ill patients on ventilation in intensive care reports that the use of etomidate is associated with a significant increase in hospital mortality compared to ketamine [22]. This increased risk of mortality in critically ill patients receiving etomidate is confirmed by other studies independent of corticosteroid administration [23]. In a multicentre emergency department cohort, etomidate was associated with higher 7- and 28-day hospital mortality than ketamine [19]. Conversely, other randomised clinical trials have found no significant difference in 30-day mortality between the two agents in critically ill patients [16]. A specific multicentre randomised trial also failed to demonstrate a reduction in 28-day mortality with ketamine compared to etomidate [9]. Similarly, for patients with severe head trauma in the prehospital phase, the choice between etomidate and ketamine does not influence 30-day mortality [24].

2.4. Morbidity and organ failure assessment

Beyond survival, the impact on overall recovery is essential. No significant difference has been demonstrated between ketamine and etomidate in terms of the maximum SOFA score in intensive care patients [16]. Identical results for the maximum SOFA score were reported in randomised clinical trials comparing the two molecules [25]. In trauma patients, the length of hospital stays and duration of mechanical ventilation did not differ depending on the agent used [8].

2.5. Specific applications and side effects

Each agent has advantages in specific clinical niches or requires adjustments to limit its adverse effects. Etomidate is still considered an effective and stable agent in emergency medicine, with a limited clinical impact of its adrenal suppression according to some systematic reviews [4]. To reduce the myoclonus frequently induced by etomidate, pretreatment with a low dose of ketamine (0.15 mg/kg) has been shown to be effective without altering haemodynamic stability [26]. In complex paediatric cases, particularly in children with asthma and allergies, etomidate combined with ketamine provides effective and stable induction [27]. For orthopaedic reductions in emergency departments, ketamine is a safe option that causes fewer respiratory events than etomidate [28]. Finally, a consensus of experts recommends the expanded and cautious use of ketamine in intensive care for its sedative and analgesic properties, particularly in the context of sepsis or neuro-resuscitation [29].

3. Paradigm shifts: survival, mental health and specific surgical contexts

Beyond immediate haemodynamics, research is shifting towards more comprehensive endpoints, including long-term survival, psychological sequelae, and protocol optimisation through combinations of agents.

3.1. Survival dynamics and critical pathologies

The impact of the induction agent on mortality appears to fluctuate depending on the time window observed. A randomised study on emergency intubation shows that ketamine is associated with better 7-day survival compared to etomidate [17]. However, this difference diminishes over time, with no significant difference observed in 28-day survival in the same population [17]. This finding is supported by a meta-analysis of randomised controlled trials, which reveals no difference in 28-day mortality between the two molecules [13]. In septic patients, etomidate does not appear to increase mortality (at 24 hours, 7 days or 28 days) compared to ketamine, although it is associated with more frequent use of vasopressors and corticosteroids [30]. Similarly, during the COVID-19 pandemic, the use of etomidate for emergency intubation was not associated with an increase in short-term morbidity or mortality [31]. Nevertheless, some data suggest that etomidate may be linked to higher hospital mortality in specific cohorts, possibly due to the adrenal suppression it induces [32].

3.2. Psychological impact and quality of awakening

One innovative aspect of the research concerns the long-term effects on the mental health of patients who have undergone emergency intubation. Induction with ketamine is associated with a significant reduction in post-traumatic stress disorder (PTSD) symptoms at 12 months compared to the use of etomidate [7]. In procedural sedation in the emergency department, although the two agents are comparably effective, patients receiving etomidate report more frequent intra-procedural awakenings and painful memories [33].

3.3. Stability in specialised surgery and neurosurgery

The choice of agent must also be dictated by the specific requirements of the surgical procedure. In cataract surgery, dexmedetomidine offers deeper sedation and greater patient satisfaction than ketamine or etomidate, although it does prolong recovery time [34]. For patients with cyanotic congenital heart disease, ketamine and etomidate (alone or in combination) are particularly suitable as they preserve systemic vascular resistance and pulmonary blood flow [35]. In neurosurgery (craniotomies for supratentorial tumours), research is comparing the impact of the ketamine-propofol mixture with that of etomidate on cerebral blood flow and oxygenation in order to identify the most stable agent [36]. Etomidate remains the preferred choice for its neuroprotection and cardiovascular stability, despite its lack of intrinsic analgesic properties and transient adrenal suppression [2].

3.4. Synergies and drug combinations (ketofol vs etofol)

The use of combinations often compensates for the adverse effects of each molecule taken individually. During laparoscopic sterilisation procedures, the combination of ketamine and propofol (ketofol) and the combination of etomidate and propofol (etofol) offer equivalent conditions for laryngeal mask insertion (LMA Supreme) and haemodynamic stability [37]. Similarly, in patients undergoing emergency surgery for peritonitis, the combinations of propofol-ketamine and etomidate-ketamine effectively maintain cardiovascular stability in a similar manner [38].

4. Deepening safety profiles: pathophysiology, emerging toxicity, and specialized applications

While initial debates focused on overall survival, current research is refining indications based on the patient's underlying physiological condition and exploring previously unknown complications.

4.1. Reassessment of the risk of post-intubation hypotension

Contrary to certain preconceptions, the superiority of etomidate in terms of immediate blood pressure stability is called into question by contextual data. In patients undergoing emergency intubation, ketamine is not associated with an increased risk of post-intubation hypotension compared to etomidate [10]. The major predictor of collapse after induction is not the agent chosen, but a high pre-intubation shock index [10]. A systematic review confirms that there is no significant difference between the two molecules in terms of days without vasopressors or overall haemodynamic stability in critical patients [11].

4.2. Endocrine risks and emerging toxicology

Adrenal suppression induced by etomidate remains its main vulnerability, with sometimes serious consequences. One clinical case documents a severe adrenal crisis with haemodynamic collapse triggered by a single dose of etomidate in a patient with pre-existing adrenal insufficiency, highlighting a critical risk in this population [39]. More unusually, a new form of abuse has emerged among adolescents: inhalation of etomidate via electronic cigarettes ('space oil'), leading to cases of prolonged adrenal insufficiency requiring hydrocortisone replacement [40]. During coronary artery bypass grafting (CABG) surgery, although etomidate ensures haemodynamic stability, it causes a significant decrease in perioperative cortisol levels [41]. Conversely, the combination of ketamine and propofol (ketofol) shows a more marked and physiological cortisol response in this context [42].

4.3. Paediatric specificities and cardiac surgery

The safety profile in children appears to be more consistent than in adults. A retrospective study of children undergoing emergency intubation shows that a single dose of etomidate does not increase the risk of adrenal insufficiency or mortality compared to ketamine [43]. In cardiac surgery (CABG), ketamine-midazolam and etomidate-midazolam combinations offer comparable haemodynamic stability [41]. For the induction of ketofol or etomidate in coronary patients, both strategies provide satisfactory stability, confirming the versatility of these agents [42].

4.4. Neuroplasticity and interventional psychiatry

The use of these agents in electroconvulsive therapy (ECT) for treatment-resistant depression opens up interesting therapeutic prospects. The combination of ketamine and etomidate during ECT sessions not only improves haemodynamic stability, but also increases neuroplasticity biomarkers (BDNF, NGF) and cognitive function in patients compared to etomidate alone [44]. Furthermore, ketofol and etomidate are considered superior to propofol or thiopental for ECT because they better preserve the quality and duration of seizures, a key factor in the effectiveness of treatment [45].

4.5. Side effects and optimisation of induction

The management of adverse effects remains an active area of research. Experimentally, ketamine induces nausea/vomiting-type behaviours (pica model) via the activation of D2 dopaminergic and 5-HT3 serotonergic receptors in the area postrema [46]. To mitigate etomidate-induced myoclonus, pretreatment with a low dose of ketamine (0.1 mg/kg) significantly reduces its incidence without compromising haemodynamics [47]. Despite its advantages, etomidate remains criticised for its persistent effects (pain, myoclonus, adrenal suppression), leading some authors to call for the development of new, safer derivatives [5].

5. Optimisation of protocols in vulnerable subjects

The accumulation of data from large randomised trials now makes it possible to refine the safety profile of ketamine and etomidate using advanced statistical tools, while exploring co-administration techniques to limit endocrine toxicity.

5.1. Comparative analysis of survival and mortality

The most recent meta-analyses provide important nuances on the prognosis depending on the statistical methodology used. A Bayesian meta-analysis suggests a moderate probability that ketamine reduces mortality compared to etomidate in critically ill adults, although this trend is not confirmed by secondary criteria [14]. Conversely, a conventional meta-analysis of 11 randomised trials (2,704 patients) concludes that etomidate significantly increases mortality in critically ill patients compared to other induction agents, with a high probability of death associated with its use in critical care [15]. However, other studies found no significant difference in 30-day survival in a hospital setting [48] or in septic patients specifically [49].

A comprehensive analysis of 10 randomised trials (2,862 patients) confirms this lack of difference in mortality and hypotension, while highlighting that ketamine presents a significantly lower risk of adrenal insufficiency [50].

5.2. Issues with induction in elderly patients (≥ 65 years)

The geriatric population presents particular challenges in terms of haemodynamics and cognition. In elderly patients intubated in the emergency department, there is no statistical difference between etomidate and ketamine in terms of peri-intubation hypotension (PIH) [51]. However, in elderly patients who developed PIH requiring vasopressors, the use of ketamine was associated with lower 28-day mortality than etomidate [51]. The pre-intubation shock index remains a warning sign: high induction doses for either agent drastically increase the risk of PIH in this population [51]. Cognitively, while ketamine and propofol can influence postoperative cognition in seniors, the combination of ketamine and propofol (ketofol) may reduce the incidence of postoperative delirium compared to other regimens [52].

5.3. Co-administration strategies and adrenal protection

Hybrid approaches attempt to preserve the advantages of etomidate while neutralising its deleterious effects. Adding a low dose of ketamine to etomidate significantly reduces the decrease in cortisol levels induced by the latter in critically ill cardiac patients [53]. This 'protection' strategy limits adrenal suppression while maintaining satisfactory clinical stability [53]. For the management of motor effects, preventive administration of ondansetron (4 mg IV) has been shown to be effective in reducing the incidence, duration and severity of etomidate-induced myoclonus [54].

5.4. Focus on septic shock and the use of vasopressors

The behaviour of these agents in the context of sepsis remains a point of clinical vigilance. Although long-term survival is similar, etomidate is associated with a significantly higher use of vasopressors within 24 hours of intubation in septic patients [49]. Paradoxically, other meta-analyses indicate that ketamine may be linked to a more frequent need for vasopressors immediately after intubation in a general hospital setting [48]. This apparent contradiction highlights that while ketamine may cause transient instability, etomidate appears to induce more prolonged haemodynamic fragility, possibly via its endocrine impact, in patients who are already inflammatory [50].

6. Clinical implications of induction agent choice

The choice of induction agent in rapid sequence induction cannot be standardized and must be individualized according to the clinical context. Available data highlight a complex balance between immediate hemodynamic stability and later systemic effects, particularly endocrine and prognostic effects.

In the context of trauma, the results are mixed. Some studies show that ketamine can induce more pronounced hemodynamic instability than etomidate [8], which may seem counterintuitive given its sympathomimetic properties. However, this effect likely depends on the patient's pre-existing physiological state (catecholaminergic reserve, hemorrhagic shock). Furthermore, no significant difference was observed in major endpoints such as mortality or intubation success [8, 29, 3]. Thus, in stable or moderately unstable trauma patients, etomidate may be preferred for its immediate stabilization, while ketamine remains relevant in cases of bronchospasm or the need for analgesia [39, 47].

In patients in shock or hemodynamically unstable, the situation is more nuanced. Meta-analyses confirm that etomidate reduces the risk of post-induction hypotension [12], which has historically made it a preferred agent in critical situations. However, more recent data reveal that ketamine may improve blood pressure in hypotensive patients [18] and that the main determinant of hypotension remains the pre-intubation state rather than the agent itself [5]. Furthermore, ketamine is associated with a higher risk of peri-intubation cardiovascular collapse in some trials [9], which necessitates caution in patients in deep shock with catecholamine depletion.

In sepsis, the debate is particularly important. Although several randomized trials show no significant difference in mortality between ketamine and etomidate [35, 55], etomidate is consistently associated with a cumulative use of vasopressors and corticosteroids [35, 55]. This is explained by its well-documented adrenal suppression [6, 50, 56]. Even though some reviews suggest that this effect has a limited clinical impact [4], other studies report an increase in mortality associated with etomidate in critically ill patients [22, 23, 57]. In practice, this is increasingly leading to a preference for ketamine in septic patients, particularly in cases of suspected adrenal insufficiency or severe distributive shock.

In critically ill ICU patients, overall data show comparable efficacy between the two agents in terms of mortality, SOFA score, and intubation success [16, 25, 46, 56]. However, an adverse safety signal persists for etomidate regarding in-hospital mortality in some cohorts [11, 19, 22, 57], possibly related to its

endocrine effects. Conversely, ketamine has a more complete profile (analgesia, maintenance of respiratory reflexes), but at the cost of greater hemodynamic variability [1, 47].

In specific situations, the choice can be more clearly guided:

- In intracranial hypertension or neurotrauma, etomidate is often preferred for its hemodynamic stability and neuroprotective effect [39].
- In asthma or bronchospasm, ketamine is superior due to its bronchodilator properties [39, 47].
- In patients with endocrine risk factors, etomidate should be avoided due to the risk of adrenal crisis [53].
- In pediatrics, both agents appear generally safe with no major difference in mortality [58].
- In elderly patients, no clear difference was found in hypotension or mortality, but dosage adjustments are essential [59].

Finally, combination strategies are emerging to take advantage of the benefits of both agents. For example, adding ketamine to etomidate can limit cortisol suppression [60] or reduce adverse effects such as myoclonus [26, 54]. Similarly, ketamine-propofol combinations (ketofol) offer interesting hemodynamic stability in several settings [21, 48]. Table 1 shows a comparison between ketamine and etomidate according to clinical situations. Table 2 shows an overall comparison between ketamine and etomidate.

Table 1. Comparison (Ketamine vs. Etomidate) according to clinical situations

Clinical situation	Preferred agent	Justification	References
Shock / hypotension	Ketamine	Sympathomimetic effect	[18, 39]
Sepsis	Ketamine (often)	Less adrenal impact	[35, 56]
HTIC / neuro	Etomidate	↓ intracranial pressure	[39]
Asthma	Ketamine	Bronchodilation	[47]
Pediatrics	Both	Comparable security	[58]
Elderly human	Ketamine (± propofol)	Improved stability	[21]
Congenital heart defects	Both	Hemodynamic maintenance	[31]

Table 2. Overall Comparison: Ketamine vs. Etomidate

Criteria	Ketamine	Etomidate	References
Hemodynamic stability	Variable, sometimes unstable or collapsing	More stable overall	[8, 9, 12]
Post-intubation hypotension	↔ or ↑ slightly according to studies	↓ risk of hypotension	[3, 5, 12]
Patients in shock/hypotension	↑ blood pressure, beneficial	Less favorable	[18]
Successful intubation	Comparable	Comparable	[3, 8, 12, 46]
Mortality	↔ or sometimes ↓	↔ or sometimes ↑	[19, 33, 57]
Adrenal effect	No harmful effects	Adrenal suppression	[6, 50, 56]
Side effects	Hallucinations, nausea	Myoclonus, injection pain	[45, 52]
Use in RSI	Effective alternative	historical standard	[4, 39]

7. Conclusion and general outlook

At the end of this review, it appears that the opposition between ketamine and etomidate cannot be resolved according to a dichotomous logic. Current data confirm that these two agents are effective and widely validated tools for rapid sequence induction in emergency medicine and intensive care, but their pharmacodynamic profiles and prognostic implications differ significantly.

Etomidate retains an undeniable advantage in terms of immediate haemodynamic stability and intracranial pressure control, making it a relevant agent in patients with severe cardiovascular instability or intracranial hypertension. However, documented adrenal suppression and persistent evidence of a possible increase in mortality in the most critically ill patients require careful and judicious selection, particularly in subjects at risk of adrenal insufficiency.

Ketamine, meanwhile, is gradually establishing itself as a robust alternative in critical care. Its lack of deleterious effects on the corticotropic axis, its potential benefits in septic or traumatic shock, and its longer-term psychological benefits — particularly in the prevention of post-traumatic stress — reinforce its

appeal. Although some studies report slightly more frequent post-induction hypotension, this seems to be more correlated with initial haemodynamic severity than with any major intrinsic effect of the molecule, with no demonstrated impact on mortality.

Thus, the optimal strategy is based on an individualised approach, taking into account the patient's pathophysiological status, the clinical context (sepsis, trauma, intracranial hypertension, circulatory collapse), and short- and long-term objectives. The recent shift in paradigms, from an exclusive focus on immediate stability to a comprehensive assessment including 28-day survival, endocrine morbidity and neuropsychological sequelae, reflects the maturing of this field of research.

- ✓ Future prospects revolve around several major areas: the completion of large-scale multicentre trials evaluating mortality and endocrine complications;
- ✓ the identification of patient subgroups likely to benefit preferentially from one or the other agent;
- ✓ optimisation of combination protocols (co-administration, dose adjustment) aimed at minimising toxicity while maintaining haemodynamic stability;
- ✓ and the integration of predictive biomarkers enabling more personalised medicine in critical situations.

Ultimately, rather than a universal 'winner', current literature advocates for a nuanced and contextualised strategy. Ketamine is becoming the preferred agent in critical care due to its overall safety profile, while etomidate retains a specific place when immediate haemodynamic stability is the absolute priority, subject to careful assessment of adrenal risk.

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