Etomidate in pediatric anesthesiology: Where are we now?

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ABSTRACT

Etomidate is an intravenous anesthetic agent released for clinical use in the United States in 1972. Its popularity in clinical practice is the result of its beneficial effects on intracerebral dynamics with limited effects on hemodynamic function. These properties have made it a safe and effective anesthetic induction agent in both adult and pediatric patients with altered myocardial performance, congenial heart disease, or hypovolemia. However, recent concern has been expressed regarding its effects on the endogenous production of corticosteroids and the impact of that effect on patient outcomes. The following manuscript reviews clinical reports regarding etomidate use in the pediatric population and discusses recent concerns regarding its effects on corticosteroid metabolism and the implications of such effects for clinical use.

Key words: *Adrenal suppression, endotracheal intubation, etomidate, pediatric anesthesia*

INTRODUCTION

Etomidate is an intravenous anesthetic agent whose clinical effects are the result of potentiation of the gamma-amino butyric acid inhibitory neurotransmitter system with the alteration of transmembrane chloride conductance. It was released for clinical use in the United States in 1972. Unlike other sedative and hypnotic agents, only the R(+) enantiomer has clinical effects. Following the intravenous administration of a single bolus dose, loss of consciousness occurs in 15-20 s with the rapid recovery of 5-10 min related to rapid drug redistribution and not primary metabolism.[1] As with the barbiturates and propofol, etomidate decreases the cerebral metabolic rate for oxygen thereby leading to cerebral vasoconstriction with a reduction of cerebral blood flow (CBF) and volume. These physiologic effects result in a decrease of cerebral blood volume and intracranial pressure (ICP) especially in the setting of intracerebral hypertension.[2-4] In a prospective study of 8 children with traumatic brain injury, etomidate (0.3 mg/kg) was administered when there was a sustained ICP elevation ≥20 mmHg for >5 min.[5] The average ICP for the 5 min before etomidate administration was 32.8 ± 6.6 mmHg, decreasing to 21.2 ± 5.2 mmHg with the greatest difference being noted at 5-10 min after etomidate administration. The average mean arterial pressure for all patients increased after etomidate resulting in an increase in the cerebral perfusion pressure (CPP) from 49.1 ± 5.3 mmHg at baseline to 65.3 ± 13.1 mmHg.

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When compared to other commonly used anesthetic induction agents such as propofol or the barbiturates, etomidate is generally devoid of adverse effects on cardiovascular function and hemodynamic performance.[6] Using a balloon-tipped pulmonary artery catheter to evaluate hemodynamic changes following a bolus dose of 0.3 mg/kg in a cohort of 12 children, there were no significant changes in right atrial, aortic, or pulmonary artery pressure; oxygen saturation, calculated shunt (Qp:Qs) ratio or systemic/pulmonary vascular resistance.[7] A similar lack of hemodynamic changes with no change in shunting were noted in 30 children with congenital heart disease, 15 with right-to-left shunts and 15 with left-to-right shunts.[8] These properties have led to its use as an anesthetic induction in both adult and pediatric patients with altered myocardial performance, congenial heart disease, or hypovolemia.

In contrary to the large amount of clinical experience with its use in the adult population, the clinical experience in the pediatric-aged patient is somewhat limited. The following manuscript reviews clinical reports regarding etomidate

use in the pediatric population, outlines its physiologic effects and discusses recent concerns regarding its effects on corticosteroid metabolism and the implications for clinical use.

CLINICAL APPLICATIONS

Anesthetic induction and endotracheal intubation

In the first clinical trial using etomidate in the pediatric population, etomidate (0.2 mg/kg) was used for the induction of anesthesia in a cohort of 198 children, ranging in age from 1-day to 15 years.[9] Induction was graded as good in only 59% of patients with 19% experiencing inadequate hypnosis. In a follow-up study, the dose was increased to 0.3-0.4 mg/kg.[10] Because most of the study patients had also received a neuromuscular blocking agent immediately following etomidate, the true adequacy of the higher dose of etomidate could not be evaluated. However, more recent pharmacokinetic data provide support for the use of a larger dose in pediatric patients with the general conclusions that due to enhanced clearance and increased central compartment volume, younger children will require a higher etomidate bolus dose than older children to achieve equivalent plasma concentrations.[11,12]

Other authors have reported anecdotal success with the use of etomidate for anesthetic induction in infants and children with depressed myocardial function related to cardiomyopathy.[13,14] Two additional series report the use of etomidate for anesthetic induction in children.[15,16] Although these series were primarily evaluating the onset of action of neuromuscular blocking agents, they also reported the safe and effective use of etomidate for anesthetic induction in doses ranging from 0.2 to 0.4 mg/kg.

Endotracheal intubation in the emergency department

There are also several pediatric reports regarding the use of etomidate for endotracheal intubation in the emergency department. As in the operating room, the impetus behind its use in the emergency department for critically ill patients include its lack of adverse hemodynamic effects and beneficial effects on the intracerebral dynamics of ICP, CBF, and CPP.[17-20] In a retrospective chart review of the use of etomidate during endotracheal intubation in 105 children, with an average age of 3 years, minimal changes in blood pressure were noted following endotracheal intubation using a median dose of etomidate of 0.32 mg/kg.[21] The systolic blood pressure increased an average of 4 mmHg, and the diastolic blood pressure increased an average of 7 mmHg within 10 min of receiving etomidate. Complications included three patients who vomited within 10 min of etomidate administration. A similar lack of hemodynamic effects was noted with the administration of etomidate for endotracheal intubation in the prehospital setting.[22] Whereas these case series or reviews provide clinical evidence regarding the efficacy of etomidate in this setting, there are no prospective randomized trials comparing etomidate to other agents.

Maintenance anesthesia

In a limited number of pediatric patients, etomidate has also been used to provide maintenance anesthesia. Doom and Mundeleer compared etomidate and methohexitone to provide maintenance anesthesia during tonsillectomy in 80 children.[23] Intermittent bolus doses of one these agents (methohexitone 1 mg/kg or etomidate 0.3 mg/kg) were administered as needed to supplement nitrous oxide anesthesia. No adverse effects were reported with etomidate and when compared to methohexitone, the emergence time was shorter. Kay published the first studies evaluating the use of etomidate as part of a total intravenous anesthesia technique in children.[24,25] Anesthesia was induced with etomidate (0.3 mg/kg) and fentanyl (2-5 μg/kg). Anesthesia was maintained with an etomidate infusion starting at 40-50 μg/kg/min and titrated according to the clinical assessment of the depth of anesthesia. Neuromuscular blockade was administered according to the requirements of the surgical procedure. Etomidate infusion requirements varied from 7 to 39 μg/kg/min (mean = 32 μg/kg/min). Although the technique was successful in 79 of 80 patients, the author concluded that "the technique demands constant observation of the patient, looking for signs of consciousness; and trying to avoid having an awake, paralyzed patient, or giving an overdose of etomidate" and that the technique was unlikely to find widespread use. In a similar study, an etomidate infusion was used to provide general anesthesia in a cohort of 62 children during direct laryngoscopy and bronchoscopy for foreign body removal.[26] Following anesthetic induction with halothane, jet ventilation was started and anesthesia provided by an etomidate infusion at 10-20 μg/kg/min with intermittent thiopental boluses (2-3 mg/kg).

Procedural sedation

Given its sedative and anxiolytic effects, various clinical trials have evaluated the potential efficacy of etomidate in the arena of procedural sedation for nonpainful as well as invasive procedures. In a prospective, randomized trial of 60 pediatric patients undergoing the intrathecal administration of stem cells to treat autism, patients were randomized to receive a bolus dose of etomidate (0.2 mg/kg) or propofol (2 mg/kg), followed by additional doses of either etomidate (0.1 m/kg) or propofol (1 mg/kg).[27] Following the inhalational induction of anesthesia with sevoflurane, either etomidate or propofol was administered to provide ongoing sedation. Blood pressure and heart rate were significantly lower with propofol when compared

to etomidate. The incidence of adverse effects including respiratory depression, bradycardia, hypotension and pain on injection, was significantly higher with propofol while the incidence of myoclonus was greater with etomidate. There were no differences in anesthesia induction, surgery duration, recovery time, sedation score, and physician satisfaction between the two groups.

In a prospective, open-label trial of sedation in the emergency room setting, 60 pediatric patients received fentanyl 1 μg/kg and etomidate (0.1-0.2) mg/kg.[28] An additional dose of etomidate (0.1 mg/kg) was administered if needed. The most common procedure was fracture reduction (50 of 60 patients). Procedures were successfully completed for 59 of the 60 patients (98.3%). An initial dose of etomidate (0.2 mg/kg) provided adequate sedation for 33 of 50 patients (66.7%) requiring fracture reduction and for 6 of 10 patients (60%) for other procedures. Respiratory depression was noted in 9 of 55 patients (16.4%) with oxygen desaturation occurring in 23 of 59 patients (39%). 21 of 58 patients (36.2%) experienced a respiratory adverse event requiring brief intervention including oxygen supplementation, stimulation, and/or airway repositioning. No patient required positive pressure ventilation. Median time to discharge readiness was 21 min.

When comparing ketamine/midazolam to etomidate/fentanyl for fracture reduction in 23 children, the ketamine/midazolam group had lower pain/distress scores.[29] The parents also rated the procedural distress as lower and favored the combination of ketamine and midazolam. However, total sedation and recovery times were shorter with the combination of etomidate and fentanyl (49.6 vs. 77.6 min and 24.7 vs. 61.4 min). There were no significant differences with respect to procedural amnesia and orthopedic practitioner satisfaction. Adverse effects noted with ketamine and midazolam included dysphoria and vomiting. Vomiting, injection-site pain, myoclonus, the need for airway readjustment, and the requirement for supplemental oxygen were reported with etomidate and fentanyl.

When compared to midazolam, it appears that etomidate may be more effective.[30] In a cohort of 100 patients for sedation during fracture reduction in the emergency department, a higher proportion attained adequate sedation with etomidate than with midazolam (92% vs. 36). However, induction and recovery times were longer with etomidate. The rates of adverse events were similar in both groups, except for myoclonus and pain at the injection site, which were more frequent in the etomidate group. Similar findings on the efficacy and adverse effects have been reported in several other nonrandomized trials using the etomidate.[31-35]

EFFECT ON THE PRODUCTION OF ADRENOCORTICOSTEROIDS

The most significant concern with etomidate remains inhibition of the endogenous production of corticosteroids. The impact of this effect was first reported when an increased risk of mortality was noted in adult Intensive Care Unit (ICU) patients who were receiving a continuous infusion of etomidate for sedation.[36] Etomidate inhibits the enzyme system (11-β hydroxylase) that is necessary for the production of cortisol, aldosterone, and corticosterone. These effects and its impact on the outcome should preclude its use by repeated bolus dosing or continuous infusion. Although the inhibition is present after a single dose of etomidate, the effect was not initially thought to be clinically significant, and etomidate continued to be used in clinical practice for the next 20-30 years.

Duthie *et al.* demonstrated a decrease in plasma cortisol levels 1 h following an induction dose of etomidate; however, at 24 h no difference was noted between patients who received etomidate versus other induction agents.[37] However, other studies have suggested that suppression of adrenocortical function may be more prolonged. Following a single etomidate dose (0.3 mg/kg) in pediatric patients undergoing surgery for congenital heart disease, plasma cortisol levels were depressed during cardiopulmonary bypass, at the end of the operation, and at 24 h.[38] A similar effect with ongoing suppression of adrenal function at 24 h was reported in a cohort of critically ill adult patients.[39] Adrenal insufficiency, defined as a failure of the serum cortisol level to increase by 9 μg/dL after a 250 μg adrenocorticotropic hormone (ACTH) stimulation test, was 80% at 12 h, 9% at 48 h, and 7% at 72 h following a single dose of etomidate.[40] Despite these findings, no difference in outcome was reported and in fact a potential clinical benefit was noted as vasopressor therapy was required less frequently and in smaller doses when etomidate was used in a cohort of 159 adult patients with septic shock.[41]

Concerns regarding the potential impact of a single dose of etomidate on outcome were most recently raised by data from the CORTICUS trial.[42] The primary objective of the trial was to evaluate the effect of corticosteroid therapy on outcome in adults with septic shock and adrenal insufficiency. However, a *post-hoc* analysis revealed that the 28-day mortality rate was 42.7% in patients who received etomidate versus 30.5% in those who had not received etomidate. The increased risk of mortality in patients who had received etomidate was not prevented by the exogenous administration of corticosteroids (45% vs. 40%).[43]

Similar outcome data regarding etomidate was noted in a retrospective study of American Society of Anesthesiologists physical status III and IV patients presenting for noncardiac surgery.[44] Anesthesia was induced with either etomidate or propofol and then maintained with a volatile anesthetic agent. Propensity matching was used to pair 2144 patients who received etomidate with 5233 patients who received propofol. Patients who received etomidate had a 2.5 increased risk of dying when compared to those who received propofol. Etomidate patients also had significantly greater odds of having cardiovascular morbidity and significantly longer hospital stays. Infectious morbidity and intraoperative vasopressor use did not differ between the agents. However, other studies in the adult population had found no difference in the outcome in various clinical scenarios when evaluating patients who received etomidate. These studies have included cohorts of adult patients with sepsis, traumatic injury, and cardiac surgery.[45-47]

In addition to its effects on adrenal function, there is also a suggested link between etomidate administration and infectious morbidity. Neutrophils incubated *in vitro* with etomidate demonstrate depressed chemiluminescence, an index of oxygen free radical generation, suggesting that etomidate may interfere with white blood cell bactericidal activity.[48] Subset analysis of the HYPOLYTE study (a multicenter trial evaluating the use of hydrocortisone in trauma patients) noted that 49 of the 95 patients (51.6%) who received etomidate developed hospital-acquired pneumonia compared to 16 of the 54 patients (29.6%) who did not receive etomidate ($P = 0.009$).[49] The hazard ratio for the hospital acquired pneumonia was 2.48 with etomidate.

THE CONTROVERSY

Despite the ongoing controversy and the lack of clear evidence-based medicine demonstrating a deleterious effect of etomidate on outcome, it has been suggested that its use should be abandoned.[50-52] In some institutions, etomidate has been removed from the hospital formulary, the operating rooms, the emergency department and the ICU. Resuscitation guidelines from the American Academy of Pediatrics state "etomidate should not be routinely used when intubating an infant or child with septic shock." In the case, that it is used, recognition of adrenal suppression as a consequence is advocated.[53] The guidelines cite the adult CORTICUS trial and also a study of mortality and adrenal function in 60 children with meningococcal sepsis.[42,54] Of the 31 patients who required endotracheal intubation, 23 received etomidate and 8 did not. Those patients who received etomidate had significantly lower cortisol levels, higher ACTH levels, and higher 11-deoxycortisol levels. Mortality occurred in 7 of 23 patients who received etomidate versus 1 of 8 who did not. Although this could suggest etomidate as a risk factor for mortality, the authors acknowledge that it is difficult to identify the relative contribution of disease severity, endotracheal intubation, and etomidate to mortality.

Clinical practice guidelines for the treatment of septic shock in pediatric and neonatal patients from the American College of Critical Care Medicine have also cautioned against the use of etomidate.[55] The recommendations state that: "Etomidate is popular as an induction agent because it maintains cardiovascular stability through blockade of the vascular K + channel; however, even one dose used for intubation is independently associated with increased mortality in both children and adults with septic shock, possibly secondary to inhibition of adrenal corticosteroid biosynthesis. Therefore, it is not recommended for this purpose." Only one member of the task force supported the use of etomidate in pediatric septic shock with the caveat that stress dose hydrocortisone be administered.

FUTURE PERSPECTIVES

Given the concerns surrounding the administration of etomidate, especially in the setting of potential sepsis, it has been suggested that it may be prudent to use alternative agents in this clinical setting. However, commonly used agents including the barbiturates and propofol should not be used in patients with hemodynamic instability given their impact on cardiovascular function. Ketamine has been suggested as an alternative agent given its limited effects on hemodynamic function related to the release of endogenous catecholamines.[56] *In vitro* and animal studies demonstrate that ketamine has direct negative inotropic properties.[57,58] Although the indirect sympathomimetic effects from endogenous catecholamine release generally predominate, hypotension and even cardiovascular collapse may occur in patients with diminished myocardial contractility and depleted endogenous catecholamine stores.[59] These concerns are supported by recent reports of cardiovascular collapse following the administration of ketamine to critically ill pediatric patients.[60] As such it appears that the time has come for a re-evaluation of the current practice of rapid sequence intubation and to reconsider the advice to abandon etomidate.

Various factors may be responsible for cardiovascular changes including cardiac arrest in critically ill patients who require endotracheal intubation. The shift from spontaneous to positive pressure ventilation can have significant effects on cardiovascular performance. These changes may be exacerbated by co-morbid conditions, relative hypovolemia,

ablation of the sympathetic stress response, lowering of endogenous catecholamines as hypercarbia is corrected, and direct effects of the anesthetic agents used. The recommendation from the American College of Critical Care Medicine state: "If possible, volume loading and peripheral or central inotropic/vasoactive drug support is recommended before and during intubation because of relative or absolute hypovolemia, cardiac dysfunction, and the risk of suppressing endogenous stress hormone response with agents that facilitate intubation."[55]

Given the paucity of evidence-based medicine on which to base this clinical decision, randomized trials with the power to answer the question regarding the impact on morbidity and mortality are clearly needed. If etomidate does have deleterious physiologic consequences, it also remains to be determined it these can be reversed by the administration of exogenous corticosteroids.[61,62] Carbo-etomidate, an analog of etomidate with similar hypnotic properties and cardiovascular stability, does not seem to suppress steroid synthesis in animal studies and thus may be a promising alternative.[63]

SUMMARY

Etomidate is an intravenous anesthetic agent released for clinical use in the United States in 1972. Its clinical effects are the result of potentiation of the gamma-amino butyric acid inhibitory neurotransmitter system with the alteration of transmembrane chloride conductance. It remains an effective agent for anesthetic induction in the operating room as well as for sedation during endotracheal intubation in the ICU and emergency room setting. In addition to beneficial effects on intracerebral dynamics, it has limited effects on hemodynamic function even in the setting of hypovolemia, congenital heart disease, and depressed myocardial function. Although it results in the depression of adrenal function for up to 24 h following a single dose, there is controversy regarding the clinical impact of this effect. These concerns have led to the recommendation that it not be administered to patients with sepsis or at risk of sepsis. However, a more widespread restriction of its use is apparent in common clinical practice. Given its potential beneficial role in clinical practice, it appears that a reappraisal of such restrictions is indicated.

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