Comments on Etomidate Usage in the Emergency Department

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Certainly for emergency medicine specialists, sedative hypnotic agents play an important role during difficult times in their professional life. These molecules are indispensable agents, especially in the emergency department, for the induction of "rapid sequence intubation" performed during unprepared conditions or "procedural sedation and analgesia" for children and adults. Though not a novel drug, etomidate challenges all algorithms prevalent in the field of anesthesia over the last 10 years. I wanted to remind you and share my humble opinions about this agent, which has been subjected to many positive and negative comments.

Etomidate is a preferred induction agent because of its substantially increased lipid solubility for critically ill patients whose blood pressure should be maintained at a stable level. At the beginning, consciousness of the patient is impaired because of a first-pass effect through the brain following its intravenous injection. A single bolus dose induces hypnosis within 10 s and terminates within 3–5 min. It does not have any analgesic effect. It depresses electroencephalography (EEG) activity and cerebral blood pressure similar to the effects of barbiturates. Because it does not affect the mean arterial pressure and decreases intracranial pressure without lowering cerebral perfusion pressure, it is especially useful in hemodynamically instable patients with increased intracranial pressure. Because etomidate is the only intravenous anesthetic agent that does not affect histamine release, it is also safe in patients with a reactive airway. For "rapid sequence intubation" and "procedural sedation and analgesia," its intravenous doses are 0.2–0.4 mg/kg in adults and 0.1–0.2 mg/kg in children. Its effects start at the most within 15 s and end at the most within 15 min.

Its adverse effects are as follows:

- Nausea and vomiting
- Injection side pain: For the treatment of pain along the intravenous route, opening of a large vascular access, saline infusion, and the use of a local analgesic are recommended.
- Myoclonus: This can be seen in one-third of cases and is caused by interruption of the inhibitory synapses on the thalamocortical pathway. The use of opioid analgesics and benzodiazepines as premedication can decrease this side effect. Unfavorable effects of this side effect on patient's clinical status have not been reported so far. However, when it is manifested in cases where it cannot be discriminated from seizure activity, it can lead to the conduction of unnecessary tests and a prolonged stay of the patient in the emergency department.
- Suppression of the adrenocortical hormone: This can emerge as a result of the inhibition of 11-β hydroxylase enzyme. It certainly suppresses adrenocortical hormone synthesis in a dose-dependent manner. A single dose inhibits adrenocortical hormone synthesis for 5 h. Some studies have demonstrated its suppressive effects even after 12 h following its use.

Owing to the abovementioned characteristics, as an induction agent, etomidate essentially resembles propofol and thiopental. Its extremely rapid onset together with short-acting effects decreases intracranial pressure. However, etomidate does not decrease blood pressure or cerebral perfusion pressure while depressing intracranial pressure, which may confer major advantages to etomidate.

Etomidate can also be compared with ketamine. Both of these drugs do not decrease blood pressure, and they can be used in patients with reactive airways. As an important advantage, ketamine also has an analgesic effect. Despite this, ketamine increases endogenous catecholamine sensitivity, which can create problems, especially in adult patients carrying a risk of coronary disease. Besides, as an important difference, ketamine increases intracranial pressure and secretions. Because recovery from ketamine anesthesia in adults is somewhat problematic, it has established its place in daily practice in the pediatric age group. In adults, ketamine has been replaced by an opiod-etomidate combination.

After briefly giving a reminder of the effects of etomidate, let us now discuss the main controversies. Although, etomidate is believed to be mostly beneficial for hemodynamically instable, critically ill patients, for this patient group, including patients with sepsis, the adrenal insufficiency-inducing effects of etomidate could be associ-

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ated with mortality, and this has also been a matter of concern. It has been demonstrated that etomidate administering, even as a single dose or as an infusion, absolutely decreases cortisol levels and suppresses the adrenal system. However, one thing we do not know yet is if this effect is really associated with an increased mortality for relevant patient groups. If the answer to this question is "yes," then the following question is "Is it possible to avoid these adverse effects if corticosteroid replacement is employed after etomidate usage?" To answer these questions, I tried to screen all the meta-analyses and review articles and important clinical trials about etomidate on search motors such as "tripdatabase," "Cochrane," and "pubmed," It was possible to find many papers addressing the first question; however, I could find only one randomized controlled study that dealt with the second question. Following a screening, I will try to summarize the publications that may be most useful for us.

The first systematic analysis on etomidate was first published in the journal of *Critical Care Medicine* in 2012 (1). This meta-analysis included studies using etomidate in patients who had undergone rapid successive intubation in the emergency department with the indication of sepsis. A total of five studies, whose etomidate arm included 865 patients with a primary end point of "mortality," were included in the analysis. Seven studies with a primary end-point of adrenal suppression performed on 1303 patients were analyzed separately. These studies were observational or randomized controlled trials (RCT). The all-cause mortality (n=865) was found to be RR (95% CI) 1.20 (1.02–1.42) in the pooled analysis. The mortality of RCTs (n=759) was only found to be RR (95% CI) 1.26 (1.06–1.50). As can be clearly seen, mortality was found to be statistically significantly higher in the group of patients using etomidate, as demonstrated in all the studies and RCTs. Besides, when evaluated regarding the development of adrenal insufficiency, the possibility of developing adrenal insufficiency was found to be 30% higher in the etomidate group. The pooled RR (95% CI) was found to be 1.33 (1.22–1.46) for all the studies (n=1303) and 1.35 (1.24–1.47) for RCTs only (n=944).

Publication of this study has generated considerably important consequences, and despite it being a meta-analysis with significant heterogeneity performed by a single center, significant limitations have been started to be imposed on the use of this drug. Because this drug has not been used very widely in our country and as it is not easily available, these arguments did not create an agenda in our country, whereas this issue was regarded as a great problem in the international emergency medicine arena, with a critical review published in *The Annals of Emergency Medicine* in 2013. (2). In this critical review, methodologies of the studies were criticized for their especially problematic randomization, blinded design, and follow-up. They argued that only two publications included in the meta-analysis were RCTs, whereas the other three studies had an observational design. More importantly, although in the etomidate group, higher mortality rates of 20% were demonstrated, confidence intervals very close to 1 [RR 1.20 (1.02–1.42)], with a considerably large range emphasized that this statistically significant result did not have a possible clinical significance. In conclusion, as a "take home message," the reviewers stated that the mortality-increasing effects of etomidate in patients with sepsis who required intubation could not be demonstrated. However, more robust randomized studies are needed to arrive at a definitive conclusion.

Another RCT relevant to this subject matter was published in 2014. The reliability of the studies and their outcomes have increased in parallel with the number of RCTs. In this study, adrenal insufficiency was markedly demonstrated in the etomidate group, while a lack of difference between etomidate and other induction agents, such as for the mortality rates, was also indicated. (3).

In 2015, a meta-analysis was published in Cochrane. This meta-analysis included only seven randomized controlled studies. They indicated a low degree of bias in only two of these seven RCTs. As a result of the meta-analysis, a difference between the odds ratios of the group who used etodimate and those of other groups could not be demonstrated (OR 1.17; 95% CI 0.86–1.60). However, adrenal insufficiency within the first 4–6 h was clearly demonstrated (OR 19.98; 95% CI 3.95–101.11). Besides this, adrenal insufficiency demonstrated a statistically significant difference even after 12 h. This meta-analysis indicated that this adrenal insufficiency did not lead to a clinically significant difference in mortality. Moreover, in the same meta-analysis, higher SOFA (Sequential Organ Failure Assessment) scores were reported in the etomidate group [mean difference (MD) 0.70; 95% CI 0.01–1.39]. These results were interpreted as statistically significant, but with clinically insignificant outcomes (4). As was seen, the true difference was very close to "0." Finally, in the same meta-analysis, a difference between the etomidate and other groups, such as for the length of the hospital stay, the day of mechanical ventilation, and the need for vasopressor use, was detected. In the "Comments of The Author" section, the author stated that etomidate did not exert apparently adverse effects on mortality. However, its somewhat lesser effects on the SOFA scores and adrenal insufficiency were reported in this meta-analysis. The authors also emphasized that the adverse effects on SOFA scores might be related to comatose patients, who constituted 42% of the patients included in the meta-analysis.

Most recently, a meta-analysis was published in the *Chest*, which analyzed two RCTs and 16 observational studies. The study mostly consisted of observational studies. However, when all the results of the RCTs (RR, 1.20; 95% CI, 0.84–1.72) and observational studies (RR, 1.05; 95% CI, 0.97–1.13) and both of them in combination (RR 1.05 (95% CI, 0.79-1.39) were analyzed, any increase in mortality rates could not be demonstrated in the etomidate group. However, as seen in other studies and in the meta-analyses, adrenal insufficiency was found to be significant both from a statistical and clinical aspect (5). The investigators who performed the meta-analysis, like the Cochrane investigators, expressed that single doses of etomidate could not be associated with mortality. However, they also reported that this meta-analysis mostly included observational studies, and selection bias is a possibility. They also added that for more definitive results, RCTs with a larger patient population should be conducted. .

In addition, it will be proper to remind that another argument is related to steroid replacement therapy after etomidate use. The most comprehensive randomized study on this issue was published in 2012. In this study, the patients who used etomidate were randomized into two groups, and one group received hydrocortisone infusion for 42 h at a daily dose of 200 mg at 6 h after intubation. The development of adrenal insufficiency, SOFA scores, length of hospital stay, duration of mechanical ventilation, length of hospital stay, and need for vasopressor use were compared between groups who had and who had not received replacement therapy. No intergroup difference was found for any parameter (6). Therefore, currently, steroid replacement therapy has not been recommended in patients using etomidate.

In this final paragraph, I will make comments based on my personal experience and knowledge. However, before I make my

final comment, these comments will be my personal sophisticated interpretation on the drug based on the integration of the review of the literature with an evaluation of the results obtained, and as aforementioned, my experiences. Finally, if a truly common language were to be formulated, it would be a more accurate approach to realize a "national identity of politics" with our research groups and even to share these politics with official organizations and finally to publish these politics for the benefit of the citizens of our country.

- *There is no such a thing as a "good" or a "bad" drug; it is related to our level of knowledge and experience. Only ignorance is the issue.*
- *Etomidate has important advantages at an extremely early onset of its short-acting effects.*
- *As is known, it does not affect hemodynamic data.*
- *If a contraindication for ketamine use is suspected or definitively demonstrated, etomidate can be used in hemodynamically instable* or *critically ill patients.*
- *If critically ill or sepsis patients are hemodynamically stable, then we have no reason to prefer etomidate. Indeed, definitive information about its adrenal insufficiency-inducing effects are available.*
- *Corticosteroid replacement used in patients who received etomidate did not demonstrate positive effects on adrenal insufficiency or hemodynamic data.*

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