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Masterthesis / Original study

Duration and depth of anaesthesia after administration of a single dose of etomidate combined with remifentanil in healthy patients: a survey and a randomised controlled double-blind pilot study

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Abstract

Background: **Etomidate is a hypnotic agent frequently used to induce general anaesthesia, primarily in frail patients and in emergency situations. The depth of etomidate-induced general anaesthesia in healthy patients is currently poorly studied.**
Objectives: **The purpose of this study was to evaluate the depth and duration of general anaesthesia by bispectral analysis of the electroencephalogram following the administration of an induction dose of etomidate, combined with remifentanil. We also aimed to gain insight into the attitudes of French-speaking-Belgian anaesthesiologists regarding the use of etomidate.**
Design: **Prospective, randomised, controlled, double-blind, single-centre trial, pilot study.**
Setting: **A university hospital, CUB Erasme, Brussels, Belgium, between 11 January and 08 April 2022**
Methods: **Healthy patients (ASA score I/II), < 75 years (n=18) scheduled for minor stomatological, cervico-facial or reconstructive surgery were included. Patients were randomly assigned to receive either 0.2 mg/kg (n=8) or 0.3 mg/kg (n=10) of etomidate as an induction bolus.**
Main Outcome Measures: **Practices regarding the use of etomidate were assessed using online survey. We evaluated the onset of general anaesthesia (clinically and time for bispectral index <60) and the duration of an "adequate" depth of general anaesthesia (bispectral index 40-60).**
Results: **Most of the ninety-six responding anaesthetists believe that etomidate is not very effective or ineffective for inducing general anaesthesia in healthy patients. When used, the common dosage of etomidate for induction ranges from 0.2 mg/kg to 0.3 mg/kg. The onset time of general anaesthesia was similar between the two groups. Patients who received 0.3 mg/kg spent a longer time within adequate depth of anaesthesia (396 ± 175 sec) compared with the lower dose of 0.2 mg/kg (156 ± 91 sec) ($p<0.01$)**
Conclusion: **Most anaesthesiologists express concerns regarding the low efficacy of etomidate when administered as a hypnotic agent in healthy patients. Our findings suggest that etomidate can induce a general anaesthesia of adequate depth, of which the duration double when administered using bolus of 0.3 mg/kg compared with 0.2 mg/kg.**
Trial Registration: **ClinicalTrials.gov ID : NCT05862753**

Keywords: **Etomidate, Anaesthetics, intravenous, Consciousness Monitors.**

Presentation: Data from this study were presented as a poster at Euroanaesthesia, 25 to 27 May 2024, Munich, Germany.
Consent statement: Written informed consent was obtained from all patients in accordance with the journal's patient consent policy.
Ethics: approval from the Ethics Committee Erasme Hospital (808, route de Lennick, 1070 brussels; Chairman Pr J.-M. Boeynaems) was received on Decembre 14, 2021, with reference P2021/554/ B4062021000287.
Clinical Trials Registry of the United States National Library of Medicine: NCT05944887. Patients were included between 11 January 2022 and 20 April 2022.

Introduction

Induction agents are pharmacological substances used to initiate and sustain general anaesthesia. They dose- and drug-dependently modify the electroencephalogram (EEG), resulting in variable depths and durations of general anaesthesia. An ideal anaesthesia ensures loss of consciousness and amnesia without excessive depth which could result in a flattened electroencephalographic (EEG) tracing and burst suppression (BS). Furthermore, the administration of excessive hypnotic agents increases the risk of postoperative complications, including delayed emergence, somnolence, and cognitive impairment[1]. The depth of anaesthesia can be monitored, notably through bispectral analysis of the EEG, allowing the detection of any over- or under-dosage of hypnotic agents[2]. This monitoring (Bispectral IndexTM Brain Monitoring System, Medtronic), coupled with an undisclosed internal algorithm (protected by an industrial patent), provides a bispectral index (BIS) ranging from 0 to 100. Several levels of anaesthesia depth are described: The BIS values are, respectively, indicative of an awake patient when above 80, a state of sedation when ranging from 80 to 60, an appropriate general anaesthesia when between 60 and 40, and a state of excessive general anaesthesia when below 40, often concurrent with an iso-electric EEG tracing.

The induction of general anaesthesia has two main objectives: firstly, ensuring an adequate level of anaesthesia, and secondly, to maintain haemodynamic stability and safety. Etomidate is a commonly used hypnotic agent for this purpose. The pharmacological characteristics of etomidate namely mild respiratory depression and little effect on the cardiovascular system[3], render it a preferred choice for patients who are particularly vulnerable and in emergency situations[4]. Nevertheless, the existing literature offers only limited insights into the depth of anaesthesia following etomidate administration. Most studies are outdated and primarily rely on a clinical evaluation of the patient, including loss of responsiveness[5-7] and the persistence of an absence of respiration and palpebral reflex[8]. However, the aforementioned clinical manifestations originate in the brainstem and are not a reliable indicator of cortical activity. Furthermore, these factors may contribute to some anaesthetists' concern regarding inadequate anaesthesia, which may prevent favourable conditions for endotracheal intubation. A review of recent literature reveals a paucity of studies using a monitoring of depth of general anaesthesia. Furthermore, there is a dearth of information on the duration of the hypnotic effect following the administration of etomidate[9].

This study had two main objectives. The first was to gain insight into the attitudes and beliefs surrounding etomidate as an induction agent in healthy patients among a group of French-speaking Belgian anaesthesiologists. The second objective was to better characterize the hypnotic effect of etomidate in this specific patient population through bispectral analysis of the EEG.

Methods

Survey on the use of etomidate

An online survey was conducted via email among anaesthesiologists practicing in the Wallonia-Brussels Federation and affiliated with the Université Libre de Bruxelles, Université Catholique de Louvain, and Université de Liège in Belgium. The survey was designed as an anonymous multiple-choice questionnaire, designed to inquire about anaesthesiologists' practices and beliefs related to the use of etomidate for anaesthesia induction. The questions included the practitioner's experience level, their practice in a university hospital, the efficacy of etomidate when used for elective or urgent induction of general anaesthesia in patients with an American Society of Anaesthesiologists (ASA) physical status score of I or II, the typical concentration of etomidate used, and the use of depth of anaesthesia monitoring.

Clinical Investigation

Ethical information

This single-centre, prospective, randomized, controlled, double-blind study was conducted at HUB-Erasme Hospital (Brussels, Belgium) from 11 January to 20 April 2022, in accordance with the Declaration of Helsinki and the CONSORT recommendations for randomised controlled trials. This study was approved on 10 December 2021, by the Erasme-ULB Hospital-Faculty Ethics Committee (Brussels, Belgium, Chairperson Prof J-M Boeynaems; Protocol Reference: P2021/554/B4062021000287) and was registered in the European Union Drug Regulating Authorities Clinical Trials database (EudraCT CCB B4062021000287) and with the Clinical Trials Registry of the United States National Library of Medicine (Registration number: NCT05862753). All patients provided written informed consent.

Inclusion and exclusion criteria

After obtaining written informed consent, we enrolled patients aged between 18 and 75 years

with an ASA score of I/II, scheduled to undergo minor to moderate cervico-facial, stomatological, and reconstructive surgeries. Exclusion criteria comprised pregnant women, chronic alcohol abuse, psychotropic or opioid usage, central nervous system diseases and body weight < 70% or > 130% of their ideal body weight.

Randomization and blinding

The eligible patients were randomized into two groups. According to a pre-established and investigator-blinded randomization list, generated by a computer programme (Sealed Envelope© Ltd. 2022) with a ratio of 1:1 and blocks of 4, general anaesthesia was induced by administering either 0.2 mg/kg or 0.3 mg/kg of etomidate (Hypnomidate©, Piramal Critical Care B.V.). The etomidate dose was prepared by a collaborator, blinded to the investigators, as follows: 0.2 mg/kg or 0.3 mg/kg of etomidate were drawn and diluted to a volume of 30 ml with 0.9% saline solution, constituting the "induction dose".

Protocol

To avoid any interference with EEG analysis, preoperative anxiolysis using benzodiazepines was excluded. Similarly, all external interferences that could affect bispectral analysis of the EEG were carefully avoided (such as the use of a warming blanket or movement of the operating table and/or patient). After positioning the patient in a supine position on the operating table, standard monitoring was applied, including non-invasive blood pressure measurement using an inflatable cuff, an electrocardiogram, and pulse oximetry. A peripheral intravenous catheter of 18 or 20 gauge was inserted for intravenous infusion of a crystalloid solution (PlasmaLyte®, Baxter SA). A unilateral electrode, the BISTM quatro sensor, was positioned on the patient's forehead following the manufacturer's instructions and connected to the BISTM Vista monitor (Bispectral IndexTM Brain Monitoring System, Medtronic).

After preoxygenation using a facial mask, intravenous administration of remifentanil (Ultiva®, Aspen Pharma Trading Limited) was initiated with a target effect-site concentration of 2 ng/ml. Once the desired remifentanil concentration was reached, the previously prepared etomidate induction dose was administered, and the infusion line was flushed. Following the loss of patient responsiveness, gentle manual ventilation was provided through the facial mask, and muscle paralysis was induced with rocuronium (1 mg/kg; Esmeron®, MSD Belgium). When the BIS values rose above the threshold of 60 and remained at that level for more than 10 seconds, general anaesthesia was further deepened by administering propofol, at the discretion of the attending anaesthesiologist, marking the completion of the current protocol.

Outcomes Measurements

Using the BIS monitoring, we recorded the time required for the BIS value to decrease below the threshold of 60, indicating the onset of general anaesthesia, and the duration spent within an "adequate" depth of general anaesthesia, defined by a BIS value between 40 and 60. To assess the presence of excessive depth of anaesthesia, we registered the percentage of time (Suppression Ratio, SR) and cumulative time (Suppression Time, ST) spent with a flat EEG. BIS values were recorded every 15 seconds. Clinical evaluation of anaesthesia depth included monitoring the onset of loss of responsiveness and loss of eyelash reflex, if they occurred. The occurrence of side effects, such as pain upon injection and myoclonus, was also registered.

Heart rate (HR) and mean arterial pressure (MAP) were recorded every three seconds and 3 minutes, respectively. The recorded values were averaged for each specific period: from the patient's positioning in the operating room until the induction of anaesthesia for the "pre-injection" period, and from the administration of etomidate until the BIS values rose above the threshold of 60 for the "post-injection" period. These hemodynamics parameters were recorded using the Innovian® Anaesthesia program (Draeger, Germany).

Statistical Analysis

The results are presented as median and interquartile range Q1 to Q3. A Mann-Whitney-Wilcoxon test was used for the analysis of quantitative data, while a Fisher's exact test was used for the analysis of qualitative data. For the analysis of hemodynamic data, a repeated measures analysis of variance (ANOVA) followed by Bonferroni post-hoc correction was employed. The threshold for statistical significance was set at a P-value of < 0.05. The analyses were conducted using Stata/SE 17.0 software.

Results

Responses to the survey regarding the use of etomidate among anaesthesiologists

Between 16 December 2021 and 01 February 2022, ninety-six French-speaking Belgian anaesthetists anonymously responded to the online survey regarding their practice of using

etomidate. Among the respondents, 49% were trainees in anaesthesiology, 14% were young anaesthesiologists with less than 5 years of experience, and the remaining 37% were experienced anaesthesiologists. Most respondents worked in a university hospital, with only 6% working in a non-university hospital, and 2% having a mixed activity. Most of them believe that etomidate is not very effective or ineffective for inducing general anaesthesia in healthy patients, whether for elective or emergency surgery. As a result, they often opt to use or add another hypnotic agent. Among those who use etomidate in such cases, the common dosage ranges from 0.2 mg/kg to 0.3 mg/kg. Responses to the survey on the use of etomidate are presented in Fig. 1.

Depth and duration of anaesthesia following etomidate administration

Out of the 236 patients assessed for eligibility during the study-period, eighteen patients were included and received an induction dose of etomidate of either 0.2 mg/kg (n=8) or 0.3 mg/kg (n=10). The Flow Chart of this study is presented in Fig. 2. The demographic characteristics of the patients were similar between the two groups and are detailed in Table I.

The onset time of general anaesthesia was similar between the 0.2 mg/kg and 0.3 mg/kg groups, as assessed by both clinical and electroencephalographic criteria. Clinically, the time to loss of contact was 46 ± 26 seconds in the 0.2 mg/kg group and 34 ± 13 seconds in the 0.3 mg/kg group ($p>0.05$), while the time to loss of eyelash reflex was 57 ± 29 vs. 41 ± 14 seconds, respectively ($p>0.05$). Electroencephalographically, the time to reach a BIS < 60 was 59 ± 27 vs. and 54 ± 20 seconds respectively in the 0.2 mg/kg group and in the 0.3 mg/kg group ($p>0.05$) (Fig. 3). One patient in the 0.2 mg/kg group and three patients in the 0.3 mg/kg group did not experience a loss of eyelash reflex.

Patients who received the higher dose of etomidate (0.3 mg/kg) maintained an adequate depth of anaesthesia (BIS 40–60) for a longer duration compared to those who received the lower dose (0.2 mg/kg) (respectively 396 ± 175 seconds vs. 156 ± 91 seconds; $p<0.01$) (Fig. 4). Three out of the eight (37.5%) patients who received 0.2 mg/kg of etomidate and five out of the ten (50%) patients who received 0.3 mg/kg of etomidate temporarily presented BIS values that fell below the threshold of 40 ($p>0.05$). However, none of the patients presented an isoelectric EEG trace, characterized by both an SR and ST of zero. The overtime evolution of BIS values following etomidate administration are shown in Fig. 5.

Hemodynamic parameters were comparable between the two groups and remained stable after the induction of general anaesthesia. No patient experienced arterial hypotension (MAP < 65 mmHg) or bradycardia (HR <50 bpm). One out of the 8 patient (12.5%) and 4 out of the 10 patients (40%) who received respectively 0.2 mg/

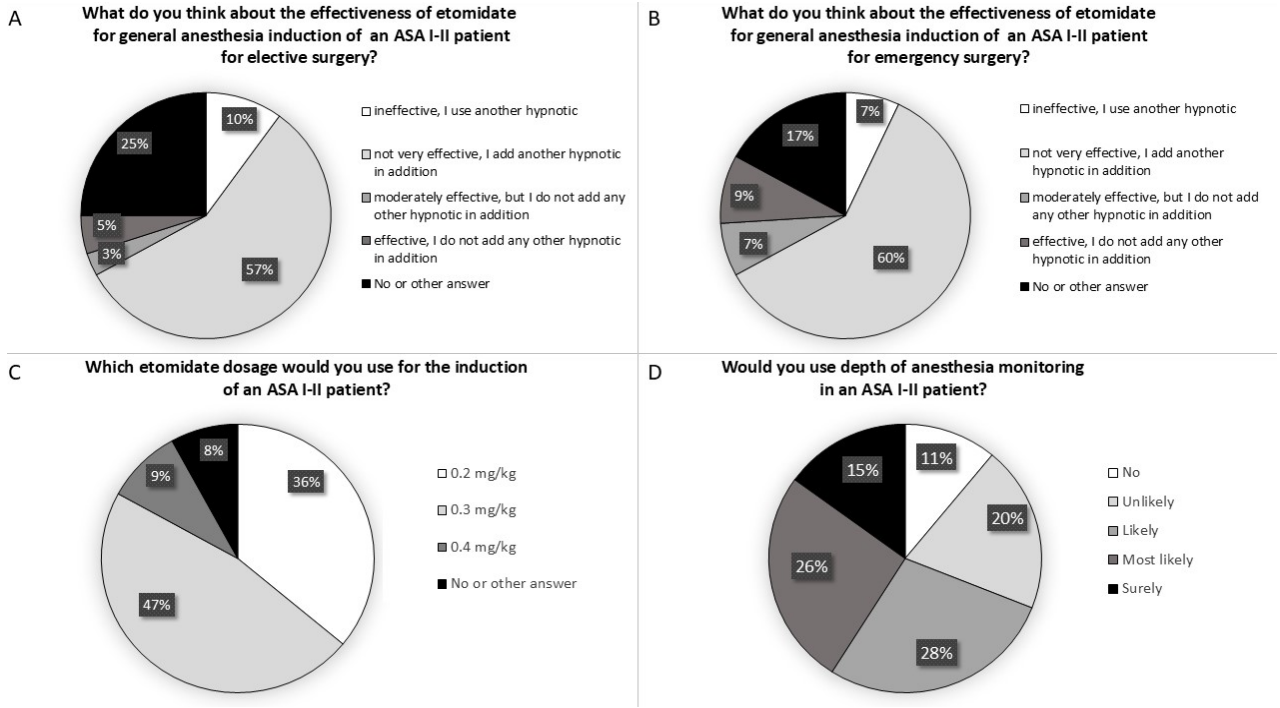

Fig. 1 — Survey responses on the use of etomidate. Ninety-six French-speaking Belgian anaesthesiologists answered anonymous multiple-choice questions regarding their beliefs and practices regarding the use of etomidate in ASA I and II patients in elective (A) or emergency (B) situations, the usual doses of etomidate they employ (C), and their use of depth of anaesthesia monitoring (D).

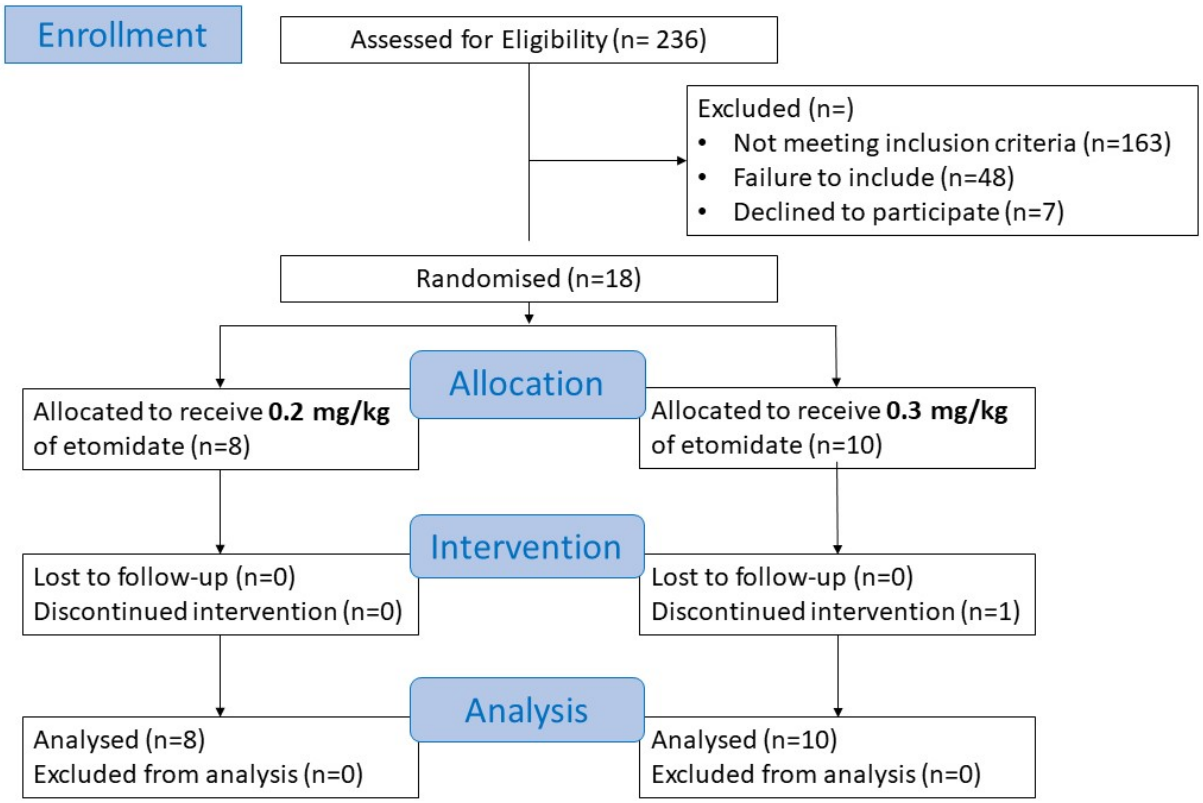

Fig. 2 — CONSORT flow diagram.

Table I. — Demographic characteristics of patients.

	Etomidate Dosage	
	0.2 mg/kg (n=8)	0.3 mg/kg (n=10)
Age (years)	48 [34 to 60]	44 [39 to 57]
Weight (kg)	77 [69 to 87]	72 [64 to 86]
Height (cm)	170 [161 to 174]	169 [159 to 171]
BMI (kg.m^{-2})	27 [25 to 32]	25 [23 to 28]
Sex (male/female)	2/6	4/6
ASA Score I/II	3/5	3/7
The values are expressed as median [min-max]. BMI, Body Mass Index; ASA score, Physical status score from the "American Society of Anesthesiologists."		

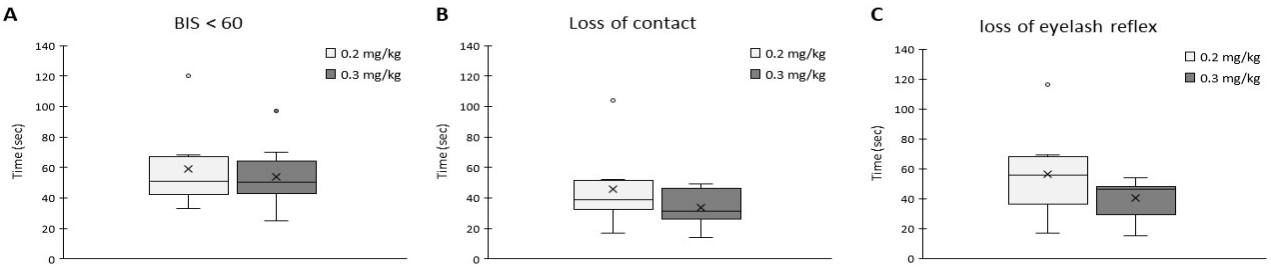

Fig. 3 — The onset time of general anaesthesia. Both electroencephalographic criteria, characterized by a bispectral index (BIS) value < 60 (A), and clinical criteria, characterized by loss of contact (B) and loss of eyelash reflex (C), of the onset of general anaesthesia, appeared simultaneously whether the patient received a 0.2 mg/kg or 0.3 mg/kg bolus of etomidate. One patient in the 0.2 mg/kg group and three patients in the 0.3 mg/kg group did not experience a loss of eyelash reflex. The boxes represent the interquartile range (IQR, 25th to 75th percentiles), while the horizontal line inside the box marks the median (50th percentile). The 'X' indicates the mean value for each dosage group. The black whiskers mark the 5th and 95th percentiles, and values beyond these upper and lower bounds are considered outliers, marked with '*'.

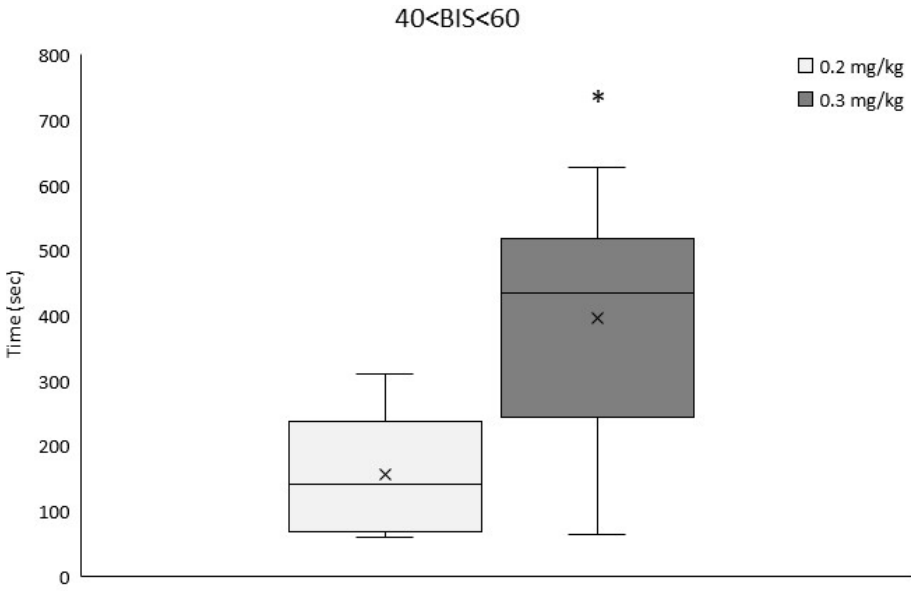

Fig. 4 — Time spent within an adequate depth of general anaesthesia following administration of etomidate. Patients who received the higher dose of etomidate (0.3 mg/kg) spent a longer time within adequate depth of anaesthesia. Adequate depth of anaesthesia was defined by a Bispectral Index (BIS) value between 40 and 60. * $p<0.01$. The boxes represent the interquartile range (IQR, 25th to 75th percentiles), while the horizontal line inside the box marks the median (50th percentile). The 'X' indicates the mean value for each dosage group. The black whiskers mark the 5th and 95th percentiles, and values beyond these upper and lower bounds are considered outliers, marked with '*'.

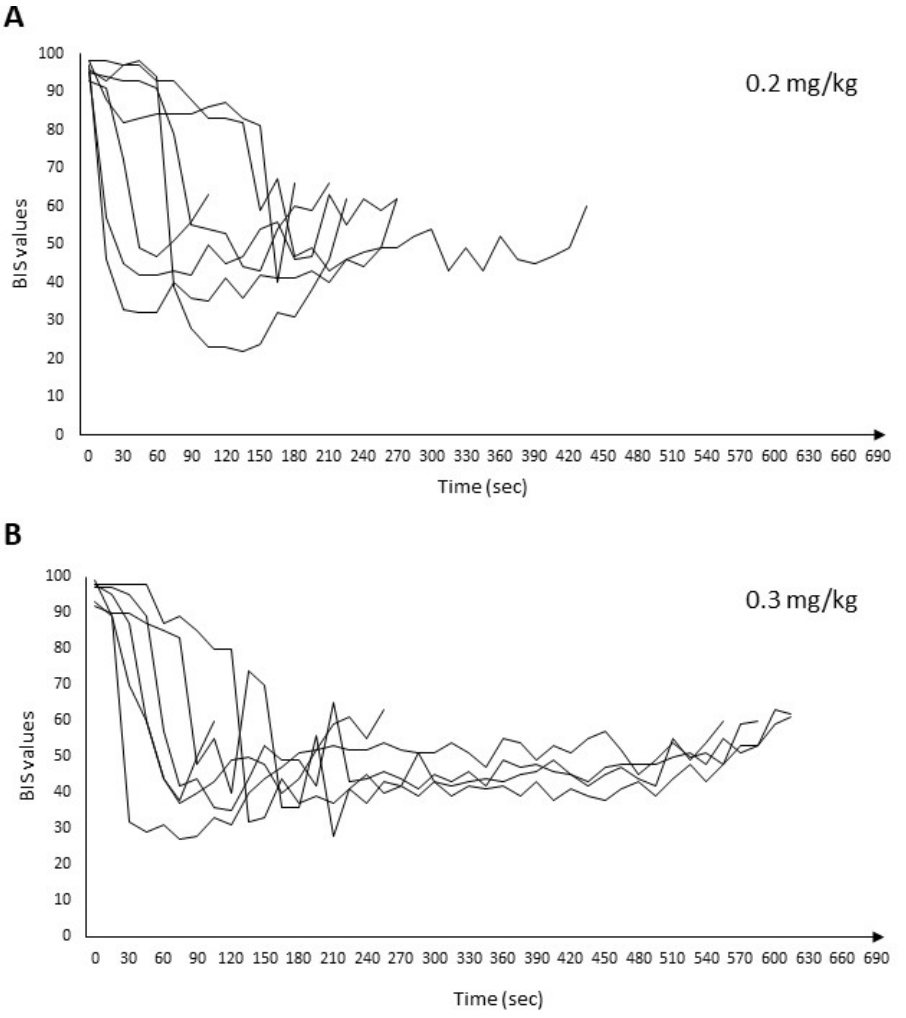

Fig. 5 — Evolution of Bispectral Index (BIS) values over time. Representation of BIS values' evolution for each patient following the injection of a bolus of etomidate, at a dosage of 0.2 mg/kg in (A), and at a dosage of 0.3 mg/kg in (B).

kg or received 0.3 mg/kg of etomidate, experienced myoclonus ($p>0.05$) and 3 of the 8 (37.5%) and 2 of the 10 (20%) of patients experienced pain after etomidate injection of respectively 0.2 mg/kg or 0.3 mg/kg ($p>0.05$).

Discussion

The survey conducted among French-speaking Belgian anaesthesiologists regarding the use of etomidate demonstrates that most of them believe that the use of etomidate is not very effective in healthy patients (ASA score I and II), both in elective and emergency situations. This concern is supported by some "free" responses expressed in the survey, such as "subjective impression of insufficient depth of anaesthesia" or "some efficacy but limited duration of action". This fear of inadequate anaesthesia leads clinicians to add a second hypnotic agent, the propofol, for induction of such patients. This concurrent administration of two hypnotic agents may lead to excessively deep anaesthesia, characterized by an isoelectric EEG trace. It may also result in reduced hemodynamic stability, especially in more frailty patients. Another potential limitation in the use of etomidate that may contribute to its low popularity among anaesthetists is its 20mg/10ml vial presentation. Nearly half of the respondents reported using an induction dose of 0.3 mg/kg, which typically necessitates the use of two vials for an average-weight adult. In the survey on the utilisation of etomidate, most participants were trainees. It should be noted, however, that the survey did not assess experience with etomidate nor the frequency with which respondents used this drug. Consequently, the validity of this survey must be considered with great caution, particularly given that the aforementioned two factors are probably insufficient among trainees. The aim of this study was to provide an objective response to the fear of inadequate depth of anaesthesia associated with the use of etomidate, in the context of a recent resurgence of interest in this drug. Indeed, because of its favourable haemodynamic profile and its ability to prolong seizures with minimal interference with seizure dynamics, etomidate appears to remain the recommended hypnotic, in the context of electroconvulsive therapy[10]. This hypnotic is also commonly used for endotracheal intubation in critically ill patients[11].

The present results suggest an adequate depth of anaesthesia after the administration of an etomidate bolus, either at 0.2 mg/kg or 0.3 mg/kg, in ASA I or II patients. Indeed, all patients showed BIS values descending below the threshold of 60, while none of them exhibited an isoelectric EEG trace. As described by Lallemand et al.[12], we observed loss of eyelash reflex preceding the decrease of BIS values below 60 but the induction doses do not predict the onset time of general anaesthesia whether assessed clinically or by monitoring depth of anaesthesia. Furthermore, not all patients exhibited this loss of eyelash reflex. The persistence of eyelash reflex, combined with spontaneous respiration and/or the presence of myoclonus, may explain the subjective impression described by some anaesthesiologists of etomidate's limited efficacy. However, when anaesthesia induction was achieved with 0.2 mg/kg of etomidate, the duration corresponding to an adequate depth of anaesthesia, characterized by a BIS value between 40 and 60, appeared too short to allow adequate endotracheal intubation conditions. In contrast, patients receiving a higher dose of etomidate (0.3 mg/kg) spent nearly double of time within an adequate depth of anaesthesia. Therefore, etomidate could be considered as an induction hypnotic agent at a dose of 0.3 mg/kg for ASA I and II patients.

Previous studies mostly relied on subjective clinical evaluations of the depth of anaesthesia achieved with a single dose of etomidate8. More recent studies have also monitored the depth of anaesthesia using the bispectral index during continuous etomidate infusion, which does not provide information on the duration of the hypnotic effect following a single bolus dose of etomidate[9,13]. Moreover, in these studies, patients received preoperative anxiolysis with benzodiazepines, which could affect the EEG trace and potentially introduce bias in the interpretation of the results. To our knowledge, only one study, conducted by Lallemand et al., has assessed changes in the bispectral index following a bolus of etomidate used for induction of general anaesthesia[12].

Hemodynamic parameters remained stable in both groups, consistent with numerous observations in the literature[3,14-17]. However, the considerable rate of pain upon injection and myoclonus, similar to literature, does not make it the agent of choice[1,3,18,19]. The pharmaceutical preparation of Etomidate (Hypnomidate®, Piramal Critical Care B.V.) contains propylene glycol, a commonly used solvent for water-insoluble medicinal products, which is frequently associated with pain at the injection site. In the present study, regardless of the determined etomidate dose, all syringes containing the "induction dose" were diluted with saline to a uniform final volume of 30 mL for each patient. Although the volume of saline used for dilution was minimal, it varied between patients. This variability may have influenced the pain experienced upon injection, suggesting that

these specific outcomes should be interpreted with caution. However, diluting such medications in a large volume of saline solution may help minimize this adverse effect linked to this solvent[20].

The bispectral index (BIS), which is employed to monitor the depth of anaesthesia, may be influenced by muscle activity, as captured through the electromyogram (EMG). The objective of our study being the determination of duration for which patients could maintain an adequate level of anaesthesia (BIS 40-60), we administered rocuronium to induce neuromuscular blockade and avoid any EMG interference from involuntary facial muscle contractions, particularly during the gradual dissipation of the hypnotic effect of etomidate. Moreover, to prevent any potential interference from head movements during intubation, this procedure was deliberately postponed until the conclusion of the protocol, which was defined as the moment when BIS values exceeded 60 for a duration of more than 10 seconds, after general anaesthesia was deepened.

Although our results already appeared to be relevant, this was a pilot study which aimed to determine the sample size for a subsequent study assessing the depth of anaesthesia when using etomidate for induction. The central question of this study was the reliability of inducing general anaesthesia, including the phase of endotracheal intubation, in healthy patients. Etomidate was administered in combination with a low dose of remifentanil, with a target site-effect concentration of 2 ng/ml. The synergistic interaction between these two drugs must be carefully considered when interpreting the results. Endotracheal intubation was not performed on patients in this study. However, endotracheal intubation stimulates cerebral cortex activation[21-22]. Etomidate exhibits a weaker inhibitory effect on the pharyngo-laryngeal reflex compared with other hypnotic agents[16]. The effect-site concentration of remifentanil required to blunt tracheal intubation responses in 50% and 95% of patients undergoing etomidate anaesthesia was evaluated at 7.7 ng/ml and 8.7 ng/ml, respectively[23]. This limitation impedes the direct extrapolation of our findings to the specific situation of endotracheal intubation. Nonetheless, it was essential, initially, to evaluate the quality of general anaesthesia achieved after etomidate induction and determine the optimal dose of etomidate in this indication. Therefore, it would be of interest to further investigate the feasibility of inducing general anaesthesia and orotracheal intubation in ASA I – II patients. While bispectral monitoring has been validated for other hypnotic agents (propofol, sevoflurane, ketamine, etc.), its validation for etomidate is currently lacking. Therefore, a key objective for future studies is to validate the bispectral index as a measure of anaesthesia depth following etomidate administration. This will involve analysis of the different EEG bands, including delta, theta, alpha, and beta[21,24-27], as well as performing spectral edge frequency analysis[28].

In conclusion, most anaesthesiologists express concerns regarding the low efficacy of etomidate when administered as a hypnotic agent in ASA I and II patients. Our findings suggest that etomidate can induce a general anaesthesia of adequate depth, characterized by BIS values between 40 and 60, of which the duration double when administered using bolus of 0.3 mg/kg compared with 0.2 mg/kg.

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