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Original Contribution

The effects of propofol-midazolam-ketamine co-induction on hemodynamic changes and catecholamine response

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Abstract
Study Objective: To compare the clinical efficacy of co-induction with propofol-midazolam-ketamine with etomidate as the sole induction agent.
Design: Prospective, double-blinded, randomized controlled trial.
Setting: Operating room of a university hospital.
Patients: 60 ASA physical status 1 and 2 patients scheduled for limited elective surgery requiring general anesthesia.
Interventions: Patients were randomized to two groups to receive etomidate 0.3 mg/kg (single-drug group) or propofol 0.6 mg/kg + ketamine 0.8 mg/kg + midazolam 0.06 mg/kg (three-drug group).
Measurements: Hemodynamic responses (systolic and diastolic blood pressure, and mean arterial pressure) were examined at baseline and at one, three, and 5 minutes after tracheal intubation. Plasma catecholamine levels were measured at baseline, one, and 5 minutes after tracheal intubation.
Main Results: Heart rate (HR) changes differed significantly between the two groups at three minutes ($P = 0.01$) and 5 minutes ($P = 0.00$) after tracheal intubation. However, the HR increase in the three-drug group was in the acceptable range. Percentage changes of epinephrine level differed between the two groups at 5 minutes after tracheal intubation ($P = 0.03$).
Conclusions: The higher norepinephrine/epinephrine ratio noted in the single-drug group may be implicated in lower adrenal sympathetic activity. Propofol-midazolam-ketamine co-induction may be used instead of etomidate for anesthesia induction in patients with hemodynamic instability.

1. Introduction

The principal goal of anesthesia is to maintain optimum autonomic cardiovascular homeostasis in response to stress in the surgical patient [1]. Because etomidate causes less

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hemodynamic instability, this drug seems to be suitable for anesthesia induction in critically ill patients and those with cardiovascular disease. However, the incidence of postoperative nausea and vomiting (PONV) after anesthesia with etomidate is relatively high. The main side effects of etomidate include inhibition of adrenal corticosteroidogenesis. These problems were observed not only during long-term infusion but also in single-dose administration for anesthesia induction [1,2].

The use of combined anesthesia, or co-induction, in patients with poor hemodynamic stability may result in the administration of lower doses of intravenous (IV) anesthesia and fewer side effects [1,3]. The ketamine-propofol combination is believed to provide both sedation and analgesia, with fewer cardiovascular effects due to the opposing effects of each drug [4–6]. Propofol has rapid onset and recovery, a low incidence of PONV, and euphoric effects. It depresses cardiovascular function and the decrease in systolic blood pressure (SBP) may be more prevalent in the older population [1,7,8]. In contrast to propofol, ketamine's cardiovascular stimulatory effects, including increases in heart rate (HR) and cardiac output, may be dangerous in some patients, such as those with coronary artery disease. Restlessness and unpleasant hallucinations after anesthesia limit its usage [1,9]. By using these two drugs together, some unpleasant side effects would not be observed. For instance, propofol-induced hypotension might be compensated by ketamine [1,3,4]. Midazolam, a short-acting benzodiazepine with anxiolytic and antegrade amnestic effects, also may be used as an anesthetic drug. The side effects of midazolam are preventable if used with other drugs for co-induction [10,11].

The aim of this study was to compare the effect of combined anesthesia induction with propofol-midazolam-ketamine with single-drug anesthesia induction with etomidate on the stress response and hemodynamic responses [HR, SBP, diastolic blood pressure (DBP), and mean arterial pressure (MAP)] after tracheal intubation.

2. Materials and methods

This randomized, double-blinded, controlled trial was approved by the Institutional Review Board and Ethics Committee of Urmia University of Medical Sciences. Inclusion criteria were patient age between 18 and 60 years, ASA physical status 1 and 2, and limited elective surgery requiring general anesthesia. Patients with a contraindication to propofol, such as those with allergy to egg and seafood; contraindication to ketamine, such as glaucoma, aneurysm of the large vessels, and schizophrenia; history of diabetes and kidney disease or drug or alcohol abuse; and those undergoing emergency surgery were excluded from the study. Patients with predicted difficult mask ventilation or difficult tracheal intubation according to physical examination (thyromental distance < 6 cm, mouth opening < 4 cm, and inability to protrude the mandible) and Mallampati score ≥ 3 also were excluded from the study.

After routine monitors (electrocardiography, pulse oximetry, noninvasive blood pressure, and capnography) and bispectral index (BIS; Aspect Medical Systems, Norwood, MA, USA) were attached, an IV catheter was placed in all patients. At the same time, blood samples were obtained to measure baseline plasma epinephrine (E) and norepinephrine (NE) concentrations. For premedication, IV midazolam 0.015 mg/kg and fentanyl 1.5 μg/kg were injected three minutes before anesthesia induction. Patients were then randomly allocated to two groups in equal numbers by simple random sampling. The single-drug group received etomidate 0.3 mg/kg (routine induction dose) and the three-drug group received a mixture solution of propofol 0.6 mg/kg + ketamine 0.8 mg/kg + midazolam 0.06 mg/kg. Combination drug dosage was determined based on the hemodynamic changes of each drug and the fact that the combination of two or more anesthetic drugs has additive effects. Anesthesia level was adjusted to achieve a BIS value less than 60. There was no case in which the BIS value was ever higher than 60.

Anesthesia was maintained with 50% nitrous oxide and 50% oxygen (N_2O - O_2) with 1.2% isoflurane. After anesthesia induction, all patients received a nondepolarizing muscle relaxant (atracurium 0.5 mg/kg) to facilitate tracheal intubation three minutes before intubation. Thereafter, patients from both the single-drug and three-drug groups received an injection of vitamin C (500 mg/5 mL) or normal saline, respectively. No study patient received steroids. Drugs were injected by an anesthesiologist who was blinded to the monitored parameters. Tracheal intubation was completed within 15 seconds. Recording of vital signs (at one, three, and 5 min after tracheal intubation) and ethyldiaminetetraacetic acid (EDTA) blood sample collection (one and 5 min after tracheal intubation) were done by an anesthesiology resident who was blinded to the drugs administered. Plasma samples were stored at -20 °C and measured using the ELISA Kit (2 CAT EIA kit; LDN GmbH, Nordhorn, Germany; detection limit 10 pg/mL for E and 50 pg/mL for NE).

2.1. Statistical analysis

The Kolmogorov-Smirnov test was used to assess normality of the samples. Unpaired t-test was used for statistical analysis of continuous quantitative variables with normal distribution. The Mann-Whitney U-test was performed to analyze nonparametric quantitative variables. Data are expressed as means (SD). A P-value < 0.05 was considered statistically significant. To compare values with baseline, percentage changes of the variables were calculated as follows:

$$\text{Percentage variable changes} = \text{measured value/value before tracheal intubation(baseline)} \times 100$$

3. Results

Three patients from each group were excluded from the study due to technical problems with blood sample handling.

The mean age of patients was 36.0 years in the single-drug group and 32.3 in the three-drug group; the two groups were statistically identical in age ($P = 0.25$).

3.1. Comparison of hemodynamic criteria

For mean baseline SBP, a significant intergroup difference was noted between the two groups at baseline [144.5 (18.2) mmHg in the single-drug group and 135.3 (14.7) mmHg in the three-drug group ($P = 0.04$)], but SBP values were statistically similar between the groups at one, three, and 5 minutes after tracheal intubation (Fig. 1). Systolic blood pressure percentage changes from baseline at one, three, and 5 minutes after tracheal intubation were not statistically significant between the two study groups (Table 1).

Diastolic blood pressure differences in baseline and at one and three minutes after tracheal intubation were nonsignificant between the two study groups. Nevertheless, 5 minutes after tracheal intubation, mean values differed significantly (Fig. 2). As with SBP, DBP percentage changes from baseline at one, three, and 5 minutes after tracheal intubation showed no statistically significant differences between the two groups (Table 1).

Mean arterial pressure did not differ statistically between the two groups during the periods of our study (Fig. 3). In addition, MAP percentage changes from baseline at one, three, and 5 minutes after tracheal intubation were similar in the two groups (Table 1).

Mean baseline HR was similar between the two groups. However, HR values in the single-drug and three-drug groups were 83.0 (16.7) bpm versus 91.3 (13.1) bpm at one minute ($P = 0.04$), 77.1 (16.8) bpm versus 91.7 (12.7) bpm at three minutes ($P = 0.04$), and 71.1 (14.7) bpm versus 88.6 (13.6) bpm at 5 minutes after tracheal intubation ($P = 0.00$), respectively (Fig. 4). In addition, significant intergroup differences were noted in HR percentage changes between the two groups at three and 5 minutes versus baseline after tracheal intubation. Three minutes after tracheal intubation, the mean HR percentage decrease was 3.2% in the single-drug group, reaching 96.8%. In contrast, in the three-drug group, HR percentage increased 11.7%, reaching 111.7% ($P = 0.01$). Five minutes after tracheal intubation, the mean HR percentage decrease was 9.9% in the single-drug group, reaching 90.0%, while mean HR percentage increased 8.1% in the three-drug group, reaching 108.1% ($P = 0.00$; Table 1).

Table 1 Percentage changes in hemodynamic criteria and catecholamines in patients receiving etomidate (single-drug group) or propofol-ketamine-midazolam (three-drug group) as induction agents

	Single-drug group (n = 27)	Three-drug group (n = 27)	*P*-value
SBP changes (%)			
PI1	103.8 (16.8)	103.4 (14.2)	0.92 *
PI3	97.9 (15.2)	95.3 (11.0)	0.47 *
PI5	90.5 (14.5)	90.1 (12.2)	0.90 *
DBP changes (%)			
PI1	117.1 (21.6)	111.8 (18.9)	0.34 *
PI3	105.8 (23.2)	102.8 (14.9)	0.57 *
PI5	100.2 (23.5)	91.1 (14.5)	0.09 *
MAP changes (%)			
PI1	110.6 (17.1)	107.8 (14.9)	0.52 *
PI3	101.8 (18.2)	99.2 (12.3)	0.54 *
PI5	95.4 (18.1)	90.4 (12.3)	0.25 *
HR changes (%)			
PI1	104.1 (21.8)	110.7 (16.2)	0.21 *
PI3	96.8 (22.0)	111.7 (18.6)	0.01 *
PI5	90.0 (25.1)	108.1 (20.3)	0.00 *
E changes (%)			
PI1	162.8 (180.2)	140.5 (179.2)	0.67 †
PI5	206.6 (520.4)	247.2 (352.2)	0.03 †
NE changes (%)			
PI1	111.3 (45.6)	105.0 (26.9)	0.54 *
PI5	103.9 (54.3)	105.3 (36.3)	0.91 *

Values are means (SD).

SBP = systolic blood pressure, DBP = diastolic blood pressure, MAP = mean arterial pressure, E = epinephrine, NE = norepinephrine, PI1 = one minute after tracheal intubation, PI3 = three minutes after tracheal intubation, PI5 = 5 minutes after tracheal intubation.

* t-test used to compare values.

† Mann-Whitney U-test used to compare values.

3.2. Comparison of plasma catecholamine concentration

Plasma E concentration increased one minute after tracheal intubation in both groups, with no significant differences noted between the groups. Five minutes after tracheal intubation, plasma E concentrations differed significantly between the two groups, with a decrease seen in the single-drug group but an increase noted in the three-drug group ($P = 0.04$; Table 2). In addition, E percentage

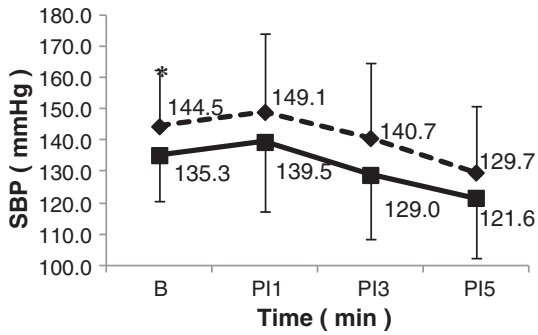

Fig. 1 Comparison of systolic blood pressure (SBP) changes in patients receiving etomidate (■) and propofol-ketamine-midazolam (◆) as induction agents. Values are means (SD). B = baseline, PI1 = one minute after tracheal intubation, PI3 = three minutes after tracheal intubation, PI5 = 5 minutes after tracheal intubation. *$P < 0.05$, t-test.

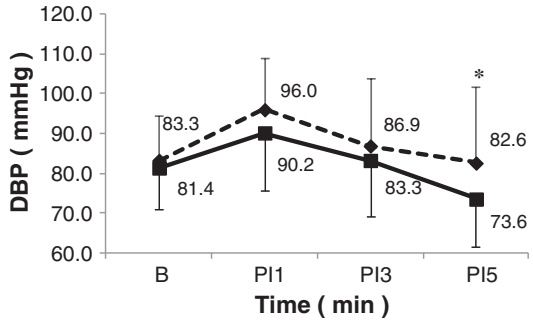

Fig. 2 Comparison of diastolic blood pressure (DBP) changes in patients receiving etomidate (■) and propofol-ketamine-midazolam (◆) as induction agents. Values are means (SD). B = baseline, PI1 = one minute after tracheal intubation, PI3 = three minutes after tracheal intubation, PI5 = 5 minutes after tracheal intubation. *$P < 0.05$, t-test.

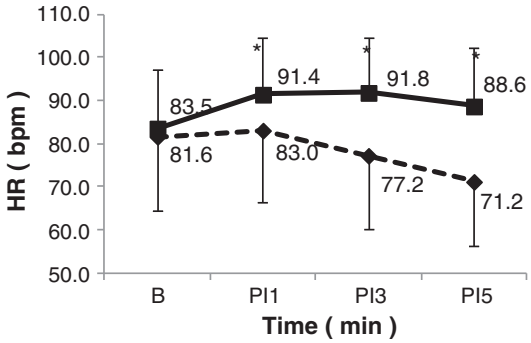

Fig. 4 Comparison of heart rate (HR) changes in patients receiving etomidate (■) and propofol-ketamine-midazolam (◆) as induction agents. Values are means (SD). B = baseline, PI1 = one minute after tracheal intubation, PI3 = three minutes after tracheal intubation, PI5 = 5 minutes after tracheal intubation. *$P < 0.05$, t-test.

concentration changes were significantly different 5 minutes after tracheal intubation (Table 1).

The NE percentage concentration changes were similar between the study groups at 1 minute after tracheal intubation (Table 2). Norepinephrine concentration and NE percentage changes were similar between the study groups 5 minutes after tracheal intubation (Table 1).

After calculation of the NE/E ratio, the ratios showed statistically significant differences between the two groups only at 5 minutes after tracheal intubation, with a higher ratio noted in the three-drug group ($P = 0.04$; Table 2).

4. Discussion

The changes in blood pressure during anesthesia induction with the combination of propofol-midazolam-ketamine were similar to those with etomidate. The HR increase in the three-drug group was in the acceptable range for the most high-risk patients. Although the E percentage changes in the three-drug group were greater than in the single-drug group, NE percentage changes were comparable in both groups.

Changes in HR during anesthesia induction with etomidate are in the range of 15% decrease to 5% increase [1]. In the current study, in an interval of one to 5 minutes after tracheal intubation, the recorded HR changes ranged from a 9.9% decrease to a 4.1% increase in the single-drug group and an 8% to 12% increase in the three-drug group. Even if the changes in the three-drug group were greater than in the single-drug group, the variation range of HR was small and acceptable for most of the patients.

During anesthesia induction with etomidate, MAP changes range from 0% to 17% [1]. The range of MAP in this study varied between a 4.5% decrease and a 10.6% increase in the single-drug group, and a 0.5% to 7.8%

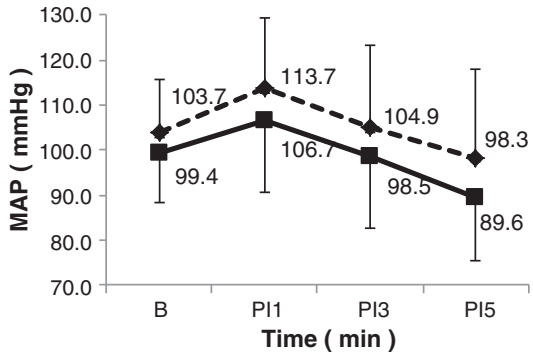

Fig. 3 Comparison of mean arterial pressure (MAP) changes in patients receiving etomidate (■) and propofol-ketamine-midazolam (◆) as induction agents. Values are means (SD). B = baseline, PI1 = one minute after tracheal intubation, PI3 = three minutes after tracheal intubation, PI5 = 5 minutes after tracheal intubation. *$P < 0.05$, t-test.

Table 2 Comparison of plasma catecholamine concentrations in patients receiving etomidate (single-drug group) or propofol-ketamine-midazolam (three-drug group) as induction agents

	Single-drug group	Three-drug group	P-value
E (ng/mL)			
B	2.9 (3.3)	3.7 (3.4)	0.40 *
PI1	4.0 (5.7)	4.4 (7.1)	0.83 *
PI5	2.7 (4.7)	7.3 (10.6)	0.04 *
NE (ng/mL)			
B	24.0 (13.4)	30.7 (9.9)	0.04 †
PI1	24.7 (12.5)	31.1 (10.4)	0.04 †
PI5	24.0 (16.7)	31.0 (12.0)	0.08 †
NE/E ratio			
B	15.3 ± 22.3	11.0 ± 4.9	0.82 *
PI1	16.4 ± 18.0	12.5 ± 6.4	0.79 *
PI5	35.1 ± 89.7	10.4 ± 7.5	0.04 *

Values are means (SD).
E = epinephrine, NE = norepinephrine, B = baseline, PI1 = one minute after tracheal intubation, PI5 = 5 minutes after tracheal intubation.
* values compared with the Mann-Whitney U-test.
† values compared with the t-test.

increase in the three-drug group. The largest increase (10.6%) occurred with etomidate one minute after tracheal intubation, while at that same time it was 7.8% in the three-drug group. The differences between these values did not reach statistical significance. Goyal et al [12] compared the quality of anesthesia with ketamine and fentanyl as co-induction agents with propofol. Because of significant decreases noted in HR, SBP, and DBP in the fentanyl group, Goyal et al concluded that ketamine was a better premedicant than fentanyl. In their study, SBP decreased 1.2% in the fentanyl group one minute after anesthesia induction. However, in this study, the SBP percentage decrease in the three-drug group was 3.4%. This difference may have arisen from the use of the Laryngeal Mask Airway (LMA) instead of tracheal intubation. In another study, Ghatak et al [13] reported that the addition of ketamine to propofol provided hemodynamic stability and comparable conditions for LMA insertion, with significantly less prolonged apnea. Uri et al [14] indicated that this combination decreased the overall rate of respiratory and hemodynamic adverse events. Lim et al [15] showed that a small dose of midazolam with a lower propofol dosage prevented cardiovascular changes at tracheal intubation in aged patients.

Honarmand and Safavi [16] examined the effect of anesthesia induction and tracheal intubation with thiopental-fentanyl, thiopental-ketamine, and thiopental-fentanyl-ketamine on hemodynamic stability. They showed that thiopental-fentanyl-ketamine offered greater stability in hemodynamic variables, which were in the range of ± 20%. Nishiyama et al [10] compared hemodynamic and catecholamine responses to tracheal intubation during anesthesia induction using midazolam-thiopental with thiopental alone. The midazolam-thiopental combination was effective in reducing hemodynamic and cardiac autonomic nervous system responses to tracheal intubation in comparison to conventional anesthesia induction with thiopental alone. Only at 5 minutes after tracheal intubation were E percentage changes and NE/E ratio in the three-drug group more and less, respectively, than those in single-drug group. The NE/E ratio is a good marker for assessment of the balance between peripheral sympathetic nervous system and adrenal sympathetic activity. A high NE/E ratio is accompanied by an increase in peripheral sympathetic activity and/or a decrease in adrenal sympathetic activity [17]. Hence, a higher ratio in the single-drug group was implicated in the lower adrenal sympathetic activity noted.

A single dose of etomidate may result in prolonged adrenal insufficiency and the lack of stress hormones such as cortisol [18]. After anesthesia induction with etomidate, vitamin C and corticosteroids are recommended so as to avoid this complication [1,19]. Compared with propofol-midazolam-ketamine, etomidate is more expensive and less available. Other unwanted side effects of etomidate include pain on injection, thrombophlebitis, PONV, and heightened susceptibility to pneumonia in trauma patients [20].

The combination of propofol 0.6 mg/kg + ketamine 0.8 mg/kg + midazolam 0.06 mg/kg appears to be associated with an acceptable hemodynamic outcome and less adrenal insufficiency. Abbasivash et al reported that co-induction with propofol-ketamine in a ratio of 50-50 maintained hemodynamic variables (except HR changes) in the < 20% range. Adding midazolam to propofol-ketamine produced hemodynamic stability comparable to etomidate.

In conclusion, combined anesthesia with propofol-midazolam-ketamine may be a good alternative to etomidate in patients requiring hemodynamic stability.

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