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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.