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Original Article

Comparison of the hemodynamic effects of etomidate-midazolam and ketamine-midazolam combinations in anesthesia induction in coronary artery bypass surgery

Koroner arter bypass cerrahisinde anestezi indüksiyonunda etomidat-midazolam ve ketamin-midazolam kombinasyonlarının hemodinamik etkilerinin karşılaştırılması

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ABSTRACT

Aim: We aimed to compare the effects of anesthesia induction on hemodynamic parameters of ketamine-midazolam or etomidate-midazolam combinations and coronary artery bypass grafting surgery.

Material and Methods: 40 adult patients undergoing Coronary artery bypass graft (CABG) were randomly allocated into two groups for this prospective randomized double-blinded study. Ketamine group (n = 20) and Etomidate group (n = 20). Intraoperative and postoperative hemodynamic variables, adrenal gland functions and intensive care period were compared after anesthesia induction with etomidate and ketamine.

Results: Perioperative hemodynamic parameters were not significantly different between the groups. Despite similar baseline measurements, cortisol levels were significantly higher 5 minutes after induction, during rewarming, and after Adrenocorticotropic Hormone (ACTH) stimulation test at postoperative day 1 in group ketamine than group etmidate. The groups were not significantly different in terms of duration of postoperative mechanical ventilation, frequency of postoperative delirium, and intensive care unit and hospital lengths of stay.

Conclusion: Ketamine-midazolam combination is an acceptable alternative to etomidate-midazolam combination in terms of hemodynamic stability. Compared with the ketamine-midazolam combination, the etomidate-midazolam combination significantly decreased cortisol levels during the intraoperative and early postoperative periods

Keywords: Coronary artery bypass grafting, hemodynamic instability, adrenal suppression, etomidate, ketamine

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Öz

Amaç: Ketamin-midazolam veya etomidat-midazolam kombinasyonları ile koroner arter bypas greftleme (KABG) cerrahisinin anestezi indüksiyonunun hemodinamik parametreler üzerindeki etkilerini karşılaştırmayı amaçladık.

Gereç ve Yöntemler: KABG cerrahisi uygulanan 40 yetişkin hasta, prospektif randomize çift kör çalışma için rastgele iki gruba ayrıldı. Ketamin grubu (n = 20) ve Etomidat grubu (n = 20). Anestezi indüksiyonu sonrası her iki grupta intraoperatif ve postoperatif hemodinamik değişkenler, adrenal bez fonksiyonları ve yoğun bakım süreci karşılaştırıldı.

Bulgular: Perioperatif hemodinamik parametreler gruplar arasında anlamlı farklılık göstermedi. Benzer başlangıç ölçümlerine rağmen kortizol seviyeleri, indüksiyondan 5 dakika sonra, yeniden ısınma sırasında ve postoperatif 1. gün ACTH (Adrenokortikotropik hormon) stimülasyon testinden sonra grup ketaminde, grup etmidata göre anlamlı derecede yüksekti. Gruplar arasında postoperatif mekanik ventilasyon süresi, postoperatif deliryum sıklığı, yoğun bakım ve hastanede kalış süreleri açısından anlamlı fark yoktu.

Sonuç: Hemodinamik stabilite açısından ketamin-midazolam kombinasyonu, etomidat-midazolam kombinasyonuna göre kabul edilebilir bir alternatiftir. Ketamin-midazolam kombinasyonu ile karşılaştırıldığında, etomidat-midazolam kombinasyonu, intraoperatif ve erken postoperatif dönemlerde kortizol seviyelerini önemli ölçüde azalttır.

Anahtar kelimeler: Koroner arter baypas greftleme, hemodinamik instabilite, adrenal supresyon, etomidat, ketamin

Introduction

During anesthesia induction in cardiovascular surgery, achieving hemodynamic stability should be the primary goal [1, 2]. Different anesthesia induction protocols are administered for this purpose. Etomidate and ketamine are potentially more suitable agents in terms of preventing hypotension, one of the problems that arise during anesthesia induction [3].

Etomidate is among the preferred agents in cardiovascular anesthesia due to the hemodynamic stability it provides. Although this agent is often used as an induction agent, due to its undesirable effects on the synthesis of cortisol in the adrenal gland, practices in the form of recurrent and continuous infusion are avoided [4, 5].

Ketamine increases arterial blood pressure and heart rate by causing sympathetic stimulation in the cardiovascular system (CVS) [6]. It can cause pulmonary artery pressure to increase the burden on the right ventricle by increasing pulmonary vascular resistance [7].

The primary aim of our study is to examine the effects of etomidate-midazolam and ketamine-midazolam combinations used in coronary artery bypass grafting (CABG) surgery anesthesia on hemodynamics, and the secondary aim is to evaluate the etomidate-induced adrenal suppression and ketamine-induced delirium during the intensive care period.

Material and Methods

This study was approved by the Medical and Health Sciences Research Board and Ethics Committee of Baskent University (KA10-114).

The study was a prospective, randomized and double-blinded study. A total of 40 patients who were planned to undergo elective CABG were included in the study. Patients who did not agree to participate in the study, who were younger than 30 years of age or older than 80 years, who had an ejection fraction (EF) rate < 40%, who had an urgent surgical need, who were also planned to undergo a cardiac valve or aorta surgery, who previously used corticosteroids, who had a history of adrenal insufficiency, who used imidazole-type antifungal drugs, who had hypoalbuminemia, who were known to be allergic to study drugs, who had a history of psychotic disorders, who had severe hypertension, which had unstable angina pectoris, who had a chronic renal failure or compensated renal failure, and who had liver failure were not included in the study.

During anesthesia induction, one group was given etomidate 0.3 mg/kg, the other group was given ketamine 1 mg/kg, and both groups were given midazolam 0.025 mg/kg through a peripheral venous access. In addition to those, during induction, they were given fentanyl 10 mcg/kg, as well as vecuronium bromide 0.1 mg/kg as a myorelaxant drug. Both groups were given 1 ml of lidocaine 2% before induction to prevent pain caused by etomidate injections. To maintain anesthesia, the patients were given fentanyl at a rate of 15 mcg/kg/h, and isoflurane 0.5–1.5% in 40% oxygen + 60% air mixture. Systolic, diastolic, average arterial pressures and heart rates were recorded immediately before the anesthesia induction (at minute 0) and during the first 5 minutes after induction at intervals of 1 minute, followed by recordings at intervals of 15 minutes.

Blood was drawn prior to and after induction, and during the warming phase (when body temperature was at 35 °C) for cortisol and ACTH measurements. In order to compare the effects of etomidate and ketamine on steroid synthesis in the adrenal gland, the patients were subjected to ACTH stimulation tests with 1 mg of Synacthen Depot (ACTH synthetic product) i.m. on days 1 and 4. Basal samples of blood were drawn before stimulation tests, and blood was drawn for serum cortisol at the 2nd and 3rd hours after Synacthen Depot injections.

Durations of postoperative mechanical ventilation and intensive care, the need for analgesia, blood pressures, heart rates, inotropic agents that were used, antihypertensives, sedatives and their maximum and minimum amounts, discharge times, and additional problems were recorded.

The Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) scale was used to investigate the delirium that could be caused by the use of ketamine.

Statistical analysis

The main goal of the study was to achieve >15% reduction in blood pressure after induction compared to the initial average blood pressure. In this respect, during the calculation of the sample size, it was seen that it was sufficient to include 18 patients in each group in order for the alpha value to be .80 and the p value to be 0.05. Considering that there may be a 10% difference during the study in normal conditions, 2 patients were added to this number. Consequently, 20 patients were included in each group. The data were examined with the help of the SPSS statistics program. For within-group comparisons, Friedman and Wilcoxon tests were used. And for between-group comparisons, Mann-Withney U tests were carried out for numerical parameters, and Chi-square tests for categorical parameters. $p < .05$ was considered significant.

Results

Considering the demographic characteristics of the groups, the proportion of women to men in the etomidate group was found to be 1/19, and in the ketamine group, it was 9/11 (p=0.04). This difference was caused by randomization. The demographic characteristics and systemic diseases of the patient groups are summarized in Table 1.

Table 1. According to the groups of patients' demographic characteristics, coexisting systemic diseases

	Ketamine (n=20)	Etomidate (n=20)	P
Age (years) ± SD	62,6 ± 7,9	60,9 ± 10,3	0,523
Body weight (kg) ± SD	78,7 ± 10,8	80,2 ± 11,8	0,724
Gender (female) %	45	5	0,040
Systemic Disease			
Diabetes mellitus %	45	35	0,748
Hypertension %	85	75	0,695

In both groups, durations of surgeries; maximum doses of positive inotropic and vasodilator drugs, intravenous fluid, blood and blood products given during surgery; hemodynamic variables; and the amounts of urine during surgery were similar (Table 2).

Table 2. According to the groups of patients surgery, cardiopulmonary bypass and aortic clamp times, the maximum inotropic drug dose during surgery, the intravenous fluid, the amount of blood and blood products, hemodynamic changes occurring during surgery, patients urine volume (mean ± standard deviation [95% confidence interval] or the number [%]).

	Ketamine (n=20)	Etomidate (n=20)	P
Surgical time (minutes) ± SD	252,8 ± 38,6	265,5 ± 40,5	0.239
CPB time (minutes) ± SD	86,2 ± 17,2	92,9 ± 26,5	0.685
Aortic clamp time (minutes) ± SD	52,0 ± 16,5	56,0 ± 15,4	0.685
Maximum dopamine infusion (mcg / kg / min) ± SD	5,3 ± 2,6	5,5 ± 2,2	0.685
Maximum perlinganit infusion (mcg / kg / min) ± SD	7,9 ± 3,7	9,9 ± 3,4	0.351
Intraoperative ES (unit) ± SD	1,8 ± 0,5	2,0 ± 0,3	0.290
Intraoperative FFP (unit) ± SD	1,6 ± 0,5	1,7 ± 0,8	0.405
Intraoperative crystalloid (ml) ± SD	512 ± 445	275 ± 412	0.083
Intraoperative colloid (ml) ± SD	525 ± 111	500 ± 000	0.317
Intraoperative urine volume (ml) ± SD	1078 ± 534	927 ± 408	0.448
Intraoperative bradycardia %	5	5	1
Intraoperative hypertension %	30	30	1
Intraoperative hypotension %	50	20	0,096

CPB: Cardiopulmonary Bypass, ES: Erythrocyte Suspension, FFP: Fresh Frozen Plasma

There were no significant differences between the groups in terms of the systolic, diastolic, and average arterial pressures, heart rates, and percentages of oxygen saturation recorded immediately before the anesthesia induction (at minute 0) and during the first 5 minutes after induction at intervals of 1 minute, followed by recordings at intervals of 15 minutes for 60 minutes (p> 0.05)

Blood ACTH and cortisol levels measured before induction were similar between the ketamine-midazolam and etomidate-midazolam groups (p>0.05). Cortisol levels were found to be suppressed in the etomidate-midazolam group compared to the ketamine-midazolam group at the 5th

minute after induction and while warming up during the CPB (while the body temperature was 35 °C) (p<0.05). At the 5th minute, the average amount of blood cortisol was measured to be 8.2 mcg/dl in the etomidate-midazolam group, and 11.1 mcg/dl in the ketamine-midazolam group (p=0.04). During the CPB warming phase (while the body temperature was 35 °C), the amount of blood cortisol was measured to be 10.0 mcg/dl in the etomidate-midazolam group and 28.3 mcg/dl in the ketamine-midazolam group (p=0.02). Contrary to the amounts of cortisol suppressed in the etomidate-midazolam group, the amounts of ACTH were significantly increased at the 5th minute after induction and while warming up during CPB (while the body temperature was 35 °C), compared to the ketamine-midazolam group (p<0.05). The average amount of ACTH at the 5th minute was measured to be 27.7 pg/ml in the etomidate-midazolam group and 13.0 pg/ml in ketamine-midazolam group (p=0.018). During the CPB warming phase (while the body temperature was 35 °C), the amount of ACTH was measured to be 59.7 pg/ml in the etomidate-midazolam group and 30.7 pg/ml in the ketamine-midazolam group (p=0.038). Blood cortisol levels in the etomidate-midazolam group were found to be suppressed compared to the ketamine-midazolam group during the ACTH stimulation test on the first day after surgery (p<0.05). In the etomidate-midazolam and ketamine-midazolam groups, the amount of blood cortisol before the ACTH stimulation test was 12.6 mcg/dl and 26.5 mcg/dl, respectively (p=0.048); the amount of blood cortisol at the first hour after the ACTH stimulation was 30.3 mcg/dl and 42.9 mcg/dl, respectively (p=0.05); blood cortisol 2 hours after the ACTH stimulation test was measured to be 31.4 mcg/dl and 46.5 mcg/dl, respectively (p=0.011). During the ACTH stimulation test on the 4th day, blood cortisol levels were similar in both groups (Table 3). In both groups; Postoperative mechanical ventilation duration, intensive care time, hospital duration, inotrope, and antihypertensive agent usage amount were found to be similar (Table 4).

The patients were assessed in terms of postoperative delirium, with the help of the CAM-ICU scale consisting of the headings of sudden changes in consciousness, attention disorder, thought/orientation disorder, and lost consciousness levels. There were no signs of delirium in the postoperative period among the patients in either of the groups who were assessed under four headings.

Table 3. Amounts of ACTH and cortisol during surgery according to the groups of patients, the 1st and 4th day after surgery, according to the ACTH stimulation test and blood cortisol levels (mean ± standard deviation [95% confidence interval])

	Ketamine (n=20)	Etomidate (n=20)	P
ACTH (pg/ml) ± SD			
Beginning	8,7 ± 4,7	11,9 ± 5,8	0.070
5 minutes after induction	13,0 ± 10,9	27,7 ± 27,0	0.018
Re-warming (35 ° C)	30,7 ± 23,9	59,7 ± 55,2	0.038
Cortizol (mcg/dl) ± SD			
Beginning	7,3 ± 3,5	5,5 ± 1,8	0.118
5 minutes after induction	11,1 ± 5,1	8,2 ± 3,2	0.040
Re-warming (35 ° C)	28,3 ± 32,9	10,0 ± 4,1	0.002
1st day ACTH stimulation test (pg/ml) ± SD			
Initial cortisol	26,5 ± 25,7	12,6 ± 8,32	0.048
1 hour after stimulation	42,9 ± 21,0	30,3 ± 4,5	0.050
After 2 hours stimulation	46,5 ± 21,7	31,4 ± 4,1	0.011
4th day ACTH stimulation test (pg/ml) ± SD			
Initial cortisol	18,0 ± 11,7	20,0 ± 12,6	0.725
1 hour after stimulation	41,1 ± 16,2	38,8 ± 8,4	0.588
After 2 hours stimulation	43,3 ± 15,2	42,8 ± 10,6	0.914

ACTH: Adrenocorticotropic hormone

Table 4. Postoperative mechanical ventilation, intensive care, hospital time, use of inotropes, antihypertensive agents for groups.

	Ketamine (n=20)	Etomidate (n=20)	P
Mechanical ventilation (hours) ± SD	21,8 ± 3,3	22,1 ± 3,9	0.976
ICU LOS (days) ± SD	3 ± 1,17	3 ± 1,07	0.818
Hospital LOS (days) ± SD	10,4 ± 2,3	10,1 ± 2,5	0.442
Maximum dopamine (mcg / kg / min) ± SD	5,2 ± 2,8	5,1 ± 2,1	0.453
Maximum perlinganit (mcg / kg / min) ± SD	4,3 ± 2,1	5,1 ± 2,1	0.189

ICU: Intensive care, LOS: length of stay

Discussion

The combination of ketamine and midazolam was concluded to be able to be used as an alternative induction agent to the combination of etomidate and midazolam in patients who undergo CABG surgery without causing any hemodynamic instability. In our study, in the etomidate-midazolam group, it was shown that adrenal suppressants developed after the intraoperative etomidate injection and in the ACTH stimulation tests on day 1. No significant difference was found

between the two groups in the ACTH stimulation test on day 4. There was no significant difference between the two groups, either, in terms of postoperative delirium that we compared with the help of the CAM-ICU scale, which we thought might be related to ketamine. Duration of postoperative mechanical ventilation, intensive care and hospital stay, blood and blood products that were given, and positive inotropic amounts were also similar between the two groups.

Hemodynamic instability that can occur after induction of anesthesia significantly increases morbidity and duration of hospital stay [8-10]. Post-induction hypotension can set the stage for major complications such as cerebrovascular disease (CVD) and myocardial infarction (MI) with high mortality and morbidity [11, 12]. In the retrospective study of Reich et al. examining 2152 patients, the effects of intraoperative hemodynamic variables on mortality, CVD and myocardial damage were examined in patients undergoing CABG surgery, and hemodynamic instability was reported to be a predictor of myocardial injury, CVD, and mortality after surgery [13]. In our study, decreases in systolic, diastolic and average arterial pressures were detected in both the etomidate-midazolam group and the ketamine-midazolam group after induction compared to the initial levels. However, no significant difference was found between the two groups. In within-group comparisons, compared to the initial values in the etomidate-midazolam group, in the first 60 minutes after induction of anesthesia, systolic blood pressure, diastolic blood pressure and average blood pressure was found to decrease more frequently than those in the ketamine-midazolam group. The number of heart beats in the ketamine-midazolam group decreased significantly in the first 60-minute period after anesthesia induction in within-group comparisons, whereas it was unchanged in the etomidate-midazolam group. Ketamine affects CVS through the adrenergic central pathway. For this reason, it is used together with medicines that suppress the central nervous system, such as benzodiazepines. In our study, midazolam was administered to both groups in order to ensure standardization. During the first 60 minutes after induction, the reductions in blood pressures in the etomidate group and the reductions in heart rates in the ketamine group were thought to be associated with midazolam.

Etomidate infusion, which was administered in 1984 for the first time by Wagner et al. to 5 patients, was shown to decrease cortisol levels [14]. In a study conducted on rats, it was shown to inhibit 11β-hydroxylase. In a study conducted in 1985 by Duthie et al. comparing etomidate and thiopental in 12 patients to undergo minor surgery under general anesthesia, it was shown that a dose of bolus etomidate caused 11β-hydroxylase inhibition. In their study conducted in 2003, Annane et al. reported that the response in 94.4% of the patients given a single dose of etomidate was impaired in the corticotropin stimulation test, whereas this rate was 71% in the group that did not receive etomidate [15, 16].

Etomidate can facilitate further suppression of cortisol, which should be released with adrenal suppression, and as a result, facilitate the development of serious postoperative complications on the one hand; and on the other, it can help protect the balance between the oxygen delivery and consumption of the myocardium and prevent deterioration in the immune system in the postoperative period as it prevents the rise in stress hormones [17-19]. Morel et al. carried out a prospective study where they compared hemodynamic results of etomidate and propofol induction on 100 patients undergoing CABG surgery. They reported that the cortisol response was suppressed in the etomidate group, but the patients in the etomidate group were hemodynamically more stable, and there was no difference between the two groups in terms of postoperative pulmonary and renal complications [20]. In our study, the blood cortisol levels were found to be suppressed in the etomidate-midazolam group compared to the ketamine-midazolam group in the postoperative ACTH stimulation tests on the first day after anesthesia induction and after surgery, whereas there was no difference between the groups in the ACTH stimulation test on the 4th day.

During waking after ketamine induction, agitation was observed in some of the patients, and this condition was linked to the hallucinogenic effect of ketamine. The incidence of hallucinations varied between 5% and 30%. The incidence was increased among females, with high doses and rapid injection. Premedication with benzodiazepines may be able to reduce hallucinations [21]. In our study, both groups were assessed based on the CAM-ICU delirium scale in the postoperative period. There were no findings of delirium during the first postoperative week both in the etomidate-midazolam group and in the ketamine-midazolam group.

There are various limitations to our study. Preoperative hospital duration was not evaluated. The number of men and women was not equal in the etomidate-midazolam group. The difference in the proportion of women and men in the etomidate-midazolam group was thought not to affect the intraoperative cortisol and

ACTH amounts, and the results of the ACTH stimulation tests on the first and fourth days due to the fact that the women included in the study were in their postmenopausal period, and therefore their ovaries were not hormonally active. The two groups were not compared with a third control group in terms of intraoperative cortisol and ACTH amounts, and the results of the ACTH stimulation tests on the first and fourth days.

Conclusion

In our study comparing the hemodynamic effects of etomidate-midazolam and ketamine-midazolam combinations in anesthesia induction in coronary artery bypass grafting surgery, it has been concluded that the combination of ketamine-midazolam can be used as an alternative induction agent to the combination of etomidate-midazolam without causing any hemodynamic instability or adrenal suppression, in patients who are planned to undergo CABG surgery.

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