Single dose esmolol attenuates bispectral index scale response to intubation during fentanyl-midazolam anesthesia for cardiac surgery

Kardiyak cerrahide fentanyl-midazolam anestezisine eklenen tek doz esmolol entübasyona verilen bispektral indeks skala yanıtını azaltır

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Background: In this study, we investigated whether esmolol prior to cardiac anesthesia induction can modify the bispectral index scale (BIS) response following orotracheal intubation.

Methods: After approval from the hospital ethics committee was obtained, we analyzed 64 ASA II patients who were scheduled for coronary artery bypass graft surgery. In the double-blind study, patients were divided into two subgroups before anesthesia induction with fentanyl-midazolam-rocuronium and randomized to esmolol (group E; n=32) or saline (group S; n=32). Following baseline measurements of vital signs and BIS score, patients received either 1 mg/kg esmolol intravenous or the equivalent volume of saline five minutes before anesthesia induction. Heart rate, mean arterial pressure and the BIS responses were recorded at baseline, at two minutes following infusion, at five minutes following induction, and at one, two and three minutes following intubation. The primary outcome of the study was Δ BIS. The study achieved a power of 95% for a-20%-change in Δ BIS.

Results: In the esmolol group, heart rate was decreased significantly compared to baseline in the second time point. Mean arterial pressure was similar between the groups at any time point. The BIS response was significantly higher in the saline group at one and two minutes following intubation, compared to esmolol group.

Conclusion: This study demonstrated that esmolol did not only decrease the heart rate within two minutes after injection but also attenuated BIS increases after the stimulation of orotracheal intubation. In addition, it seems that esmolol deepened the fentanyl-midazolam anesthesia.

Key words: Bispectral index scale; cardiac anesthesia; esmolol; fentanyl; midazolam.

Amaç: Bu çalışmada kardiyak anestezi indüksiyonu öncesi verilen esmololün, orotrakeal entübasyona verilen bispektral indeks skala (BIS) yanıtını değiştirip değiştirmediği araştırıldı.

Çalışma planı: Hastane etik kurulu onayı alındıktan sonra koroner arter baypas cerrahisi yapılması planlanan 64 ASA II hasta analiz edildi. Çift kör çalışmada, fentanil-midazolam-roküronyum ile anestezi indüksiyonu yapılmadan önce, hastalar iki gruba ayrıldı ve esmolol (grup E; n=32) veya salin (grup S; n=32) randomize edildi. Hastalara girişte hayati bulgular ve BIS monitörizasyonunu takiben, anestezi indüksiyonundan 5. dakika önce 1 mg/kg intravenöz esmolol veya aynı hacimde salin enjekte edildi. Kalp hızı, ortalama arter basıncı ve BIS yanıtı; başlangıçta, infüzyonu takiben 2. dakikada, indüksiyonu takiben 5. dakikada ve entübasyonu takiben 1, 2. ve 3. dakikalarda kaydedildi. Bu çalışmanın primer sonucu, Δ BIS idi. Bu çalışma Δ BIS'de %20 değişiklik için %95 güce sahipti.

Bulgular: Esmolol grubunda kalp hızı, başlangıca kıyasla, ikinci dönemde anlamlı düzeyde azaldı. Ortalama arter basınçları tüm zaman aralıklarında her iki grupta benzerdi. Entübasyonu takiben 1. ve 2. dakikalarda BIS yanıtı, salin grubunda, esmolol grubuna kıyasla anlamlı olarak yüksekti.

Sonuç: Bu çalışmada esmololün, verilişinden itibaren 2 dk. içinde kalp hızını düşürdüğü ve orotrakeal entübasyonun uyarımına bağlı BIS yanıtı artışını baskıladığı görüldü. Buna ek olarak, esmololün, fentanil-midazolam anestezisini derinleştirdiği görüldü.

Anahtar sözcükler: Bispektral indeks skala; kardiyak anestezi; esmolol; fentanil; midazolam.

Received: February 16, 2011 *Accepted*: February 20, 2011

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An electroencephalogram (EEG) may detect many reactions during general anesthesia, including sympathetic nervous system stimulation and arousal reactions during noxious stimulation, such as with endotracheal intubation (ETI) or a laryngoscopy.[1]

Fentanyl and midazolam are the drugs most preferred by many clinicians for the induction of cardiac anesthesia. The bispectral index scale (BIS), a processed EEG response to ETI following opioid-benzodiazepine anesthesia is still controversial. The BIS change has been found to have the same sensitivity as the hemodynamic response for detecting deficits in the analgesic component of anesthesia after a painful stimulus.[1] The adjunctive use of opioid analgesics has been reported to confound the use of BIS as a measuring instrument for anesthetic adequacy, especially when movement response to noxious stimulation such as a skin incision was used as the primary end point.[2] It has also been reported that the BIS, a helpful monitor of anesthetic depth, is not a reliable monitor of global anesthetic adequacy during total intravenous anesthesia with a combination of midazolam and fentanyl in cardiac surgical patients.[3] On the other hand, another study reported that during clinically adequate anesthesia with fentanyl and midazolam, the BIS varied considerably.[4] There are also studies which have concluded that the BIS is well correlated with the hypnotic component of anesthesia independent of the presence of an opioid.[5]

The effect of esmolol on the BIS during anesthesia or induction is still a subject for debate.[6-8] In this study, we aimed to find out whether adding a single dose of esmolol prior to the induction of fentanyl midazolam anesthesia for cardiac surgery could modify the BIS response following ETI.

PATIENTS AND METHODS

After receiving the approval of our hospital's ethics committee and having obtained informed consent, we analyzed 64 American Society of Anesthesiology (ASA) stage II patients who were scheduled for coronary artery bypass graft (CABG) surgery between June 2007 and May 2008. Patients with regulated hypertension taking anti-hypertensive drugs other than beta-blockers and/or regulated diabetes mellitus with normal sinus rhythm electrocardiography (ECG) were included in the study. Patients with previous myocardial infarction (MI) history, other coexisting diseases such as chronic obstructive pulmonary disease (COPD), or renal or hepatic failure were excluded from the study as were those patients for whom endotracheal intubation was predicted to be difficult.

All patients were monitored continuously using ECG, a pulse oximeter, and a capnograph. Their intra-arterial blood pressure was also constantly checked, and their heart rate (HR) and mean arterial pressure (MAP) levels were also monitored regularly. The BIS values were measured using the BIS Quatro Sensor (Aspect Medical Systems, Norwood, MA, USA) in real time using frontocentral channels which were continuously displayed on the monitor.

Patients received 10 mg diazepam orally the night before surgery for premedication. Upon arrival to the operating room, the above-mentioned monitorization was carried out, and the baseline (Time 1) values of HR, MAP and BIS were recorded. The patients were then randomly assigned using the block randomization method via Random Allocation Software (Version 1.0.0) in a double blind fashion to receive either esmolol (group E; n=32) or the same volume of saline intravenously (group S; n=32) prior to the induction of anesthesia. Patients and the attending anesthesiologist involved in patient management and data collection were unaware of the group assignments. Patients received either a 1 mg/kg esmolol bolus or the same volume of saline over one minute. The selected data was then recorded two minutes after the injection (Time 2). Five minutes after the administration of the esmolol or saline, all patients received 1 mg/kg midazolam, 10-15 microgm/kg fentanyl, and 0.7 mg/kg rocuronium slowly for the induction of anesthesia. The patients were then manually ventilated with a bag of 100% oxygen, and the selected data was recorded five minutes following induction (Time 3). Afterwards, endotracheal intubation was performed. The study concluded following the collection of data during the first, second, and third minutes (Times 4, 5, and 6, respectively) after intubation. The patients received no additional anesthetics during the entire study period, and those who received drugs other than the study protocol were excluded.

The primary outcome of this study was Δ BIS during the last four time periods. A 20% change in BIS as well as a p value less than 0.05 were considered significant. The study used a repeated measures design divided into two groups of 32 for a total of 64 subjects. Each subject was measured four times for Δ BIS. A power analysis indicated that a sample size of 32 patients per group would be adequate to detect a difference of 20% in the BIS after intubation with α=0.05 and a power of 95%.[7] Statistical analysis was performed with SPSS 15.0 for Windows (SPSS Inc, Chicago, IL. USA). Metric values were expressed as mean ± standard deviation (SD) and median (minimum-maximum). Group comparisons

Table 1. Demographic and operational data

Variable	Group E (n=32)				Group S (n=32)				*p*
	n	Mean±SD	Median	Min.-max.	n	Mean±SD	Median	Min-max.	
Gender									
Male	25				26				0.13
Female	7				6				
Age (year)		59.34±8.77				62.38±9.15			0.18
Weight (kg)		73.34±12.73				75.44±13.18			0.52
Co morbid disease (number of patients)									
None	7				13				
HT	12				7				0.75
DM	6				5				
HT + DM	7				7				
Number of by passed vessels			3	1-4			3	2-4	0.49

E: Esmolol; S: Saline; SD: Standard deviation; Min.: Minimum; Max.: Maximum; HT: Hypertension; DM: Diabetes mellitus.

were evaluated by Student's t-test, the Mann-Whitney U-test, and the chi-square test. For the BIS, HR, and MAP levels, repeated analysis of variance (ANOVA) measurements were used for comparisons both between and within groups. A *p* value of less than 0.05 was considered to be significant.

RESULTS

Sixty-four patients divided into groups of 32 (group E and group S) who were electively scheduled for CABG surgery were analyzed in this study. All of the patients who met the inclusion criteria finished the study. No differences were observed in the patients' demographic data, comorbid disease, or number of bypassed coronary vessels (Table 1).

The mean of the HR value was found to be insignificant in all time periods when comparing both groups (Table 2), and the 95% confidence intervals are summarized in Table 3. The HR baseline value decreased significantly in group E (7.5%) compared to group S on the second minute following study drug administration (Time 2), (Figure 1). Otherwise, HR decreased from the baseline value in the fifth minute following the commencement of induction (Time 3) in both groups. Heart rate increased significantly following a noxious stimulation such as ETI (Times 4, 5, and 6) compared with the induction values (Time 3). In both groups, p value was <0.001 (Table 2).

The means of the MAP values were similar in both groups during any time period (Figure 2), and the 95% confidence intervals are summarized in Table 4. Therefore, there was no need to do a Bonferroni-corrected Student's t-test for this data. On the other hand, the MAP value decreased following induction compared with the baseline and increased afterwards following ETI compared with the induction values in both groups (Figure 2).

The BIS value was similar and showed consciousness during the baseline (97.84) in both groups. The BIS data remained insignificant among the two groups during the second and fifth minutes following fentanyl-midazolam induction (Time 3). During the first and second minute after ETI, the BIS value changed among the groups, and the 95% confidence intervals for mean BIS values are shown in Table 5. The BIS remained at the same value during the aforementioned periods in the esmolol group (group E).

Table 2. Heart rate (beats/min) during selected time periods

Variable	Group E	Group S	*p*
	Mean±SD	Mean±SD	
Time 1	82±7	78.8±14	[a]p>0.05
Time 2	75.8±7*	77.5±12	[a]p>0.05
Time 3	66.3±7	65.6±8	[a]p>0.05
Time 4	70.2±10	70.4±10	[a]p>0.05
			#p<0.001
Time 5	72.8±9	72.5±10.2	[a]p>0.05
			#p<0.001
Time 6	71.5±10	71.5±10	[a]p>0.05
			#p<0.001

E: Esmolol; S: Saline; SD: Standard deviation; Time period values measured during 1: basal; 2: second minute following esmolol or saline injection; 3: fifth minute following anesthesia induction; 4: first minute following intubation; 5: second minute following intubation; 6: third minute following intubation. [a] No statistical difference in HR values among the groups during selected time periods. * Baseline HR decreased significantly in group E during the second minute following administration of esmolol compared with group S (Time 2). # HR increased significantly during first, second and third min. (Time periods; 4, 5, and 6) following intubation compared with the fifth minute of induction (Time 3) in both groups.

Table 3. 95% confidence interval for heart rate between groups

HR	Mean	Standard error	95% confidence lower bound	Interval upper bound
1	80.4	1.4	77.5	83.2
2	76.6	1.2	74.1	79.1
3	66	0.9	64	67.9
4	70.3	1.2	67.8	72.9
5	72.6	1.2	70.2	75.1
6	71.5	1.2	68.9	74.1

HR: Heart rate; Time period values measured during 1: basal; 2: second minute following esmolol or saline injection; 3: fifth min following anesthesia induction; 4: first minute following intubation; 5: second minute following intubation, 6: third minute following intubation.

However, the BIS value increased significantly (Time 4=21.42% increase) (Time 5=23.88% increase) in group S following ETI compared with the induction values. The BIS was again similar in both groups in the third minute of ETI as seen in Figure 3.

DISCUSSION

In this study we found that 1 mg/kg esmolol decreased HR in the second minute following injection. Single dose esmolol given before cardiac anesthesia induction with fentanyl-midazolam seems to attenuate the BIS response early in the first and second minutes following ETI. This study demonstrated that single dose esmolol given almost 10 minutes before ETI did not help to decrease the the HR and MAP levels following ETI. Instead of a single bolus dose, esmolol infusion should be considered for decreasing these hemodynamic responses.

The hemodynamic (HR and MAP) changes activated by adrenergic response during intubation are generally transient. However, in patients with coronary artery disease (CAD), an increase in these circulating parameters may precipitate unfavorable effects. The BIS, an EEG indicator that measures interfrequency phase relationships in the EEG, has been proposed as a measurement instrument for anesthetic depth.[9] The BIS change has been found to be as sensitive as the hemodynamic response for detecting deficits in analgesic components of anesthesia after a painful stimulus like laryngoscopy or ETI.[1] However, the BIS response to ETI following opioid-benzodiazepine anesthesia is still controversial. During fentanyl-midazolam anesthesia, which is usually preferred for cardiac surgery, the BIS was found to vary considerably when clinically adequate anesthesia was observed,[4] but Guignard et al.,[1] reported that the BIS is a useful monitor of the

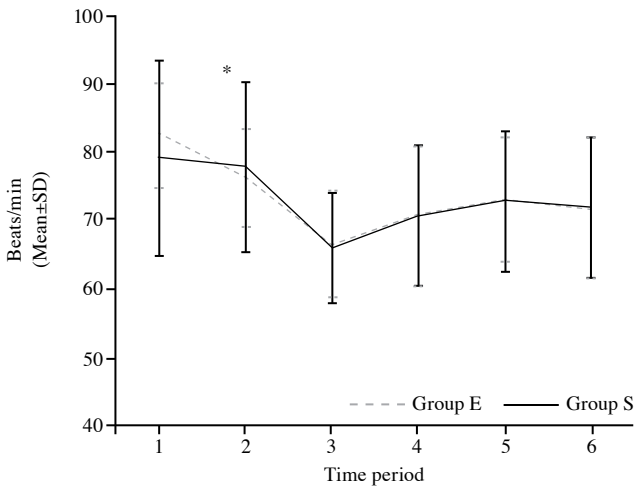

Figure 1. Heart rate changes during selected time periods. Time period values measured during 1: basal; 2: second minute following esmolol or saline injection; 3: fifth minute following anesthesia induction; 4: first minute following intubation; 5: second minute following intubation; 6: third minute following intubation. There was a significant difference in HR between the groups in the second minute following the administration of emolol or saline compared with the baseline; HR is lower in group E. *: p<0.001.

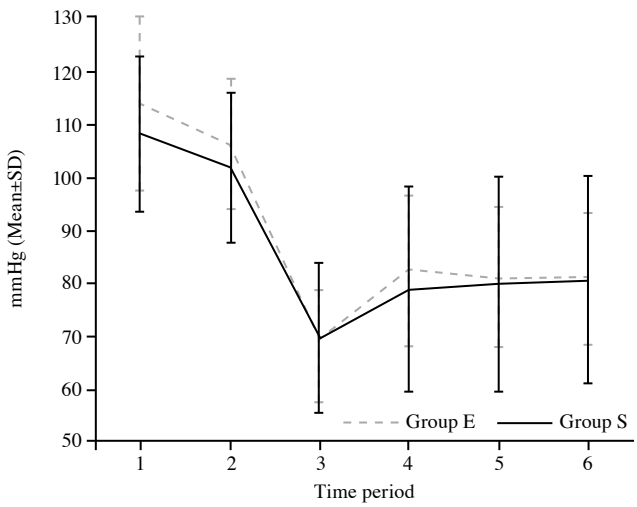

Figure 2. Mean arterial pressure changes during selected time periods. Time period values measured during 1: basal; 2: second minute following esmolol or saline injection; 3: fifth minute following anesthesia induction; 4: first minute following intubation; 5: second minute following intubation; 6: third minute following intubation. There was no significant difference between the two groups in MAP values during any time period (p>0.05).

Table 4. 95% confidence interval for the mean of mean arterial pressure between groups

MAP	Mean	Standard error	95% confidence lower bound	Interval upper bound
1	110.6	1.9	106.7	114.5
2	103.7	1.6	100.4	107
3	68.5	1.5	65.4	71.7
4	80.3	2.1	76	84.5
5	80.2	2.1	75.9	84.5
6	80.5	2	76.4	84.6

MAP: Mean arterial pressure; Time period values measured during 1: basal; 2: second minute following esmolol or saline injection; 3: fifth minute following anesthesia induction; 4: first minute following intubation; 5: second minute following intubation; 6: third minute following intubation.

Table 5. 95% confidence interval for mean BIS values between groups

BIS	Mean	Standard error	95% confidence lower bound	Interval upper bound
1	97.8	0	97.6	98
2	97.4	0	97.2	97.6
3	44.2	0	42.6	45.8
4	49.1	1	46.9	51.3
5	49.8	1.2	47.2	52.4
6	46	0	44.2	47.9

BIS: Bispectral index scale; Time period values measured during 1: basal; 2: second minute following esmolol or saline injection; 3: fifth minute following anesthesia induction; 4: first minute following intubation; 5: second minute following intubation; 6: third minute following intubation.

depth of remifentanil-propofol anesthesia for patients who are incapable of HR and MAP responses to noxious stimuli because of medications or cardiovascular disease. Conflicting results like these led us to establish Δ BIS as the primary outcome of this study. Because it reveals the differences of the BIS values detected during the postinduction and postintubation periods following fentanyl-midazolam induction for cardiac surgery patients.

Esmolol, a short-acting beta1-adrenoreceptor antagonist, produces a dose-dependent attenuation of the adrenergic response to ETI.[10] However, the effect of single dose esmolol on the BIS during anesthesia or the induction of anesthesia is still a subject for debate. One study stated that a single dose of esmolol affects the MAP and HR but has no effect on the BIS value during propofol-fentanyl anesthesia.[6] Another study found that single dose esmolol blunted the increase in the BIS to tracheal intubation during sevoflurane anesthesia but not during desflurane anesthesia.[7] It was also concluded that esmolol infusion attenuated hemodynamic and somatic responses to laryngoscopy and orotracheal intubation and also prevented the BIS arousal reactions in patients anesthetized with propofol.[8]

There are limited studies about the effect of single dose esmolol on the BIS response to ETI following fentanyl-midazolam anesthesia induction for cardiac surgery. Our hypothesis was that a single bolus dose of 1 mg/kg esmolol given before the induction of fentanyl-midazolam anesthesia would decrease HR rapidly and would blunt the BIS increase following ETI.

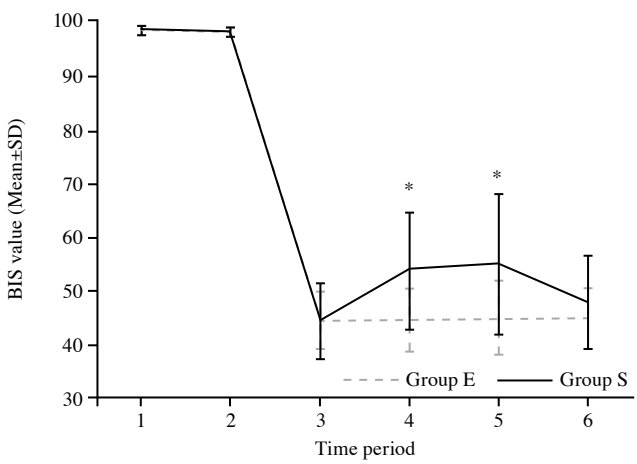

Figure 3. Bispectral index scale values during selected time periods. Time period values measured during 1: basal; 2: second minute following esmolol or saline injection; 3: fifth minute following anesthesia induction; 4: first minute following intubation; 5: second minute following intubation; 6: third minute following intubation. There was a significant difference in the BIS values between the groups in the first and second minutes following the intubation period. The BIS values were higher in group S compared with the postinduction values. *: p<0.001.

The HR levels decreased about 8% in group E in the second minute following the injection of esmolol, which is significant compared with group S which received injections of saline. This is consistent with a study which showed a rapid decrease in HR with esmolol with a response occurring within 4.8±3.0 min.[11] In another study, esmolol infusion given before propofol induction was found to decrease HR after two minutes.[12] These results are similar to our study. However, the half-life of esmolol was found only average 9.19 minutes.[13] This is why single dose esmolol given more than 10 minutes before intubation did not help to blunt HR increases following ETI in our study. We should have considered esmolol infusion following the single dose in order to decrease HR.

The mean arterial pressure did not change between the groups in our study, which ended almost 15 minutes following induction. That correlates with the findings of the Ornstein study which reported that the maximum decrease in MAP is 42.5±8.9 minutes following esmolol administration.[11] This effect was mediated by plasma renin activity which decreased within 32.1±15 minutes after esmolol infusion.[11]

It seems plausible that beta-blockers potentiate the "hypnosis part" of anesthesia.[14] Lipophilic beta-blockers appeared in brain tissue at concentrations 10-20 times greater than that of hydrophilic beta-blocker agents.[15] Esmolol is a drug which acts peripherally and does not penetrate the blood brain barrier. How it affects the depth of anesthesia and EEG activity is not yet clear.[6] However, there have been reports, based mostly on the BIS, of reducing anesthetic requirements by using 1 mg/kg single dose esmolol[7,8] or esmolol infusion.[16-18] Esmolol has also been found to blunt the increase in cerebral blood flow velocity during emergence from anesthesia in neurosurgical patients.[19]

In our study, the BIS increased significantly in the saline group in the first and second minutes after intubation (54±10 and 55±13, respectively) whereas it remained unchanged in the esmolol group (45±5 and 45±6, respectively). Comparable to our study, Oda et al.,[20] demonstrated that the short-acting beta-blockers esmolol and landiolol suppress the BIS response to tracheal intubation during sevoflurane anesthesia. Our study did not address any mechanism regarding the effect of esmolol on the central nervous system which could have explained the attenuation of the BIS response to ETI. The mechanism of action of esmolol on the central nervous system should be investigated further.

In conclusion, this study demonstrated that single dose esmolol does not help to decrease HR and MAP increases following ETI in cardiac surgery patients. We should have considered esmolol infusion for this purpose. However, esmolol not only decreased HR approximately two minutes after administration, but it also attenuated the BIS increases of the stimulation of laryngoscopy and orotracheal intubation. It seems that esmolol adds to the depth of fentanyl-midazolam anesthesia. The mechanism responsible for the BIS attenuation with esmolol should be studied further.

Declaration of conflicting interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding

The authors received no financial support for the research and/or authorship of this article.

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