Hemodynamic Response After Induction of Anesthesia in Patients with Coronary Artery Disease: A Comparison of Remifentanil and Alfentanil for Use with Etomidate

KORONER ARTER HASTALARINDA ANESTEZİ İNDÜKSİYONUNDAN SONRA HEMODİNAMİK CEVAP: ETOMİDAT İLE BİRLİKTE KULLANILAN REMİFENTANİL VE ALFENTANİLİN KARŞILAŞTIRILMASI

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Summary

Purpose: Opioids with induction agents are commonly used to ablate the hemodynamic response to intubation especially in coronary artery disease, but etomidate with remifentanil and alfentanil have not been used for this purpose. The aim of this study is to investigate the hemodynamic effects of remifentanil and alfentanil with etomidate induction in patients undergoing coronary artery bypass graft (CABG) surgery.

Materials and Methods: Forty-two adult patients undergoing CABG surgery were included in the study. Patients received either remifentanil 1 pg/kg (Group Rem, n=21) or alfentanil 40 pg/kg (Group Alf, n=21) over 2 min intravenously at the induction of anesthesia, followed by infusions of 1 pg.kg-l.min-1 remifentanil in Group Rem and 1 pg/kg/min alfentanil in Group Alf. All patients received 0.3 mg/kg etomidate and 0.1 mg/kg vecuronium. Three minutes after the injection of vecuronium the trachea was intubated. Anesthesia was maintained with isoflurane 0.6%, air in oxygen and opioid infusions during sternotomy.

Results: Although mean arterial pressure (MAP) and heart rate (HR) decreased after induction of anesthesia in both groups, decrease in HR was significantly greater in Group Rem (23,2 % decrease from baseline) than Group Alf (12,5 % decrease from baseline) ($p<0.05$). After intubation, MAP and HR increased significantly with respect to baseline ($p<0.005$), and then returned to baseline values throughout the rest of the study. Increase in MAP after sternotomy in both groups was not significant with respect to baseline values.

Conclusion: Alfentanil was ineffective to prevent hemodynamic response to intubation. Although remifentanil was effective in ablating the hemodynamic response during induction of anesthesia and noxious stimuli in CABG surgery, careful titration of the drug is necessary for patients with coronary artery disease.

Key Words: Remifentanil, Alfentanil, Etomidate,
Anesthesia Induction,
Coronary artery bypass graft surgery

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Ozet

Amaç: Entübasyon sonrası ortaya çıkan hemodinamik cevabı baskılamak amacıyla indüksiyon ajanları ile birlikte opioidler sıklıkla kullanılmaktadır, fakat etomidat ile birlikte remifentanil ve alfentanil bu amaçla kullanılmamıştır. Bu çalışmanın amacı koroner arter cerrahisi uygulanacak hastalarda etomidat ile birlikte remifentanil ve alfentanil indüksiyonunun hemodinamik etkilerini incelemektir.

Materyal ve Metod: Koroner arter cerrahisi uygulanacak 42 erişkin hasta çalışmaya alındı. Anestezi indüksiyonunda hastaların yarısına 1 pg/kg remifentanil (Grup Rem, n=21), diğer yarısına 40 pg/kg alfentanil (Grup Alf, n=21) 2 dk içinde intravenöz yoldan verildi. Daha sonra Grup Rem'de 1 pg/kg/dk remifentanil ve Grup Alfde 1 pg/kg/dk alfentanil infüzyonuna başlandı. Bütün hastalara 0.3 mg/kg etomidat ve 0.1 mg/kg veküronyum verildi. Veküronyum enjeksiyonundan 3 dk sonra entübasyon işlemi gerçekleştirildi. Anestezi idamesi %0.6 izofluran, oksijen içinde hava ve opioid infüzyonu ile sternotomi yapılıncaya kadar sürdürüldü.

Bulgular: Her iki grupta da anestezi indüksiyonundan sonra ortalama arter basıncı (OAB) ve kalp hızı (KH) düşmekle birlikte, KH'ndaki azalış Grup Rem'de (başlangıca göre %23,2 azalış) Grup Alfe (başlangıca göre %12,5 azalış) göre anlamlı oranda daha fazlaydı ($p<0.05$). Entübasyondan sonra OAB ve KH başlangıç değerine göre anlamlı oranda aitti ($p<0,005$) ve daha sonra başlangıç değerine dönerek çalışma boyunca aynı seviyede seyretti. Her iki grupta sternotomiden sonra görülen OAB'ndaki artış başlangıç değeriyle karşılaştırıldığında anlamlı değildi.

Sonuç: Alfentanil entübasyona verilen hemodinamik cevabı önleyememektedir. Remifentanil ise koroner arter cerrahisinde indüksiyon ve ağrılı uyarana verilen hemodinamik cevabı baskılamada etkili olmakla birlikte koroner arter hastalarında dozunun dikkatli olarak ayarlanması gerekmektedir.

Anahtar Kelimeler: Remifentanil, Alfentanil, Etomidat,
Anestezi indüksiyonu,
Koroner arter bypass cerrahisi

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Opioids are commonly used for preventing the acute hyperdynamic responses to laryngoscopy, tracheal intubation, and other painful stimuli. Remifentanil and alfentanil have been used with different hypnotic agents in coronary artery bypass surgery in order to control hemodynamic responses to noxious stimuli (1-4). These reports were done with different hypnotic agents and have conflicting results. Etomidate as an induction agent with remifentanil and alfentanil have not been thoroughly investigated in this regard. Therefore, we designed a double-blinded, randomized study to compare remifentanil and alfentanil with etomidate during induction with respect to hemodynamic stability in patients undergoing coronary artery bypass graft (CABG) surgery.

Methods

The protocol was approved by the local Institutional Review Board. After informed consent was obtained 42 adult American Society of Anesthesiologists physical status III patients, aged from 45 to 74 years, undergoing elective CABG surgery were studied.

Patients with obesity (weight>100 kg), significant pulmonary disease, requiring preoperative intravenous inotropic drugs, intra-aortic balloon support, congestive heart failure, emergency surgery, left ventricular ejection fraction less than 35 %, valvular heart disease, uncontrolled hypertension, and severe renal or hepatic impairment were excluded from the study.

All patients continued to receive their routine anti-anginal therapy including nitrates, calcium channel blockers, beta-blockers and/or angiotensin converting enzyme inhibitors except diltiazem until the morning of the surgery. The patients were taking this medication for at least 2 weeks. Before arrival to the operating room, all patients were given 0.1 mg/kg morphine sulphate intramuscularly. Before the induction of anesthesia, peripheral venous and radial arterial catheters were inserted with local anesthesia. Patients were randomly allocated into two groups to receive either 1 ug/kg remifentanil (Group Rem), or 40 u.g/kg alfentanil (Group Alt) intravenously (iv) over 2 minutes followed by a 1 u-g/kg/min infusion of remifentanil in the Group Rem and 1 ug/kg/min alfentanil in the Group Alf. Immediately following the bolus injection of remifentanil or alfentanil all patients received 0.3 mg/kg etomidate and 0.1 mg/kg vecuronium. Laryngoscopy and endotracheal intubation were performed 3 min after the injection of vecuronium. After intubation of the trachea, mechanical ventilation was begun. Ventilation was adjusted to achieve an end tidal carbon dioxide ($ETCO_2$) concentration of 32-35 mmHg. Anesthesia was maintained with isoflurane 0.6 %, air in oxygen and infusions of remifentanil or alfentanil I |ig/kg/min until sternotomy.

The opioid syringes were prepared by a blinded anesthesia nurse according to the randomization schedules. The data was collected by a second anesthesia staff that was unaware of the designation of the study .

Mean arterial blood pressures (MAP) and heart rate (HR) values were recorded on arrival to the operating room prior to induction of anesthesia (baseline values), after induction, immediately before intubation, and 1, 2, 3, and 5 minutes after intubation, at 1 minute after skin incision and sternotomy. Automated ST-segment analysis of leads II and V5 was monitored for detection of myocardial ischemia. Myocardial ischemia was defined as greater than 1 mm depression of the ST segment. The study was terminated after sternotomy.

If MAP fell to less than 60 mmHg and persisting for more than 1 min, isoflurane concentration was decreased, and if this provided ineffective, the opioid maintenance infusion rates were decreased and 5 mg ephedrine was given intravenously. Bradycardia (HR less than 45 bpm) was treated with atropine. Increase in MAP or HR more than 30 % above baseline values were treated with additional bolus doses of remifentanil (0.5 ug/kg remifentanil iv) or alfentanil (10 u.g/kg alfentanil iv) in the Groups Rem and Alf, respectively. To control acute hemodynamic changes that did not respond to an additional bolus dose of opioids, nitroglycerin infusion was titrated.

Descriptive variables were analyzed using Mann-Whitney U test and chi-square test as appro-

Comparisons within groups were performed by Friedman's test, followed by Wilcoxon's test. P values <0.05 was considered statistically significant. Data are expressed as mean ± SEM.

Results

The demographic data of patients are shown in Table 1. There was no statistically significant difference between the two study groups with respect to body weight, height, gender, ejection fraction, induction-incision time, and incision-sternotomy time. Baseline values of MAP and HR were similar in both groups. The number of patients taking preoperative anti-anginal medication is demonstrated in Table 2.

Mean arterial pressure and HR decreased significantly after induction of anesthesia in both groups, and increased after intubation in Group Rem but HR and MAP remained low with respect to baseline throughout the study in Group Rem (Figure 1). Heart rate decreased 23.2 % in Group Rem and 12.5 % in Group Alf relative to baseline values, and the decrease in heart rate between groups was statistically significant ($p<0.05$) (Figure 2). After induction of anesthesia, decrease in MAP with respect to baseline was greater (decrease from baseline values were 31,9 % in Group Rem, and 23,2 % in Group Alf) in Group Rem than Group Alf, but this difference was not statistically significant between study groups.

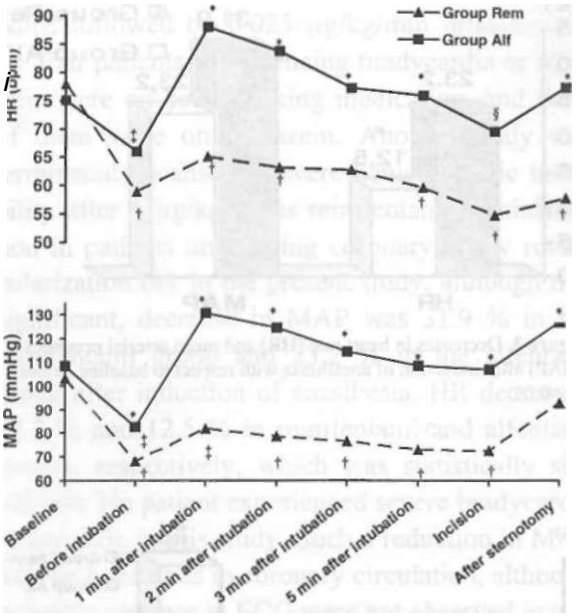

Figure 1. Heart rate (HR) and mean arterial blood pressure (MAP) values for the remifentanil and alfentanil groups at different stages of induction of anesthesia and surgery. Values are mean ± SEM.
§ $p<0.05$, * $p<0.005$ versus Groups Rem and Alf.
‡ $p<0.05$, † $p<0.005$ compared with the baseline values.

Table 1. Demographic data of the study groups (mean±SEM). EF: ejection fraction, MAP: mean arterial pressure, HR: heart rate.

	Group Rem	Group Alf
Age (yr)	62.2 ± 1.8	60.5 ± 2.4
Weight (kg)	68.6 ± 2.5	74.1 ± 2.8
Height (cm)	163.8 ± 1.7	169.0 ±1.7
Gender (M/F)	15/6	16/5
EF (%)	53.1 ± 3.0	50.6 ± 2.5
Induction – incision time (min)	27.7 ±1.0	25.5 ± 1.6
Incision – sternotomy time (min)	4.5 ± 0.3	4.4 ± 0.3
Baseline MAP (mmHg)	103.0 ± 3.9	108.5 ± 5.1
Baseline HR (bpm)	77.9 ± 3.9	75.1 ± 3.0

p>0.05

Table 2. The number of patients taking preoperative anti-anginal therapy.

Preoperative medication	Group Rem	Group Alf
Nitrates	0	1
Calcium channel blockers	18	14
Beta-blockers	12	14
ACE-inhibitors	5	4

p>0.05

One minute after intubation, increase in HR and MAP was significantly higher in Group Alf as compared to baseline ($p<0.001$ and $p<0.0001$, respectively), and then returned to baseline values. Both HR and MAP remained significantly lower after remifentanil induction than the baseline values except sternotomy. After sternotomy MAP increased in both groups, but it was not statistically significant with respect to baseline.

Mean increases in HR and MAP after intubation were significantly greater in Group Alf than Group Rem ($p<0.001$, $p<0.0001$, respectively) (Figure 3).

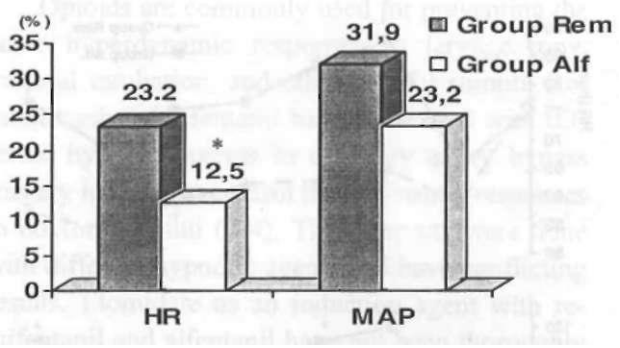

Figure 2. Decreases in heart rate (HR) and mean arterial pressures (MAP) after induction of anesthesia with respect to baseline values.
* p<0.05

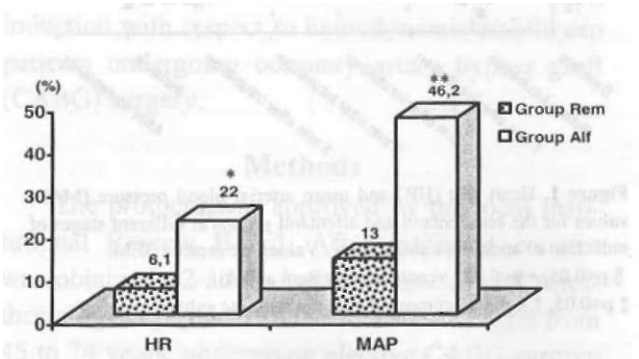

Figure 3. Increase in heart rate (HR) and mean arterial pressure (MAP) 1 minute after intubation.
* p<0.001
** p<0.0001

No ST segment changes were observed in any patient.

Six patients (28,5 %) in Group Rem required a reduction of the infusion rate of remifentanil for the treatment of hypotension after induction of anesthesia. Hypotension was not observed in Group A1f ($p<0.05$). Seven patients (3,5 %) receiving alfentanil experienced hypertension, that needed additional bolus doses of opioid, and one patient (4,7 %) needed nitroglycerine for hypertension. Remifentanil administration was associated with bradycardia in one patient that needed atropine, but baseline HR of this patient was 55 bpm, which was the lowest in that group. Five patients (23.6 %) experienced tachycardia in Group A1f.

Discussion

Opioids are used to assist in blunting the hemodynamic changes associated with intubation, sternotomy and surgical stimuli especially in patients with cardiac disease. In the present study, significant decline in MAP and HR was noted in both remifentanil and alfentanil groups after induction with etomidate, but alfentanil was ineffective in suppressing the hemodynamic response to intubation. Although HR and MAP decreased to baseline values immediately after intubation with alfentanil, it did not prevent hemodynamic response to intubation. However remifentanil caused a very severe depression in hemodynamic parameters, it was very successful in blunting the hemodynamic response.

A previous report of remifentanil pharmacodynamics employing an experimental model revealed a 20-30 times greater potency of remifentanil compared to alfentanil (5). Although differing in potency, the T % K ,o are similar for the two opioids, thus the onset time of the effects were similar between the groups (6). The dose ratio of remifentanil and alfentanil that was used in the present study was equivalent doses for suppressing stress response.

Ablation of intense stress response to intubation, skin incision, and sternotomy is desirable in patients with ischemic heart disease in order not to cause hemodynamic instability or adverse outcome. The administration of an opioid prior to, rather than after, noxious stimulation attenuates physiologic responses. Although both opioids in this study were given during the induction period, prior to a noxious stimulus, both HR and MAP decreased before laryngoscopy in both groups, and increased after intubation in the alfentanil group. In a recent study, it was shown that alfentanil is less reliable than fentanil and sufentanil in blocking increases in HR and blood pressure during anesthetic induction, sternotomy, sternal spread, and aortotomy in patients with ischemic heart disease undergoing coronary artery surgery (7). Mantz et al. (8) suggested that a very high plasma concentration of alfentanil (10 mg alfentanil bolus than 60 mg/h infusion) was needed to achieve hemodynamic stability during myocardial revascularization, however large amounts of narcotic was needed with the risk of prolonged recoveiy.

There are conflicting results about effects of remifentanil on hemodynamics. Schüttler et al (9) reported that, remifentanil (1 ug/kg bolus dose followed by 0.5 ug/kg/min continuous infusion) provided better intraoperative hemodynamic stability during anesthetic and surgical stimuli than alfentanil (25 fig/kg bolus dose followed by 1 ug/kg/min infusion) in patients undergoing major abdominal surgery (0.5 % end-tidal isoflurane in Oa/nitrous oxide), however the incidence of intraoperative hypotension and bradycardia was higher in the remifentanil group. Also the efficacy of remifentanil in patients undergoing major cardiac surgery has been demonstrated in various studies. Olivier et al (10) showed that 1 ug/kg bolus dose of remifentanil followed by 0.25-1 ug/kg/min with propofol TCI (target-controlled infusion) resulted in hemodynamic stability for patients undergoing cardiac surgery, but HR, systolic and diastolic blood pressures decreased after induction of anesthesia and remained lower than the baseline values throughout the study period. In another study, Ahonen et al (11) compared two techniques of total intravenous anesthesia (2 u.g/kg remifentanil or 40 ug/kg alfentanil with propofol and followed by 0.25-0.5 ug/kg/min remifentanil or 0.5-1 ug/kg/min alfentanil) in patients undergoing minimally invasive coronary artery bypass surgery and found stable hemodynamics after both opioid regimen. However, significantly more patients receiving alfentanil needed additional bolus doses of the opioid.

The effects of remifentanil on arterial pressure and HR after bolus administration of various doses of remifentanil (2-30 ug/kg) have been investigated in healthy patients with etomidate induction (12). Intravenous administration of remifentanil to these patients with a glycopyrrolate pretreatment was found to be associated with mean reduction of 20 % for both arterial pressure and HR, and hypotension was not associated with histamine release.

A study by Wang et al (3) was terminated due to the high incidence of bradycardic/asystolic complications in coronary artery disease with induction of sevoflurane and remifentanil 0.5 ug/kg bolus followed by 0.025 ug/kg/min infusion. All the four patients, experiencing bradycardia or asystolia were on beta-blocking medication, and three of them were on diltiazem. Another study was terminated because of severe hemodynamic instability after 1 ug/kg bolus remifentanil administration in patients undergoing coronary artery revascularization (4). In the present study, although non significant, decrease in MAP was 31.9 % in the remifentanil group and 23.2 % in the alfentanil group after induction of anesthesia. HR decreased 23.2 % and 12,5 % in remifentanil and alfentanil groups, respectively, which was statistically significant. No patient experienced severe bradycardia or asystolia in this study. Such a reduction in MAP may be hazardous to coronary circulation, although ischemic changes in ECG were not observed in any patient. The reason why severe bradycardia or asystolia was not observed in our study may be the higher baseline MAP and HR values than the other studies. In addition, the main methodological difference of our study was using etomidate for induction of anesthesia. Etomidate, lacking analgesic efficacy, may not ablate the sympathetic response to laryngoscopy and intubation (13). For this reason, etomidate was used in this study for induction of anesthesia, in order to assess the pure hemodynamic effects of opioids. Etomidate having remarkable hemodynamic stability has been recommended for the induction of anesthesia in patients with cardiovascular disease (14,15). Etomidate combined with fentanyl can provide excellent anesthetic conditions with minimal hemodynamic instability than propofol (16). It was also shown that propofol produced negative inotropy and afterload reduction than etomidate (17). Therefore combination of propofol with an opioid, especially remifentanil, may cause a very severe depression in hemodynamics.

In conclusion, alfentanil was ineffective to prevent hemodynamic response to intubation. Although remifentanil ablated the hemodynamic response to intubation and surgical stimuli, risk of intense hemodynamic depression is an undesirable effect of this agent. Careful titration of remifentanil is necessary for patients undergoing coronary artery surgery.

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