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The Effects of Perioperative Low - Moderate Doses of Dexmedetomidine Infusion on Hemodynamic and Neuroendocrine Parameters

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Aim: The aim of this study was to determine the effects of low and moderate doses of dexmedetomidine infusions by evaluating hemodynamic and neuroendocrine responses in patients undergoing elective transurethral surgery.

Materials and Methods: Fifty patients were randomly allocated to receive 0.45 (Group 1) or 0.6 (Group 2) $\mu\text{g kg}^{-1} \text{hr}^{-1}$ dexmedetomidine infusion 10 minutes before induction of anesthesia. Heart rate, blood pressures, ETCO_2 and peripheral oxygen saturation values and parameters of non-invasive cardiac output were monitored. Measurement times were baseline (I), after dexmedetomidine infusion (II), after thiopental induction (III), after intubation (IV) and at 10-minute intervals during desflurane anesthesia. Anesthesia (2L min^{-1} 50% $\text{N}_2\text{O}+\text{O}_2$) was maintained with 4-6% desflurane corresponding to a bispectral index (BIS) value of 40-60. Venous blood samples were collected prior to intubation (I), at the 30th min intraoperatively (II) and after extubation (III) to determine plasma adrenaline and noradrenaline levels. Chi-square, Student's t-test and repeated measures of variance were used for statistical analysis.

Results: Two different doses of dexmedetomidine infusion produced similar hemodynamic effects. The cardiovascular and neuroendocrine parameters were suppressed more in Group 2 than in Group 1.

Conclusions: These findings suggest that intraoperative 0.45 and 0.6 $\mu\text{g kg}^{-1} \text{hr}^{-1}$ doses of dexmedetomidine result in similar intubation, recovery and hemodynamic responses. Cardiovascular and neuroendocrine parameters were suppressed more by the moderate dose of dexmedetomidine.

Key Words: Alpha-2 agonist, dexmedetomidine, autonomic nervous system, catecholamine, neuroendocrine response

Perioperatif Düşük ve Orta Doz Dexmedetomidin İnfüzyonunun Hemodinamik ve Nöroendokrin Parametreler Üzerine Etkileri

Amaç: Bu çalışmanın amacı elektif transuretral cerrahi yapılan hastalarda, orta ve düşük doz dexmedetomidin infüzyonunun, hemodinamik ve nöroendokrin parametrelere olan etkisinin incelenmesidir.

Yöntem ve Gereç: Randomize olarak 50 hasta, anestezi indüksiyonundan 10 dakika önce 0.45 (Grup 1) veya 0.6 $\mu\text{g/kg/saat}$ (Grup 2) dexmedetomidin infüzyonu aldılar. Kalp hızı, kan basıncı, end-tidal CO_2 , oksijen satürasyonu, ve noninvasiv kardiyak output parametreleri monitorize edildi. Ölçümler, bazal (I), dexmedetomidin infüzyonu sonrası (II), tiyopental sonrası (III), entübasyon sonrası (IV) ve desfluran anestezi uygulaması boyunca her 10 dakikada bir gerçekleştirildi. Anestezi idamesi (2L dak^{-1} , % 50 $\text{N}_2\text{O}+\text{O}_2$), BIS değeri 40-60 olacak şekilde, % 4-6 desfluran kullanılarak sağlandı. Plazma adrenalin ve noradrenalin seviyelerinin belirlenmesi için venöz kan örnekleri, entübasyondan önce (I), intraoperatif dönemin 30. dakikasında (II) ve ekstübasyondan sonra (III) alındı. İstatistiksel analizde Chi- Square, Student-t test ve tekrarlı ölçümlerde varyans analizi kullanıldı.

Bulgular: Her iki dexmedetomidin infüzyonu benzer hemodinamik değişiklikler oluşturdu. Kardiyovasküler ve nöroendokrin değerler ise, Grup 2'de; Grup 1'den daha fazla baskılandı.

Sonuç: Bu bulgularla, intraoperatif 0.45 ve 0.6 $\mu\text{g kg}^{-1} \text{saat}^{-1}$ doz dexmedetomidin benzer hemodinamik yanıt oluşturmuştur. Kardiyovasküler ve nöroendokrin parametreler, orta doz dexmedetomidin ile daha fazla baskılanmaktadır.

Anahtar Sözcükler: Alfa-2 agonist; dexmedetomidin, Otonom sinir sistemi; katekolaminler, nöroendokrin yanıt.

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Introduction

Dexmedetomidine is a new generation highly selective α_2 adrenoreceptor agonist that dose-dependently reduces blood pressure (BP) and heart rate (HR) and has a sedative effect (1). It might permit sedation and analgesia without the unwanted vascular effects from activation of α_1 receptors (2). In addition, it has been shown to induce a centrally mediated reduction of sympathetic nervous system activity and decrease hemodynamic and plasma catecholamine response to stressful events. Effective attenuation of the sympathoadrenal stress responses is an important goal in anesthesiology. These properties theoretically make it a suitable agent for use as part of an anesthetic regimen.

The sedative properties of α_2 agonists are well documented. When infused at rates of 0.2 and 0.7 $\mu\text{g kg}^{-1} \text{hr}^{-1}$, dexmedetomidine produced clinically effective sedation and reduced the analgesic requirements of ventilated intensive care unit (ICU) patients (3). There have been a number of studies on dexmedetomidine and sedation, ventilation and metabolic rate in volunteers (2), oxygen consumption in dexmedetomidine-premedicated patients (4) and postoperative sympatholytic effects (5). However, its role in contemporary intraoperative anesthesia practice has not yet been established and there have been few studies on the cardiovascular parameters in humans during continuous infusion of the drug in the perioperative period. Dexmedetomidine has been used as a low- (0.25-0.5 $\mu\text{g kg}^{-1} \text{h}^{-1}$) or high-dose (1-2 $\mu\text{g kg}^{-1} \text{h}^{-1}$) infusion in volunteers to determine its hemodynamic effects (6). It has been used with fentanyl infusion and a 0.5% inspiratory concentration of enflurane in elective coronary bypass surgery to determine its effects on intraoperative sympathetic tone (7). Dexmedetomidine does not cause respiratory depression and has been infused at a dose of 0.7 $\mu\text{g kg}^{-1}$ intraoperatively to avoid respiratory depression due to narcotic usage in a morbidly obese patient (8).

Thoracic electrical bioimpedance (TEB) is a unique method of the cardiac parameter measurement techniques. Moreover, it is a non-invasive, safe and comfortable method for the patient (9,10). When routine invasive monitoring can not be performed, it has been shown that TEB is an acceptable alternative method to thermodilution technique (11).

The purpose of this research was to evaluate the effects of "low" and "moderate" doses of dexmedetomidine infusion on hemodynamic, cardiac and neuroendocrine parameters in the perioperative stage in patients undergoing desflurane anesthesia.

Materials and Methods

Approval from the Local Research Ethics Committee was obtained together with written informed consent. We studied 50 ASA I-II patients, aged 20-60 years, scheduled for elective transurethral surgery. The patients were randomly assigned to receive 0.45 $\mu\text{g kg}^{-1} \text{hr}^{-1}$ or 0.6 $\mu\text{g kg}^{-1} \text{hr}^{-1}$ dexmedetomidine accorded to one of two parallel groups. Randomization was achieved by closed envelopes chosen by patients prior to the procedure. Exclusion criteria included a history of alcohol abuse or of cardiac, pulmonary, hepatic or renal disease, a positive urine test for pregnancy, history of a serious adverse reaction or allergy to any drug and use of α_2 agonists or antagonists.

The patients had fasted for eight hours before the study and all patients were scheduled for operation. All patients were premedicated with atropine 0.5 mg intramuscularly 45 minutes before the induction of anesthesia. Cardiorespiratory measures including heart rate (HR), pulse oximetry (SpO_2), noninvasive systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), end-tidal carbon dioxide (etCO_2) and end-tidal desflurane (EtdeSF) concentrations were continuously monitored intraoperatively. In addition, electrodes for the measurement of cardiac parameters by thoracic bioimpedance were positioned on each subject according to the methods described by the manufacturer (NCCOM-3R7, BoMed Medical Manufacturing Ltd, Whatney, Irvine, CA). Intravenous fluids were infused during the first hour to replenish one half of the subject's fluid deficit and at a maintenance rate of 2.5 mL kg hr^{-1} for the remainder of the study. Another intravenous catheter was placed for administration of the dexmedetomidine infusion and sedation was monitored with the bispectral index (BIS) monitor Model A-2000 (Aspect Medical Systems, Inc., Newton, MA, USA) after placement of the BIS electrode (Aspect Medical Systems Inc., Natick, MA, USA) to the frontotemporal area. Dexmedetomidine infusion at a rate of 0.45 $\mu\text{g kg}^{-1} \text{hr}^{-1}$

was started in Group 1 and of $0.6\mu\text{g kg}^{-1}\text{ hr}^{-1}$ in Group 2. Dexmedetomidine infusion was initiated 10 minutes before anesthesia induction. Ten minutes after dexmedetomidine infusion, and after BIS values were noted, anesthesia was induced with sodium thiopental until the loss of eyelash reflexes. Vecuronium 0.1 mg kg^{-1} was used for neuromuscular relaxation. Controlled mechanical ventilation was adjusted to maintain EtCO_2 at 34-45 mmHg. Ejection fractions (EF), end-diastolic indexes (EDI), cardiac indexes (CI) and stroke indexes (SI) were recorded with noninvasive TEB for baseline (I), after dexmedetomidine infusion (II), thiopental administration (III), intubation (IV) and at 10-minute intervals until the end of the anesthesia. Anesthesia (2L min^{-1} 50% $\text{N}_2\text{O}+\text{O}_2$) was maintained with 4-6% desflurane for a BIS value of 40-60. Intraoperative BP, HR, SpO_2 , EtCO_2 and EF, EDI, CI and SI were recorded every 10 minutes. No opioids were used intraoperatively. Venous blood samples were collected prior to intubation (I), at 30 minutes intraoperatively (II) and after extubation (III) to determine plasma adrenaline and noradrenaline levels.

At the end of surgery, the study drug infusion was discontinued and the neuromuscular block was antagonized with neostigmine (0.04 mg kg^{-1}) and atropine (0.15 mg kg^{-1}). The patients were evaluated intraoperatively and postoperatively by anesthesiologists who were unaware of the prepared dexmedetomidine infusions and of the group assignments.

Plasma concentrations of noradrenaline and adrenaline were measured using a high- performance liquid chromatography electrochemical detection assay.

Data were reported as mean \pm SD. Demographic data, BIS values, and hemodynamic and neuroendocrine values between groups were analyzed using Student's *t*-test. Dependent variables were analyzed using repeated measures analysis of variance (ReANOVA) with post hoc Bonferroni correction. A *p* value <0.05 was accepted as statistically significant. The sample size was determined by power analysis. Power analysis showed that demonstration of decreased plasma noradrenaline levels with dexmedetomidine infusion of 25% compared with Group 1 would require 25 subjects in each group and that 25 patients in each group would provide a power of 0.8.

Results

The two groups were similar with respect to demographic data and the mean BIS values after 10 minutes of dexmedetomidine infusion (Table 1).

Table 1. Demographic data (mean \pm SD).

	Group 1 n = 25	Group 2 n = 25
Age (year)	39.28 \pm 12.08	37.83 \pm 13.83
Weight (kg)	72.50 \pm 10.05	70 \pm 3.41
Height (cm)	183 \pm 10.51	177.88 \pm 10.89
Sex (M/F)	12/13	14/11
BSA (m^2)	1.71 \pm 0.67	1.69 \pm 0.37
Duration of anesthesia (min)	79.28 \pm 20.27	81.66 \pm 19.69
Sodium thiopental (mg) (<i>P</i> = 0.058)	394.4 \pm 52.2	422.2 \pm 54.9
BIS values after 10 min of dexmedetomidine infusion (<i>P</i> = 0.0123)	92.1 \pm 2.3	90 \pm 1.9

BSA: Body surface area. BIS: Bispectral index.

In both groups, the HR was significantly higher after intubation compared to baseline (73 min^{-1} and 86 min^{-1} , respectively, *P* = 0.000; 69 min^{-1} and 81 min^{-1} , respectively, *P* = 0.000). In Group 2, the HR values showed more variation during the operation; however, it did not fall below 59 min^{-1} during surgery or on extubation in either group (Figure 1).

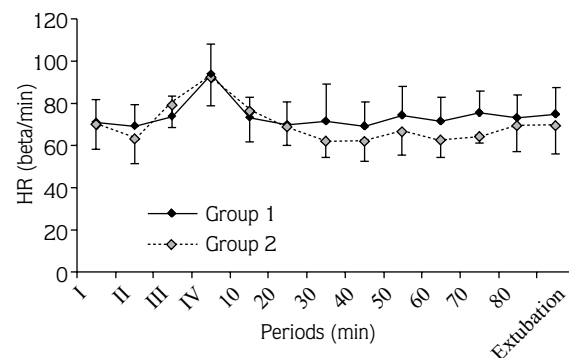


Figure 1. Heart rate responses in the two groups.

* *P* < 0.05 vs. I in Group 1 and 2.

P < 0.05 vs. II and 20, 30, 40, 60, 70 mins in Group 2.

The MAP values were significantly lower at the 50th minute in Group 2 compared to Group 1 (P = 0.018). The MAP value was significantly higher compared to stage I after tracheal intubation in both groups (Figure 2).

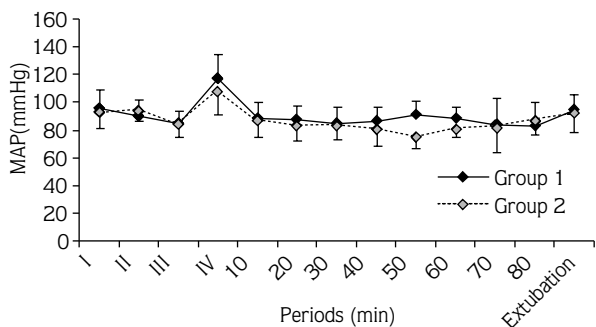


Figure 2. Mean arterial pressure values in the two groups.

* P < 0.05 vs. 50 min in Group 1.
 ** P < 0.05 vs. I in both groups.
 # P < 0.05 vs. I in both groups.

The CI value at the 20th minute in Group 1 was significantly higher than in Group 2. There was a significant decrease at all stages except stage II and following stage IV in Group 1. There was a significant decrease at all stages compared to stage I except at stage II in Group 2 (Figure 3).

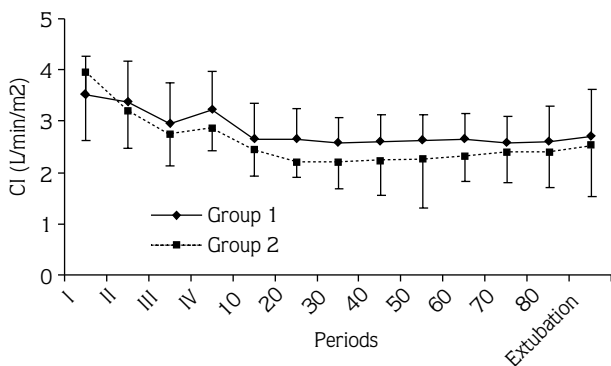


Figure 3. Cardiac index values in the two groups.

* P < 0.05 vs. Group 2.
 # P < 0.05 vs. II, III, and IV and intraoperative values in Groups 1 and 2.

The EF was significantly decreased at every stage except following stage II and IV and the 60th minute in Group 1 while it was decreased at every stage except stage II in Group 2 (Figure 4).

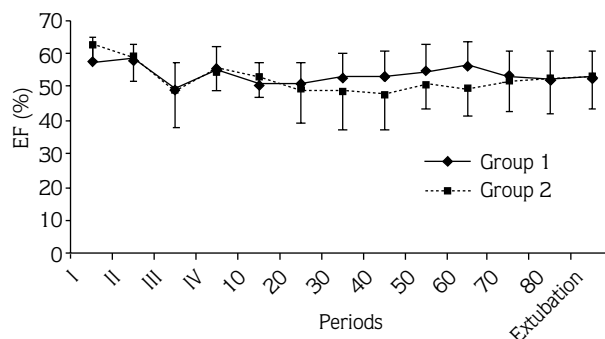


Figure 4. Ejection fraction values in the two groups.

* P < 0.05 vs. III, 10, 20, 30, 40, 50, 70, 80 mins, and extubation values in Group 1.
 ** P < 0.05 vs. III, IV, 10, 20, 30, 40, 50, 60, 70, 80 mins, and extubation values in Group 2.

The SI was significantly higher at stages II, III, and IV and at the 20th minute in Group 1 than in Group 2 (Figure 5). The EDI at stages II, III, and IV and at the 10th minute in Group 1 was significantly higher than in Group 2 (Figure 6).

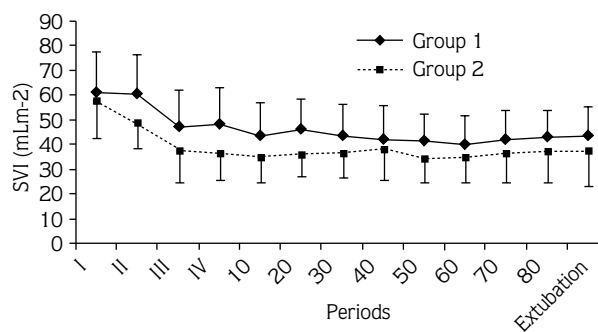


Figure 5. Stroke index values in the two groups.

* P < 0.05 vs. Group 2.
 # P < 0.05 vs. II, III, intraoperative and extubation values in Group 2.
 d P < 0.05 vs. II, III, IV, intraoperative and extubation values in Group 1.

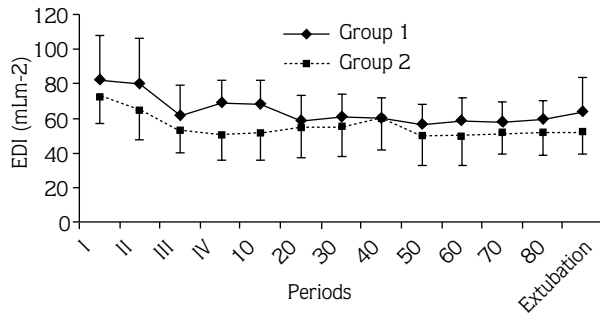


Figure 6. End-diastolic index values in the two groups.

* $P < 0.05$ vs. Group 2

$P < 0.05$ vs. II, 30, 40, 50, 60, 70, 80 mins and extubation values in Group 1.

d $P < 0.05$ vs. III, IV, 10, 50, 60, 70, 80 mins and extubation values in Group 2.

The plasma adrenaline values were significantly higher in the postoperative period in Group 1 compared to Group 2 ($P = 0.035$). In Group 2, there was a significant decrease between the preoperative-intraoperative values ($P = 0.006$) and the preoperative-postoperative values in plasma adrenaline levels ($P = 0.007$).

The plasma noradrenaline values were significantly higher at the 30th minute ($P = 0.02$) and postoperatively ($P = 0.025$) in Group 1 compared to Group 2. There was a significant decrease between the preoperative and postoperative periods in noradrenaline levels ($P = 0.011$). There was also a significant difference between the preoperative-intraoperative ($P = 0.003$) and preoperative-postoperative periods and between the stages in noradrenaline levels ($P = 0.01$) (Table 2).

Discussion

This randomized, double-blind study demonstrated that both 0.45 and $0.6 \mu\text{g}^{-1} \text{kg}^{-1} \text{h}^{-1}$ infusion (low and moderate doses) of dexmedetomidine produced similar results in hemodynamic characteristics in patients under surgical stress undergoing desflurane anesthesia, while there was a significant depression of cardiovascular and neuroendocrine parameters at $0.6 \mu\text{gkg}^{-1} \text{h}^{-1}$.

The use of α_2 agonists in the perioperative period has been associated with attenuated HR and BP responses to stressful events (12-14). Administration in lower concentrations as adjuvants during the intraoperative period has resulted in a reduced requirement for other anesthetic agents, fewer interventions to treat

tachycardia and a reduction in the incidence of myocardial ischemia (15-17). However, this use has been limited by a number of side effects, such as the greater need for pharmacologic rescue therapy for bradycardia and hypotension. These effects may be attributed to the combined properties of volatile anesthetics such as vasodilatation and myocardial depression. High concentrations of dexmedetomidine may cause systemic and pulmonary hypertension because of direct peripheral vascular effects or may compromise myocardial function and BP.

Our doses were chosen based on earlier studies of dexmedetomidine and evaluated ASA I-II patients under general anesthesia (2,6). There was a significant increase in MAP and HR values following intubations in both the 0.45 and $0.6 \mu\text{g kg}^{-1} \text{h}^{-1}$ dexmedetomidine infusion groups (21.8% and 14.4% increases in the MAP values and 17.8% and 17.3% increases in the HR, respectively, following intubations compared to baseline). The presence of tracheal tube leads to reflex sympathetic responses during both the intubation and extubation periods. Jaakola et al. (18) found decreased BP and HR during intubations following the administration of a $0.6 \mu\text{g kg}^{-1}$ bolus of dexmedetomidine preoperatively. Lawrence et al. (19) found decreased hemodynamic response to tracheal intubation or extubation following a single high dose ($2 \mu\text{g kg}^{-1}$) of dexmedetomidine. The lack

Table 2. Adrenaline and noradrenaline variability during the periods.

	Group 1 (ng L-1)	Group 2 (ng L-1)	P values
Adrenaline-I	60.4 ± 19.6	58.3 ± 17.4	0.116
Adrenaline-II	47.5 ± 21.7	32.9 ± 16.9	0.064
Adrenaline-III	74.8±20.9	35.6 ± 13.8	0.035*
P values		I-II = 0.006*	
		I-III = 0.007*	
Noradrenaline-I	490.8 ±174.6	433.6 ± 160.7	0.064
Noradrenaline-II	379 ±198.5	241 ± 158.4	0.02*
Noradrenaline-III	330.6 ±160.3	187.6 ±133.3	0.025*
P values	I-III = 0.011*	I-II = 0.003*	
		I-III = 0.01*	

Data are mean ± SD.

* $P < 0.05$ compared between and within the groups.

of hemodynamic response suppression in our study may be due to the fact that we did not use a bolus dose of dexmedetomidine before the infusion in the preoperative period that could have provided a high enough plasma level and instead used a high dose, loading dexmedetomidine infusion.

Bloor et al. (6) found decreased BP following the administration of the infusions and specified this phase as the depressor phase. The decrease, starting as a biphasic response in the HR at the 2nd and 3rd minutes, was sustained with the two higher doses but moderate with the 0.5 µg kg⁻¹ dose. Hall et al. (20) administered a 6 µg kg⁻¹ h⁻¹ loading dexmedetomidine dose for 10 minutes followed by 0.2 (small) and 0.6 (moderate) µg kg⁻¹ h⁻¹ dexmedetomidine infusions for 50 minutes to seven healthy volunteers and found a similar temporary increase in MAP and significant decrease in HR. In contrast to these studies, we did not find a biphasic response but observed a hemodynamic response to intubations since the dexmedetomidine dose we administered as a 10th minute infusion was quite low. We found a significant decrease in MAP in both groups in our study after sodium thiopental administration and not after the dexmedetomidine infusion. The predominant cardiovascular effect of barbiturates is vasodilatation followed by peripheral pooling of blood. We therefore found that there was a more significant MAP decrease when dexmedetomidine was administered with sodium thiopental. During most of the operation, the MAP and HR were significantly lower than the baseline values, indicating the depressor phase mentioned by Bloor et al. was also present in our patients under the effect of desflurane.

Bloor et al. (6) used infusion doses of 0.25, 0.5, 1 and 2 µg kg⁻¹ and reported decreases of 13%, 12% and 18% in the CO values measured using the bioimpedance method at the 95th, 150th and 105th minutes, respectively. Ebert et al. (21) in their study administered an intravenous dexmedetomidine infusion to 10 healthy volunteers for 40 minutes to keep the plasma value at 0.5-8 ng mL⁻¹ and reported a progressive decrease in CO (35%) and stroke volume together with the increase in plasma dexmedetomidine concentrations.

In our study, the CI value decreased 26.7% in Group 1 and 44% in Group 2. The EDI decreased 31.5% in Group 1 at the 50th minute and 26.6% in Group 2 at the 60th minute, and SI decreased 34.8% in Group 1 at the

60th minute and 40.6% in Group 2 at the 50th minute. The most prominent EF decrease was following thiopental administration (14% in Group 1 and 22% in Group 2) and not following the dexmedetomidine infusion. Jalonen et al. (7) administered a 7 ng kg⁻¹ min⁻¹ (0.42 µg kg⁻¹ h⁻¹) dexmedetomidine infusion during coronary bypass surgery to patients with good left ventricle function following a 30 minute 50 µg kg⁻¹ min⁻¹ (3 µg kg⁻¹ h⁻¹) loading dose in addition to fentanyl infusion and enflurane anesthesia. They found the CI and SI values similar to the baseline values throughout the loading period in both groups while intraoperatively there was an increase following induction and intubation but none in the dexmedetomidine group. They emphasized that dexmedetomidine usage protects cardiac parameters. Our results showed that low-dose dexmedetomidine protects cardiac parameters better than the moderate dose.

Perioperative stress (in which increased catecholamine is a hallmark) can result in undesirable myocardial events (22,23). Anesthetic regimens that minimize this could prove beneficial. Dexmedetomidine may serve to mitigate this response, as even a low dose reduces circulating noradrenaline. The endocrine response to anesthesia and surgery has been evaluated in terms of changes in plasma catecholamine levels. Catecholamine concentrations and the trends in the peripheral concentrations at times of maximum surgical stress reflect the magnitude of the stress reaction. Dexmedetomidine activates peripheral presynaptic α₂ auto receptors that serve to reduce the release of catecholamine (21).

We found that moderate-dose dexmedetomidine suppresses noradrenaline and adrenaline levels. The plasma noradrenaline levels were low for 285 minutes following the dexmedetomidine infusion with minor changes in adrenaline for all doses in the Bloor et al. study (6). This study was on healthy volunteers not undergoing surgical stimulation, which may have led to suppressed plasma noradrenaline levels at all doses (low or high). The low dexmedetomidine dose in our study was inadequate in suppressing noradrenaline at the 30th minute under surgical stress. Ebert et al. (21) found a significant decrease in plasma adrenaline and noradrenaline levels compared to baseline at every infusion step (noradrenaline 66% and adrenaline 40-60%). We found a 32.6% decrease in Group 1 and a more than 40% decrease in Group 2 noradrenaline levels compared to

baseline. The adrenaline levels only decreased in Group 2, again by approximately 40%.

The major limitation of our study was its design without a placebo/control group. In the literature, there are two studies about the efficacy of dexmedetomidine comparing with placebo (2,7). We thus compared two different doses of dexmedetomidine in the present study.

In conclusion, we found that infusion of 0.45 and 0.6 $\mu\text{g kg}^{-1} \text{h}^{-1}$ dexmedetomidine in patients undergoing desflurane anesthesia produced similar intubation and hemodynamic characteristics, while the moderate dose led to a more marked suppression of cardiovascular and neuroendocrine parameters. We believe that cardiac parameters should be carefully observed during dexmedetomidine use for intraoperative anesthesia as an infusion.

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