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Original Article

The effects of dexmedetomidine on hemodynamic responses to tracheal intubation in hypertensive patients: A comparison with esmolol and sufentanyl

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Abstract

BACKGROUND: Hypertension and tachycardia caused by tracheal intubation can be detrimental in hypertensive patients. This study was conducted in order to compare the effects of dexmedetomidine on hemodynamic response to tracheal intubation in hypertensive patients with esmolol and sufentanyl.

METHODS: Sixty hypertensive patients scheduled for noncardiac surgery under general anesthesia were randomly assigned to receive one of the three drugs before induction of anesthesia. Groups I, II, and III respectively received esmolol (100 mg) dexmedetomidine (1 μg/kg) and sufentanyl (0.25 μg/kg). Heart Rate (HR), systolic (SAP) and diastolic (DAP) arterial pressures were recorded before drug administration (baseline; T1), after drug administration (T2), after induction of anesthesia (T3), immediately after intubation (T4) and 3, 5 and 10 minutes after intubation (T5, T6, and T7, respectively). The mean percentage variations from T1 to T4 were calculated for all variables (HR, SAP and DAP). Thiopental dose, onset time of vecuronium and intubation time were also assessed.

RESULTS: No differences were observed between the three groups regarding demographic data ($p > 0.05$). Median thiopental dose was significantly lower in Group II (325 mg; range: 250-500) compared to Group I (425 mg; range: 325-500; $p < 0.01$) and Group III (375 mg; range: 275-500; $p = 0.02$). The onset time of vecuronium was longest in Group I (245.2 ± 63 s vs. 193.9 ± 46.6 s and 205.5 ± 43.5 s; $p < 0.01$ and $p < 0.05$). In Group I, HR significantly decreased after drug administration compared to baseline (83.8 ± 20.4 vs. 71.7 ± 14.8; $p = 0.002$). Compared to the baseline (90.4 ± 8.4), DAP decreased after induction and remained below baseline values at T5, T6 and T7 (71.3 ± 12.8, 76.2 ± 10.7, 68.9 ± 10.8 and 62.1 ± 8.7, respectively; $p < 0.05$) in Group II. According to the mean percentage variation, a significant reduction in HR was assessed in Group II compared to Group III (-13.4 ± 17.6% vs. 11.0 ± 27.8%; $p = 0.003$). Increment in SAP was significant in Group I when compared to Group II (9.8 ± 20.9% vs. -9.2 ± 20.2%; $p < 0.05$). Increment in DAP in Group III was significant compared to Group II (0.07 ± 19.8 vs. 24.5 ± 39.1; $p < 0.05$).

CONCLUSIONS: In hypertensive patients, administration of dexmedetomidine before anesthesia induction blunts the hemodynamic response to tracheal intubation and reduces the thiopental dose.

KEYWORDS: Hypertension, Tracheal Intubation, Dexmedetomidine, Esmolol, Sufentanyl, Anesthesia.

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In clinical practice, reflex tachycardia and hypertension during laryngoscopy and tracheal intubation are the results of increased sympathetic activity evoked by the stimulation of laryngeal and tracheal tissues during the procedure.[1,2] Such responses are exaggerated in hypertensive patients secondary to adaptive cardiovascular changes and sympathetic activity.[3] Although hemodynamic changes during this period can be well tolerated by healthy

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individuals, they may be detrimental in hypertensive patients leading to life-threatening complications such as myocardial ischemia, cardiac arrhythmias, and cerebrovascular hemorrhage.[4]

In the literature, various pharmacological agents, including topical, nebulized or systemic lidocaine,[5-7] opioids,[8,9] beta adrenoceptor blocking agents,[10] and other cardiovascular drugs, have been reported to be used alone or in combination to minimize hemodynamic responses to orotracheal intubation in normotensive patients.[11,12] In the recent decades, beyond pharmacological drugs, advanced laryngoscopic techniques, including video assistance, have been proposed to be advantageous over the conventional method for they caused less alterations to the mean arterial blood pressure (MABP).[13]

There have been several reports on the effects of esmolol and/or opioids on hemodynamic responses associated with laryngoscopy and tracheal intubation.[7,9,14-15] In contrast to these agents, there have been very few reports on the effects of dexmedetomidine in this regard.

Dexmedetomidine is an imidazole-derivative adrenoceptor agonist, representing high selectivity for alpha-2 receptors.[16] Alpha-2 agonists decrease central noradrenergic activity of locus cerelous[17] with a decrease in systemic adrenaline and noradrenaline production.[18,19] In light of the studies available in the literature, we hypothesis that dexmedetomidine can result in decreased heart rate, cardiac output, and doses of anesthetics. Therefore, it may be an alternative antiadrenergic therapy for the hemodynamic response to tracheal intubation in hypertensive patients. In this study, the effects of dexmedetomidine on hemodynamic response to tracheal intubation were compared with those of esmolol and sufentanyl in hypertensive patients.

Methods

The study protocol was approved by the Ethics Committee of Ministry of Health, General Directorate for Pharmaceuticals and Pharmacy. The procedure was explained to the patients and informed consents were obtained. Sixty ASA II physical status adult patients with a diagnosis of hypertension according to the World Health Organization criteria [20] (systolic blood pressure ≥ 160 mmHg or diastolic blood pressure ≥ 90 mmHg), undergoing elective noncardiac surgery were enrolled in the study. Only the patients who aged 19-70 years were included. In preoperative evaluation, patients were allowed for elective surgery only with controlled hypertension either with medication or salt restricted diet at least for one week. The type of antihypertensive medications used by the patients, as well as the existence of diabetes mellitus (DM) were noted and statistically analyzed. Anticipated difficult airway, electrocardiographic evidence of heart block, congestive heart failure, a history of cerebrovascular disease and a history of myocardial infarction within 6 months were the exclusion criteria. Intubation attempt lasting longer than 30 seconds was considered as exclusion criteria as well. All patients received their antihypertensive medication on the day of surgery and none of them was premedicated.

Patients were assigned into three groups according to a computer-generated pseudo-random number sequence. Group I received 100 mg intravenous (iv) esmolol, applying slowly over 1 minute (n = 20). Group II received an iv infusion of 1 µg/kg dexmedetomidine in 10 minutes (n = 20) and Group III received an immediate iv application of 0.25 µg/kg sufentanyl (n = 20). In the operating room, patients were monitored by pulse oximetry, electrocardiogram, and non-invasive blood pressure. Baseline hemodynamic values were represented as the mean of the first two blood pressure (BP) and heart rate (HR) values measured within 3 minutes. An intravenous infusion of 0.9% NaCl solution was started at a rate of volume composed of the fluid deficit and of the maintenance fluid calculated based on each patient's weight. Study drugs were administered by an anesthesiologist who was not involved in the study. Right after this, the anesthetic team was changed in the operating

room and general anesthesia was induced by the anesthesiologists who were blinded to the study drugs.

Neuromuscular monitoring was performed before induction of anesthesia using a TOF-Watch S instrument (Schering-Plough, Dublin, Ireland). The ulnar nerve was supramaximally stimulated near the wrist with square pulses of 0.2 ms duration, delivered as train-of-four (TOF) pulses of 2 Hz, at intervals of 15 s. Onset time of vecuronium was defined as the time from the end of its injection to disappearance of all four twitches of the TOF.

The induction of anesthesia was performed with thiopental 4-7 mg/kg (until loss of eyelash reflex) during a 45-second period. Vecuronium 0.1 mg/kg was then administered for muscle relaxation. All patients were ventilated via face mask with 100% oxygen and the trachea was intubated when no response to TOF stimulation was observed in all groups. Anesthesia was then maintained with 1.5-2.0% sevoflurane in 50% oxygen and 50% N_2O.

HR, systolic (SAP) and diastolic (DAP) arterial blood pressures were recorded before the administration of the study drug (baseline value), after study drug administration, after anesthesia induction, immediately after tracheal intubation and 3, 5 and 10 minutes after intubation. Total thiopental dose and laryngoscopy time were also assessed. The hemodynamic alternations were managed by modifying the rate of fluid administration and the inhaled concentration of the anesthetic agent. None of the patients required vasoactive or vasodilating drug support. Throughout the study period, no surgical intervention was allowed. The study was carried out in the Anesthesiology and Reanimation Clinic, Ankara Training and Research Hospital.

Statistical Analysis

A total sample size of at least 57 cases (19 per group) was required to detect at least a difference of 20% in hemodynamic parameters between any of the two groups in means of 20% with a power of 80% at the 5% significance level. Data analysis was performed by Statistical Package for Social Sciences (SPSS) version 11.5 (SPSS Inc., Chicago, IL, the United States). The normality of continuous variables distributions was determined by Shapiro-Wilk test. Levene's test was used to evaluate the homogeneity of variances. Continuous data was expressed as mean ± standard deviation or median (minimum-maximum) where applicable. Nominal variables were shown as number of cases with percentages. While the mean differences regarding age, weight, height and onset time of vecuronium among groups were compared by one way analysis of variance (ANOVA), Kruskal-Wallis test was applied for the evaluation of median differences in total thiopental dose and intubation time. Nominal data was analyzed by Pearson chi-square or Fisher's exact test where appropriate. Repeated measures ANOVA was applied to assess heart rate, systolic, diastolic and mean blood pressures. A p-value less than 0.05 was considered to be statistically significant.

Results

The demographic data of the three groups are shown in Table 1. There were no significant differences in age, gender, weight, height, accompanying DM, and antihypertensive medication use or median intubation time between the groups. The median total thiopental dose was significantly lower in Group II compared with Groups I and III ($p < 0.05$). The highest mean onset time of vecuronium was found in Group I ($p < 0.05$). The types of received antihypertensive drugs were not different among the three groups (Table 2).

In Group I, HR significantly decreased from the baseline level by the administration of the study drug ($p < 0.05$) (Figure 1). SAP decreased after induction of anesthesia ($p < 0.05$) but increased to the level of baseline by intubation. At the fifth and 10th minutes after intubation, SAP was also found to be lower than baseline values ($p < 0.05$) (Figure 2) and a transient increase in DAP was observed immediately after intubation ($p < 0.05$) (Figure 3).

In Group II, no reduction in HR was assessed after the study drug administration and it did not reach baseline levels immediately after intubation. Throughout the study period,

Table 1. Patient characteristics (Data is expressed as mean ± SD or number of patients)

	Group I (n = 20)	Group II (n = 20)	Group III (n = 20)	p
Age (y)	56.1 ± 8.3	58.1 ± 8.3	53.2 ± 10.5	NS
Gender (F/M)	17/3	16/4	18/2	NS
Weight (kg)	75.7 ± 9.9	81.1 ± 13.3	78.5 ± 12.4	NS
Height (cm)	160.6 ± 7.3	162.1 ± 11.0	162.3 ± 8.2	NS
Accompanying diabetes mellitus	5 (25%)	3 (15%)	9 (45%)	NS
Total thiopental dose (mg)	425 (325-500)[a]	325 (250-500)[a,b]	375 (275-500)[b]	0.003
Intubation time (s)	15 (7-28)	14.5 (6-25)	10.5 (6-30)	NS
Onset time of vecuronium (s)	245.2 ± 63.0[a,c]	193.9 ± 46.6[a]	205.5 ± 43.5[c]	0.007

[a] Significant difference between Group I and II ($p < 0.01$);
[b] Significant difference between Group II and III ($p = 0.020$);
[c] Significant difference between Group I and III ($p < 0.05$)

Table 2. Antihypertensive medication among groups [Data is expressed as number of patients (%)]

	Group I (n = 20)	Group II (n = 20)	Group III (n = 20)	p
Antihypertensive medication	18 (90%)	19 (95%)	20 (100%)	NS
Use of ACE inhibitors	16 (80%)	15 (75%)	15 (75%)	NS
Use of diuretics	8 (40%)	7 (35%)	6 (30%)	NS
Use of β-blockers	2 (10%)	1 (5%)	2 (10%)	NS

ACE: Angiotensin-converting enzyme

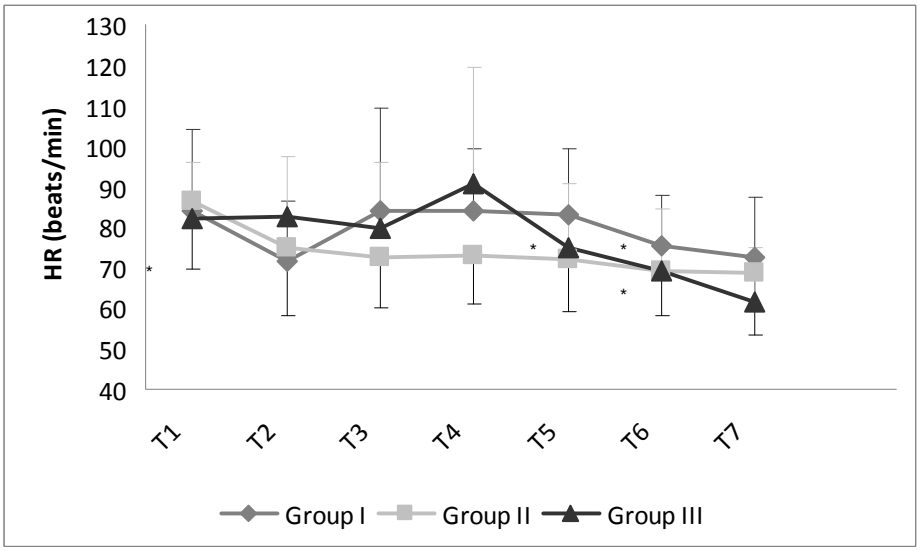

Figure 1. Changes in the heart rate values in the three groups during the study period (All values are expressed as mean ± SD. T1 = baseline; T2 = drug administration; T3 = anesthesia induction; T4 = immediately after tracheal intubation; T5, T6, T7 = Three, five and ten minutes after intubation, respectively); * $p < 0.05$ compared to baseline values

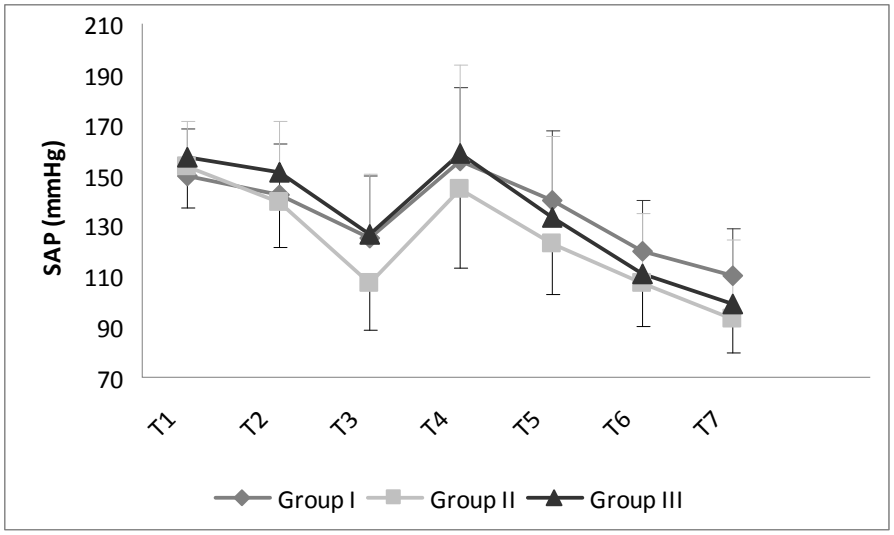

Figure 2. Changes in the systolic arterial pressure values in the three groups during the study period (All values are expressed as mean ± SD. T1 = baseline; T2 = drug administration; T3 = anesthesia induction; T4 = immediately after tracheal intubation; T5, T6, T7 = three, five and ten minutes after intubation, respectively); * $p < 0.05$ compared to baseline values

HR was only found to be lower than baseline values at the 5th and 10th minutes after intubation ($p < 0.05$) (Figure 1). SAP and DAP decreased after induction of anesthesia ($p < 0.05$) but increased to the level of baseline by intubation. SAP and DAP decreased below the baseline levels at the 3rd minute and remained lower until the end of the study ($p < 0.05$) (Figures 2 and 3).

In Group III, HR did not decrease after the study drug administration and remained at the baseline levels immediately after intubation like Group II. However, it was found to be lower than baseline values at the 10th minute

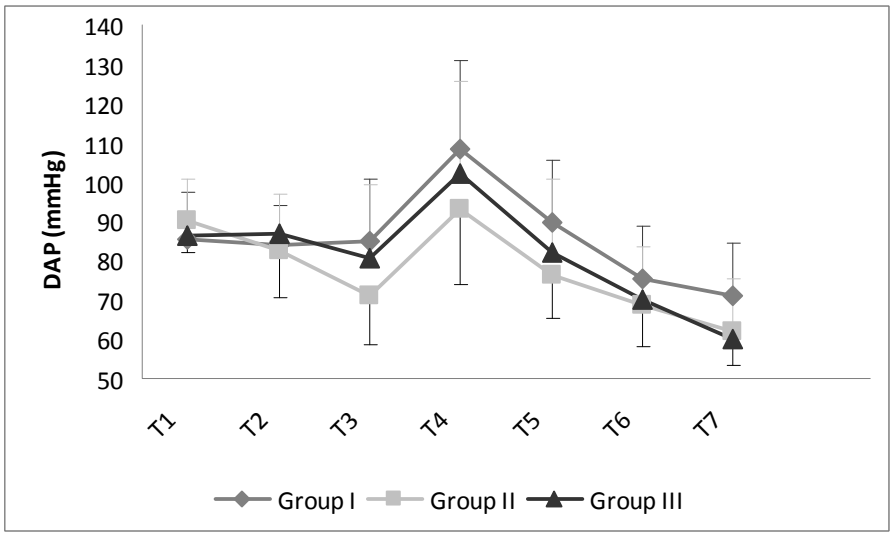

Figure 3. Changes in diastolic arterial pressure values in the three groups during the study period (All values are expressed as mean ± SD. T1 = baseline; T2 = drug administration; T3 = anesthesia induction; T4 = immediately after tracheal intubation; T5, T6, T7 = three, five and ten minutes after intubation, respectively); * $p < 0.05$ compared to baseline values

after intubation (p <0 .05) (Figure 1). SAP decreased after induction of anesthesia ($p < 0.05$) but increased to the level of baseline by intubation (Figure 2). DAP significantly decreased only at the 10th minute after intubation ($p < 0.05$) (Figure 3).

According to the mean percentage variation from "baseline" to "immediately after intubation", an increase in HR was observed in both esmolol and sufentanyl groups whereas a significant reduction compared to Group III was assessed in Group II (-13.4 ± 17.6% (Group II) vs. 11.0 ± 27.8% (Group III); $p < 0.05$). SAP decreased in Groups II and III with a higher percentage reduction in the first. However, the difference did not reach a significant level (-9.2 ± 20.2% vs. -2.6 ± 20.4%). SAP significantly increased in Group I compared to Group II (9.8 ± 20.9% vs. -9.2 ± 20.2%; $p < 0.05$). DAP increased in Groups I and III with no significant difference. The increase in DAP in Group III was significant compared to Group II (.07 ± 19.8 vs. 24.5 ± 39.1; $p < 0.05$) (Figure 4).

Discussion

This study showed that the administration of 1 µg/kg dexmedetomidine infusion prior to anesthesia induction suppressed the hemodynamic response to tracheal intubation and reduced the thiopental dose in hypertensive patients. This suppression in cardiovascular responses was found to be greater than that resulted from esmolol or sufentanyl administration.

Compared with other β-adrenergic blocking drugs, esmolol seems to be an appropriate selection for attenuating the hemodynamic response to laryngoscopy and tracheal intubation due to its cardioselectivity, rapid onset of action, and short elimination half-life.[21] There have been several reports discussing the effects of esmolol on both HR and arterial blood pressure during laryngoscopy and tracheal intubation compared to placebo. Miller et al. reported that 100 mg bolus of esmolol was effective for controlling the hemodynamic response to tracheal intubation in a Canadian multicentre trial.[10] Some studies compared patients carrying risks for coronary artery diseases (hypertension, DM, obesity) with normal patients. Sharma et al. demonstrated that 100 mg esmolol suppressed the hemodynamic response to tracheal intubation in hypertensive patients.[14] Although esmolol is considered to have a

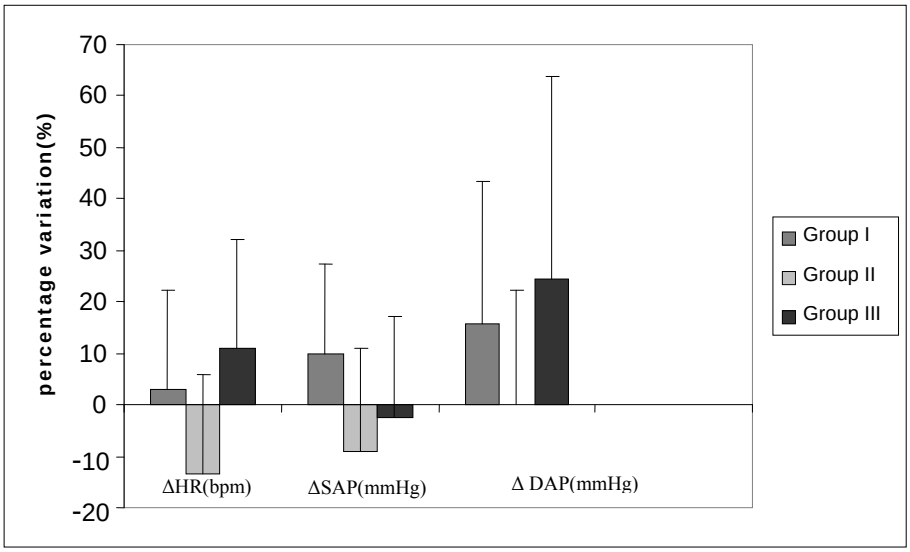

Figure 4. Mean percentage variation from T1 (baseline) to T4 (immediately after intubation) in the heart rate (HR), systolic arterial pressure (SAP) and diastolic arterial pressure (DAP) (ΔHR, ΔSAP and ΔDAP) in the three groups (Data is expressed as percentage (%). * Significant difference between Groups II and III; † Significant difference between Groups I and II)

significant effect on both tachycardic and hypertensive reactions following intubation, Oxorn et al. concluded that esmolol in bolus doses of 100 mg and 200 mg affects solely the chronotropic response in a significant manner.[22] Similarly, Kindler et al. found that esmolol administration before laryngoscopy was sufficient to control HR after intubation but it did not affect SAP.[7] Similarly, in this study, esmolol was not as effective on attenuating the blood pressure response as it was on attenuating the chronotropic response to tracheal intubation. In fact, a significant increase in DAP was observed after intubation compared to the baseline values and a greater percentage increase in SAP was revealed compared to dexmedetomidine in hypertensive patients.

At this point, it is worth mentioning a second-tier result regarding the esmolol administration on the onset time of muscle relaxants. For instance, Szmuk et al. observed that a dose of 0.5 mg/kg esmolol prolonged the onset time of rocuronium.[23] Likewise, Ezrı et al. mentioned a similar prolongation impact which they attributed to the change in cardiac output caused by the negative inotropic and chronotropic effects of esmolol.[24] Note that the aforementioned effects of esmolol are known to raise the reduction in cardiac output as well as in circulation time.[25-27] Therefore, any drug or event that alters circulation time is expected to prolong the onset time of other muscle relaxants. However, Audibert and Donati observed no prolongation of the onset time either of vecuronium or of mivacurium when muscle blood flow was reduced by inflation of a tourniquet. They also observed the same prolongation impact for rocuronium. Therefore, they reasoned that a reduction in cardiac output and circulation time produced by esmolol affects the onset time of fast-acting muscle relaxants greater than those of intermediate acting ones.[28] In contrast, we observed that esmolol administration prolonged the onset time of vecuronium, which is considered to be an intermediate acting neuromuscular blocker. However, in order to draw a solid conclusion in regards to the prolongation mechanism observed in this study, further investigation is required.

Direct acting alpha-2 adrenoceptor agonists (clonidine and dexmedetomidine) represent clinically significant effects on the anesthetic requirements and on the sympathoadrenal and hemodynamic responses induced by tracheal intubation, anesthesia and surgery.[29-31] Scheinin et al. reported that 0.6 µg/kg dexmedetomidine decreased, but not totally suppressed, the hemodynamic response to tracheal intubation in healthy individuals.[29] Menda et al. concluded that dexmedetomidine effectively blunted the hemodynamic response to endotracheal intubation in patients undergoing myocardial revascularization when combined with fentanyl. In this study, we did not observe any significant differences in HR and arterial blood pressure values between the "after intubation" and "baseline" values in the dexmedetomidine group.[30] Similar to the two studies mentioned above, the mean percentage variation analysis at the stated moments revealed an absence of any increase in HR, SAP and DAP in Group II suggesting dexmedetomidine as an effective agent for blunting the hemodynamic response to tracheal intubation in hypertensive patients.

Bradycardia and hypotension have been reported in studies concerning the effect of dexmedetomidine administration on perioperative hemodynamics.[32-34] In contrast to the previously mentioned studies, we did not detect any excessive reduction in HR or blood pressure values in the dexmedetomidine group compared to other groups. Moreover, in this study neither bradycardia nor hypotension was observed in the patients.

In this study, the thiopental dose for induction of anesthesia was significantly reduced in patients receiving dexmedetomidine compared to those under esmolol and sufentanyl. Our findings correspond with the previous reports demonstrating anesthesia to potentiate the effects of the drug. Aantaa et al. showed that preanesthetic medication with dexmedetomidine reduced thiopental dose for induction of anesthesia. They also detected lower plasma noradrenaline concentrations in this group. They therefore suggested the reduction in thi-

opental requirements in part attributed to this decrement in neuronal release.[35] Similarly, Basar et al. reported a decrease in thiopental dose in patients receiving dexmedetomidine with a single dose of 0.5 μg/kg preoperatively.[36] Dexmedetomidine produces sedation by activation of alpha-2-adrenoceptors located in the locus cerulous.[37] The reduced anesthetic requirements, reported in the studies mentioned above and also observed in this study, seems to be related to this effect of dexmedetomidine on the central nervous system.

Although various drugs have been used for attenuating the hemodynamic responses to tracheal intubation, opioid administration is still the most extensively used strategy. Sufentanyl is an analogue of fentanyl and is 5 to 10 times more potent than fentanyl.[38] Previous studies demonstrated that a range of small to high doses of sufentanyl is effective in preventing the cardiovascular response to tracheal intubation. Casati et al. found small bolus doses of sufentanyl (0.1 μg/kg) to be effective in blunting the cardiovascular response to intubation in association with propofol.[9] Another study showed that 0.2 μg/kg bolus dose of sufentanyl attenuated, but not completely abolished, the hemodynamic response to intubation in children.[39] In addition, Xue et al. demonstrated that 0.3 μg/kg bolus dose of sufentanyl completely blunted the cardiovascular intubation response.[40] As stated in previous studies, sufentanyl produces dose-related attenuation of hemodynamic response to tracheal intubation and therefore 0.25 μg/kg, which can be considered as a high dose, was used in this study. Although no difference was observed in regards to HR, SAP and DAP between the baseline and after intubation values in the sufentanyl group, according to the mean percentage variation, we detected that the increases in HR and DAP were significant compared to the dexmedetomidine group. Opioids have been found to be effective in attenuating the cardiovascular response to intubation. However, there is a concern about the effectiveness of these drugs on tachycardic response.[14] Supporting this evidence, the results of our study indicated sufentanyl to be less effective in blunting the tachycardic response to intubation compared to dexmedetomidine.

Angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor antagonists are commonly used to treat hypertension. Hypotension seen after anesthesia induction has been shown to be more excessive in patients receiving these drugs until the day of surgery.[41,42] However, the hypotension episodes may be treated by iv fluid administration, vasopressors and/or angiotensin II.[43] As the number of patients using ACE inhibitors did not differ among the three groups and most of the patients were receiving multidrug therapy, the hemodynamic alterations were thought to be due to study medications.

One limitation of our study was the lack of a true placebo group. However, the authors considered that tracheal intubation would cause detrimental results in hypertensive patients and withdrawing any medication would be unethical.

We demonstrated that administration of a single dose of dexmedetomidine before anesthesia induction was an effective method for attenuating the hemodynamic response to tracheal intubation in hypertensive patients. It was found to reduce the thiopental dose for induction of anesthesia. In addition, evaluation of "baseline" and "immediately after intubation" values revealed a greater percentage variation in HR and DAP in the sufentanyl group and a greater percentage variation in SAP in the esmolol group compared to the dexmedetomidine group. Therefore, as far as hypertensive patients are concerned, we concluded that dexmedetomidine, a highly selective alpha-2-agonist, can safely be used as an adjunct to anesthesia induction.

Conflict of Interests

Authors have no conflict of interests.

Authors' Contributions

All the authors have carried out the study, participated in the design of the study and data collection, performed the statistical analysis and wrote the manuscript. All authors have read and approved the final manuscript.

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