

The Effectiveness of Intramuscular Dexmedetomidine on Hemodynamic Responses During Tracheal Intubation and Anesthesia Induction of Hypertensive Patients: A Randomized, Double-Blind, Placebo-Controlled Study

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ABSTRACT

Background: Hypertensive patients are at risk for increased hemodynamic response to tracheal intubation. Sympatholytic drugs administered during the preinduction period may prevent adverse events.

Objective: We assessed the effectiveness of a single preinduction IM bolus dose of dexmedetomidine (DMED) 2.5 $\mu\text{g}/\text{kg}$ in attenuating hemodynamic responses to tracheal intubation and rapid-sequence anesthesia induction in hypertensive patients treated with angiotensin-converting enzyme inhibitors.

Methods: Adult patients (American Society of Anesthesiologists classification II and III) with essential hypertension, scheduled for elective abdominal or gynecologic surgery, were enrolled in this randomized, double-blind, placebo-controlled study. Patients were assigned to 1 of 2 groups: the DMED group received IM DMED 2.5 $\mu\text{g}/\text{kg}$ and the placebo group received IM saline 0.9% 45 to 60 minutes before induction of anesthesia. General anesthesia was induced with thiopental, fentanyl, and vecuronium and maintained with a sevoflurane-nitrous oxide-oxygen mixture. Hemodynamic values were recorded before (baseline) and after anesthesia induction, before endotracheal intubation, and 1, 3, and 5 minutes after intubation. The patients were monitored for hypotension (systolic arterial pressure [SAP] decreased $\geq 25\%$ from baseline or to < 90 mm Hg) or bradycardia (heart rate [HR] decreased $\geq 25\%$ from baseline or to < 50 beats/min).

Results: Nine hundred sixty patients were assessed for enrollment during a 6-month period. Sixty patients (49 women, 11 men; mean [SD] age, 59.16 [8.39] years) were eligible for the study. There were no significant differences in baseline hemodynamic values between the groups. SAP and diastolic arterial pressure (DAP) before anesthesia induction, 1 and 3 minutes after intubation, and DAP 1 minute

after intubation were significantly lower in the DMED group than in the placebo group (all, $P < 0.05$). There were no significant between-group differences in SAP or DAP 5 minutes after intubation. HR before anesthesia induction, before intubation, and 1, 3, and 5 minutes after intubation were lower in the DMED group than in the control group (all, $P < 0.05$). In the DMED group, SAP after intubation, DAP before intubation, 3 and 5 minutes after intubation, HR before induction, before intubation, and 3 and 5 minutes after intubation were significantly decreased compared with baseline values (all, $P < 0.05$). In the control group, SAP at all times, DAP before intubation, 1, 3, and 5 minutes after intubation, HR before intubation, and 3 and 5 minutes after intubation were significantly decreased compared with baseline values (all, $P < 0.05$). Hypotension and bradycardia were observed together in 3 patients, and hypotension alone was observed in 1 patient 3 minutes after intubation in the DMED group; hypotension was observed in 1 patient at 3 minutes after intubation in the control group.

Conclusion: The results of this study suggest that IM DMED 2.5 $\mu\text{g}/\text{kg}$ administered 45 to 60 minutes before anesthesia induction attenuated, but did not completely prevent, hemodynamic responses to tracheal intubation in these patients with essential hypertension. (*Curr Ther Res Clin Exp.* 2007;68:292–302) Copyright © 2007 Excerpta Medica, Inc.

Key words: intramuscular, α_2 -adrenoceptor agonists, dexmedetomidine, tracheal intubation, heart rate, hypertension.

INTRODUCTION

Tracheal intubation induces an increase in central and peripheral sympathetic activity that results in hypertension and a substantial increase in heart rate (HR) at the beginning of the operative period.^{1,2} Because of marked stimulation of the sympathetic nervous system, drugs with the ability to modulate sympathetic tone may be beneficial for patients at risk of hypertension.^{1,2} α_2 -Adrenergic agonists have anesthetic-sparing, analgesic, sedative, anxiolytic, and sympatholytic effects, thereby preventing catecholamine release, hypertension, and tachycardia.^{1,3–6} Sympatholysis achieved with IM dexmedetomidine (DMED) attenuates the catecholamine response to anesthesia induction and tracheal intubation. We hypothesize that plasma catecholamine concentration, HR, blood pressure (BP), and myocardial oxygen demand may be reduced by IM DMED, thereby possibly preventing cardiac adverse events (AEs). Although a search of MEDLINE (key terms: *intramuscular, dexmedetomidine, and anesthesia induction*) identified several studies^{1–8} regarding the use of DMED during the anesthesia, no previous study was performed on hypertensive patients.

Our purpose was to investigate the effectiveness of preoperative administration of IM DMED 2.5 $\mu\text{g}/\text{kg}$ in attenuating hemodynamic responses during rapid-sequence anesthesia induction and tracheal intubation in hypertensive patients treated with angiotensin-converting enzyme (ACE) inhibitors.

PATIENTS AND METHODS

The study was approved by the Erciyes University Medical Faculty Ethics Committee, Kayseri, Turkey. Written informed consent was obtained from all patients prior to entering the study. The study was conducted in accordance with the principles of the Declaration of Helsinki⁹ and Good Clinical Practice.¹⁰

During a 6-month period between September 2006 and March 2007, patients categorized as American Society of Anesthesiologists (ASA) classification II or III¹¹ who had been diagnosed with essential hypertension (BP >140/90 mm Hg) \geq 1 year before were eligible for the study. Eligibility was limited to patients aged 40 to 70 years, who were scheduled for elective abdominal or gynecologic surgery, and who were being treated only with ACE inhibitors 1 day before surgery. The patients were randomly assigned in an equal ratio to receive IM DMED* 2.5 μ g/kg or saline 0.9% (control group).

Exclusion criteria were as follows: history of cardiac or pulmonary disease; pregnancy; morbid obesity; allergy to the study drug; sequelae due to hypertension (eg, retinopathy, renal insufficiency, left ventricular hypertrophy); and use of any antihypertensive medication except ACE inhibitors.

All patients were monitored using electrocardiography, noninvasive blood pressure, pulse oximetry, airway gas levels, and end-tidal carbon dioxide concentration (Datex-Engstrom AS/3, Helsinki, Finland). Saline 8 mL/kg \cdot h was administered to all patients during the study. All hemodynamic data were measured at baseline, before induction, before intubation, and 1, 3, and 5 minutes after intubation by another observer who was blinded to treatment group. *Serious AEs* were defined as hypotension and bradycardia.

Patients in the DMED group received IM DMED 2.5 μ g/kg diluted to 5 mL with saline 0.9% and patients in the control group received 5 mL of IM saline 0.9% 45 to 60 minutes before anesthesia induction. To maintain blinding, the experimental and control drugs were identical in appearance.

After preoxygenation for 2 minutes, anesthesia was induced with thiopental sodium 5 mg/kg and fentanyl 2 μ g/kg. Tracheal intubation was facilitated by vecuronium 0.1 mg/kg. After orotracheal intubation, general anesthesia was maintained with 1.5% to 2.0% sevoflurane in a mixture of 66% nitrous oxide and 33% oxygen and with intermittent 2- μ g/kg bolus doses of IV fentanyl. At the end of surgery, residual neuromuscular block was reversed with IV atropine 0.015 mg/kg and IV neostigmine 0.05 mg/kg. The tracheal tube was removed after adequate spontaneous ventilation was established.

Hypotension was defined as a decrease in systolic arterial pressure (SAP) of \geq 25% from baseline or SAP <90 mm Hg, and *bradycardia* was defined as a decrease in HR of \geq 25% from baseline or HR <50 beats per minute. We planned to treat hypotension and bradycardia by decreasing the inhalation agent concentration by 50% or by administering IV ephedrine 10 mg or IV atropine 0.5 mg, respectively.

*Trademark: Precedex[®] (Abbott Laboratories, Chicago, Illinois).

Statistical Analyses

Assuming an α risk of 0.05 and a β risk of 0.20, we calculated that ≥ 22 patients should be included to provide a 90% power for each study group to detect a 20% change from baseline in SAP, diastolic arterial pressure (DAP), and HR. Normal distribution of data was determined using the Kolmogorov-Smirnov test. Results are presented as mean (SD). Parametric data were analyzed using unpaired Student *t* tests between groups. Analysis of variance was done for repeated measures within groups. Nonparametric data were analyzed using the Fisher exact test. $P < 0.05$ was considered significant. All statistical analyses were performed using Statistica 4.3 for Windows (Statsoft Inc., Tulsa, Oklahoma).

RESULTS

Nine hundred sixty patients were assessed for enrollment during a 6-month period. Sixty patients (49 women, 11 men; mean [SD] age, 59.16 [8.39] years) were eligible for the study. All 60 patients were included in the statistical analyses. There were no significant differences between the groups in terms of age, weight, height, sex distribution, or ASA risk-class status (**Table I**).

No significant differences were found in baseline SAP, DAP, and HR between the 2 groups (**Tables II–IV**). SAP and DAP before anesthesia induction, 1 and 3 minutes after intubation, were significantly lower in the DMED group than in the placebo group (all, $P < 0.05$). There were no significant between-group differences in SAP or DAP 5 minutes after intubation. HR before anesthesia induction, before intubation, and 1, 3, and 5 minutes after intubation was significantly lower in the DMED group than in the placebo group (all, $P < 0.05$).

In the DMED group, SAP after intubation, DAP before intubation, 3 and 5 minutes after intubation, HR before induction, before intubation, and 3 and 5 minutes after intubation were significantly decreased compared with baseline values (all, $P < 0.05$).

In the placebo group, SAP at all times, DAP before intubation, 3, and 5 minutes after intubation, HR before intubation and 5 minutes after intubation were significantly decreased compared with baseline values (all, $P < 0.05$) (**Table IV**).

SAP and DAP data are presented in **Figure 1** and HR data are presented in **Figure 2**. In both groups, statistically significant increases were found in SAP and DAP at 1 and 3 minutes after intubation compared with before intubation (all, $P < 0.05$). Also, in both groups, HR 1 minute after intubation was higher than before intubation. In the placebo group, HR 3 minutes after intubation was significantly higher than before intubation ($P < 0.05$), but in the DMED group, HR 3 minutes after intubation was not significantly different. In the DMED group, no values were higher than at baseline (**Tables II–IV**).

We observed hypotension and bradycardia in 3 patients and hypotension alone in 1 patient during the third minute after intubation in the DMED group. Hypotension was observed in 1 patient 3 minutes after intubation in the placebo group. No significant differences were found in prevalence of AEs between the groups.

Table I. Demographic and clinical characteristics of hypertensive study patients randomized to receive dexmedetomidine (DMED) or placebo during tracheal intubation and anesthesia induction (N = 60).*

Variable	DMED Group (n = 30)	Placebo Group (n = 30)	t_{58}	<i>P</i>
Age, mean (SD), y	59.9 (8.6)	58.4 (8.2)	0.67	0.50
Weight, mean (SD), kg	75.6 (14.9)	80.4 (11.7)	1.39	0.16
Height, mean (SD), cm	160.5 (8.6)	159.9 (8.1)	0.24	0.80
Sex			0.016	0.25
Female	26	23		
Male	4	7		
ASA Classification			0.04	0.39
II	15	17		
III	15	13		

ASA = American Society of Anesthesiologists.

*There were no significant between-group differences.

Table II. Systolic arterial pressure (in mm Hg) by treatment group. Values are mean (SD).

Time	DMED Group (n = 30)	Placebo Group (n = 30)	t_{58}	<i>P</i> *
Baseline	154.93 (19.05)	163.53 (14.67)	1.95	0.06
Before induction	141.76 (19.56) [†]	162.23 (17.20) [†]	4.24	0.002
Before intubation	108.06 (20.14) ^{†‡}	123.26 (24.26) ^{†‡}	2.64	0.01
1 Minute after intubation	134.76 (27.08) ^{†‡§}	172.40 (30.05) ^{†‡§}	5.09	0.001
3 Minutes after intubation	124.33 (22.74) ^{†‡§}	144.13 (35.31) ^{†‡§}	2.58	0.01
5 Minutes after intubation	117.20 (21.78) ^{†‡§}	128.86 (26.92) ^{†‡§ ¶}	1.84	0.07
<i>F</i>	50.70	25.41		
<i>P</i>	0.001	0.001		

DMED = dexmedetomidine; *F* = 1-way analysis of variance.

*Intergroup significance.

[†]*P* < 0.05 versus baseline.

[‡]*P* < 0.05 versus before induction.

[§]*P* < 0.05 versus before intubation.

^{||}*P* < 0.05 versus 1 minute after intubation.

[¶]*P* < 0.05 versus 3 minutes after intubation.

Table III. Diastolic arterial pressure (in mm Hg) by treatment group. Values are mean (SD).

Time	DMED Group (n = 30)	Control Group (n = 30)	t_{58}	P^*
Baseline	86.10 (12.14)	90.71 (19.17)	1.60	0.11
Before induction	83.93 (13.78)	93.76 (13.93)	2.84	0.006
Before intubation	67.56 (15.85) ^{†‡}	75.33 (15.28) ^{†‡}	1.93	0.05
1 Minute after intubation	84.76 (19.70) [§]	106.83 (22.15) ^{†‡§}	4.07	0.001
3 Minutes after intubation	76.10 (16.61) ^{†‡§}	87.46 (22.71) ^{†‡§}	2.23	0.02
5 Minutes after intubation	74.60 (15.74) ^{†‡§}	80.70 (15.28) ^{†‡§}	1.52	0.13
F	28.35	10.10		
P	0.001	0.001		

DMED = dexmedetomidine; F = 1-way analysis of variance.

*Intergroup significance.

[†] $P < 0.05$ versus baseline.

[‡] $P < 0.05$ versus before induction.

[§] $P < 0.05$ versus before intubation.

^{||} $P < 0.05$ versus 1 minute after intubation.

Table IV. Heart rate by treatment group. Values are mean (SD) beats per minute.

Time	DMED Group (n = 30)	Control Group (n = 30)	t_{58}	P^*
Baseline	86.90 (27.46)	83.3 (12.37)	0.65	0.51
Before induction	79.93 (15.12) [†]	87.93 (15.26)	2.03	0.04
Before intubation	73.43 (11.19) ^{†‡}	79.40 (10.68) ^{†‡}	2.13	0.03
1 Minute after intubation	81.06 (12.77) [§]	90.70 (15.06) [§]	2.68	0.009
3 Minutes after intubation	76.30 (10.96) [†]	84.56 (14.06) ^{†§}	2.53	0.01
5 Minutes after intubation	71.86 (8.17) ^{†‡}	78.73 (13.55) ^{†‡ ¶}	2.37	0.02
F	12.00	6.75		
P	0.001	0.001		

DMED = dexmedetomidine; F = 1-way analysis of variance.

*Intergroup significance.

[†] $P < 0.05$ versus baseline.

[‡] $P < 0.05$ versus before induction.

[§] $P < 0.05$ versus before intubation.

^{||} $P < 0.05$ versus 1 minute after intubation.

[¶] $P < 0.05$ versus 3 minutes after intubation.

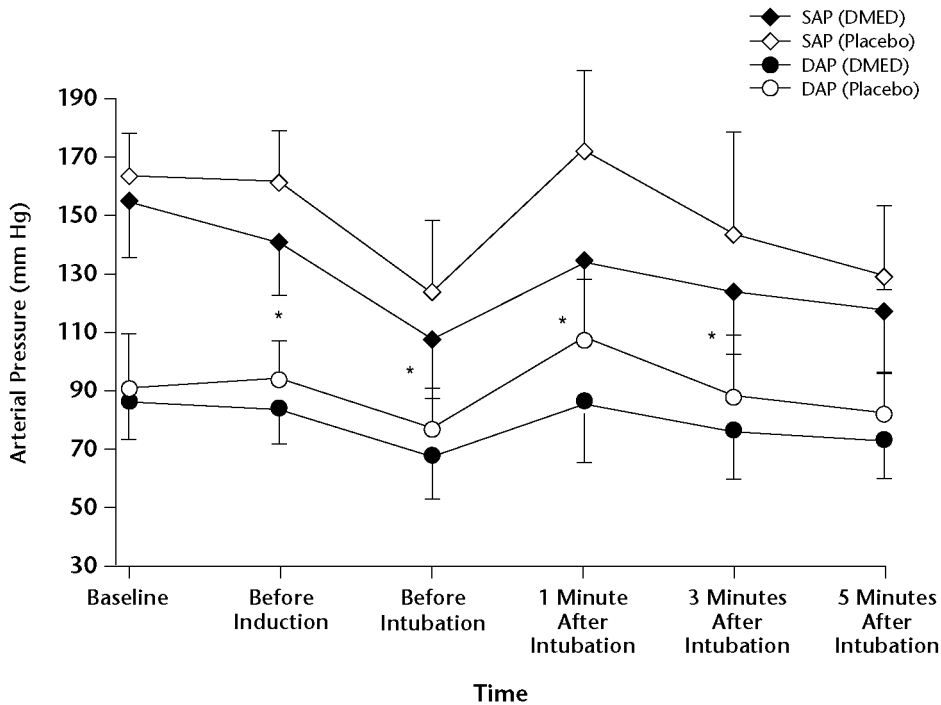


Figure 1 Systolic arterial pressure (SAP) and diastolic arterial pressure (DAP) by treatment group in hypertensive patients randomized to receive dexmedetomidine (DMED) or placebo during tracheal intubation and anesthesia induction. * $P < 0.05$ versus placebo group for both SAP and DAP.

DISCUSSION

Hypertension is a common (1 in 5 adults) medical condition that must be assessed and managed in the perioperative period.¹² Perioperative stress induces a hormonal response characterized by an increase in plasma concentrations of catecholamines and cortisol.¹³ Sympathetic activation leads to an increase in BP, HR, and energy expenditure, and thus to an increase in oxygen consumption.^{14,15} Reduction of stress is desirable, especially for patients with cardiac risk factors.¹⁶ Centrally acting α_2 -agonists have been shown to reduce the concentration of circulating stress hormones.¹⁷

Anesthetic-sparing, analgesic, sedative, and sympatholytic effects of DMED have been found in various studies.¹⁴⁻¹⁹ Erkola et al¹⁹ reported a study involving 192 women undergoing abdominal hysterectomy. Three different treatment groups ($n = 64$) were examined. One group received only IM DMED 2.5 $\mu\text{g}/\text{kg}$ followed by placebo, the second group received IM DMED 2.5 $\mu\text{g}/\text{kg}$ followed by IV fentanyl 1.5 $\mu\text{g}/\text{kg}$, and the third group received IM midazolam 0.08 mg/kg followed by IV fentanyl 1.5 $\mu\text{g}/\text{kg}$. The DMED/fentanyl combination was found

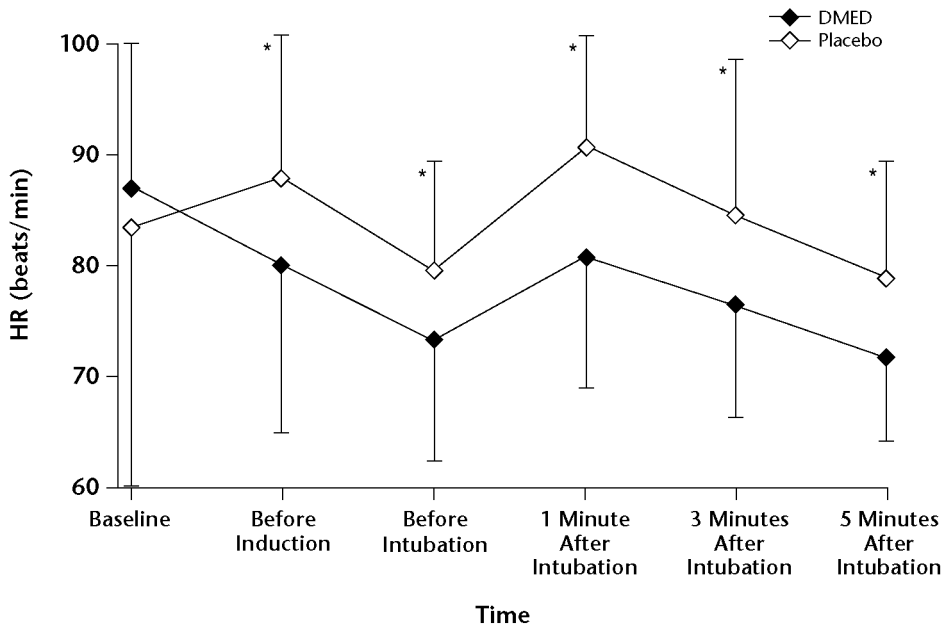


Figure 2. Heart rate (HR) by treatment group in hypertensive patients randomized to receive dexmedetomidine (DMED) or placebo during tracheal intubation and anesthesia induction. * $P < 0.05$ versus placebo group.

to most significantly attenuate sympathetic activation during tracheal intubation and to reduce the anesthetic requirement compared with both the placebo and midazolam groups. Intraoperatively and postoperatively, however, DMED-treated patients showed significantly more bradycardia than patients receiving midazolam. Levanen et al²⁰ tested the effects of premedication with DMED 2.5 $\mu\text{g}/\text{kg}$ ($n = 20$) and midazolam 0.07 mg/kg ($n = 20$) on patients undergoing minor surgery using ketamine as the primary anesthetic. DMED was associated with better hemodynamic control than midazolam during intubation. However, DMED was also more often associated with intraoperative and postoperative bradycardia. These findings agree with those of the present study. In the DMED group, we observed hypotension and bradycardia in 3 patients and hypotension alone in 1 patient 3 minutes after intubation. These patients were successfully treated with IV atropine 0.5 mg and ephedrine 10 mg.

We did not determine the concentration of circulating stress hormones, while we did monitor SAP and DAP invasively; however, our findings suggest that DMED effectively attenuated hemodynamic stress responses during anesthesia induction and intubation without serious AEs. We observed significantly lower HR values before intubation to 5 minutes postintubation in the DMED group compared with the control group. In patients with cardiac risks, lower HR may be particularly helpful in reducing myocardial oxygen demand.

Talke et al²¹ investigated the effect of DMED on hemodynamic response during emergence from anesthesia in 41 patients undergoing vascular surgery. They studied the ability of DMED to attenuate the stress response during emergence from anesthesia, the period known to be associated with a significant perioperative stress response. Patients received either IV DMED (n = 22) or placebo (n = 19) from 20 minutes before the induction of anesthesia until 48 hours after the end of surgery.²¹ During emergence from anesthesia, DMED attenuated the increases in HR and plasma norepinephrine concentration. The percentage of time during which HR was within predetermined hemodynamic limits was significantly higher in the DMED-treated patients. Serious AEs were reported for 3 DMED-treated patients and 4 placebo patients. An episode of postoperative hypotension that resolved with the administration of IV fluids and a sinus pause during intubation that resolved spontaneously were possibly related to treatment with DMED. One patient in the placebo group died of multiple organ failure.²¹ Our results regarding the attenuation of significant perioperative stress are consistent with these results.

Unlike previous studies,^{19–21} we did not investigate the effectiveness of DMED on the stress response during emergence from anesthesia. In addition, we administered IM DMED as a single dose because its elimination $t_{1/2}$ is ~2 hours.²² Also, we completed all study protocols within the drug's duration of action.

Tanaka and Nishikawa²³ and Handa et al²⁴ reported that α_2 -adrenoceptor agonists significantly reduced both baseline sympathetic tone and pharmacologically induced effects, such as activation of the sympathetic system by ketamine. In contrast, clonidine treatment before the administration of ephedrine resulted in an augmented increase in BP.²⁵ The reason for this may be that α_2 -adrenoceptor agonists enhanced the peripheral action of catecholamines. We did not observe any hypertensive response in our patients.

CONCLUSION

The results of this study suggest that IM DMED 2.5 $\mu\text{g}/\text{kg}$ administered 45 to 60 minutes before anesthesia induction attenuated, but did not completely prevent, hemodynamic responses to tracheal intubation in these patients with essential hypertension.

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