The Effects of Intramuscular Dexmedetomidine Premedication on Hemodynamics, Plasma Norepinephrine, Cortisol and Glucose Concentrations

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The aim of our study was to investigate the effect of dexmedetomidine premedication on hemodynamic parameters, plasma cortisol, norepinephrine, glucose levels and requirements of opioid for induction and postoperative period. This study was randomized controlled trial and population consisted of 57 patients (ASA I- II, aged 20-55 years) undergoing elective abdominal surgery. General anesthesia was induced with thiopental and cis-atracurium. Patients subsequently received desflurane 3-5% with \( \text{N}_2\text{O} \) 66% in \( \text{O}_2 \). Electrocardiogram, pulse oxymeter and noninvasive blood pressure were monitored. Patients were divided into two groups: Group D patients received 1 µg kg-1 dexmedetomidine in saline (total volume 3 ml) in the deltoid muscle. Dexmedetomidine premedication was not given to the control group. Plasma cortisol and norepinephrine levels were recorded 1 hour before induction, 1 and 30 min. after skin incision, 1 min after skin closure.

In control group, heart rate (HR) and mean arterial pressure (MAP) increased after intubation and extubation when compared to baseline values. In dexmedetomidine group, HR and MAP were similar to baseline values. Plasma norepinephrine level increased in control group during surgery. However, plasma norepinephrine levels 1 and 30 min after skin incision decreased when compared to baseline values.

We found that 1 µg kg-1 of intramuscular dexmedetomidine premedication reduced opioid requirement at induction and postoperative period without any changes in hemodynamic parameters, cortisol and glucose levels. We concluded that intramuscular dexmedetomidine premedication should be alternative to other premedicant agents.

Key words: Premedication, dexmedetomidine, surgery stress response

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INTRODUCTION

Preoperative visit, an indispensable part of premedication, can reduce anxiety related with anesthesia and surgery. However, additional pharmacologic premedication is frequently required. Thus, stress arising from amnesia, sedation, anxiety and surgery can be prevented. In recent years, numerous studies have been conducted as to the suppression of hemodynamic, endocrine and inflammatory response emerging against anesthesia and surgery. In the light of these studies, alpha₂ adrenergic agonists have been brought into the agenda for anesthetic practices[1-6].

The half-time of dexmedetomidine is relatively short. It has an analgesic effect in addition to its sedative and anxiolytic effect. Patients can be woke up easily under appropriate dosages. The use of dexmedetomidine during anesthesia has several advantages such as cardiovascular stability, suppression of norepinephrine concentrations and reduction of anesthetic requirements. Furthermore, dexmedetomidine has become popular as a premedication agent in recent years thanks to its minor respiratory effect and specific antagonist[7-10].

In this study, our aim was to examine the effects of dexmedetomidine used in premedication on hemodynamic parameters, narcotic consumption taking place during induction and in the postoperative period and on plasma catecholamine, glucose and cortisol levels (response to surgical stress).

MATERIAL AND METHOD

A total of 57 patients of ASA I-II on whom elective abdominal surgery under general anesthesia had been planned (laparotomy cases such as hysterectomy, hernia repair or appendectomy which do not last less than an hour) were included in the study following the approvals of Ethical Board of Ondokuz Mayis University and the patients. Patients were 20-55 years old. Our study was randomized controlled trial and it was designed as a controlled study. The patients who arrived to the operating room before 8:00 a.m. were included in the study. Patients who suffered from diabetes mellitus, renal, malignant and cardiopulmonary diseases and who were using diuretics, antihypertensive, or digoxin at the time of the study were not included in the study.

All patients were premedicated with 5 mg diazepam perorally, at 22:00 p.m. the night before the operation, which was followed, by an additional 5 mg diazepam and 40 mg famotidin given orally 2 hours before the operation. Patients were randomly divided into 2 groups. After drawing blood for NE, cortisol and glucose examinations, 1 µg kg⁻¹ dexmedetomidine hydrochloride (Precedex®, Abbott) was mixed with physiological serum to obtain a final mixture of 3 ml. This final mixture was injected into the deltoid muscle of the 30 patients forming Group D (Dexmedetomidine group) 60 minutes before the induction. Twenty-seven patients included in Group C (Control group) did not receive any premedication. During
induction. 4 mg kg$^{-1}$ thiopental was used and 66% $N_2O$, 33% $O_2$ and 3-6% desflurane were used for maintenance. Neuromuscular blocking was realized with 0.2 mg kg$^{-1}$ cisatracurium during induction and with 0.03 mg kg$^{-1}$ cisatracurium in maintenance. Liquid maintenance was provided with 15 ml kg$^{-1}$ h$^{-1}$ physiological serum and the blood lost during the operation was compensated with physiological serum three times the amount of blood lost. Bradycardia was identified as rates less than 45 beat min$^{-1}$ and was treated with 0.5 mg iv atropine. Hypotension was identified as a 25% decrease in the systolic arterial pressure (SAP) measured in the preoperative period and was treated with 5 mg ephedrine. 1 $\mu$g kg$^{-1}$ fentanyl was administered on patients whose systolic arterial pressure was over 160 or whose diastolic arterial pressure (DAP) was over 90 mmHg. This application was immediately recorded for all patients. Monitoring was conducted with routine ECG, pulse oximeter and non-invasive blood pressure measurement. Twenty G angiocath was inserted to one of the upper extremities in order to draw blood from antecubital vein for NE, cortisol and glucose measurements. In order to maintain the provision of liquid to the other extremity, 20-22 G intravenous cannule was placed. In the intraoperative period, heart rate (HR), systolic, diastolic and mean arterial pressures (MAP), peripheral oxygen saturation (SpO$_2$) were monitored. Moreover, in order to measure NE, cortisol and glucose, venous blood samples were drawn 1 hour before the induction, 1 minute before and 30 minutes after the skin incision and 1 minute after the skin was closed. SAP, DAP, MAP, HR and SpO$_2$ values were recorded immediately before the patients were taken to the operation room, in the 1, 5, 10, 15, 20, 40, 60, 90 and 120 minutes after the intubation, during the extubation and in the 5, 10, 20 minute after the extubation.

At the end of the operation, neuromuscular block was antagonized. If the patient was able to maintain normocapnia, controlled ventilation was switched to spontaneous breathing and patients were taken to the post-care unit. The presence and treatment of postoperative nausea, vomiting, hypotension, hypertension, tremor and pain were recorded. Patients were provided with 4 L min$^{-1}$ oxygen with mask. Postoperative pain was evaluated with Visual Analogue Scale (VAS). Meperidin of 0.5 mg kg$^{-1}$ was injected when VAS was above 5. Stable patients whose post anesthesia recovery score were 9 or over were sent to the clinic.

Statistical analysis was performed using the SPSS statistical package (version 10.0, SPSS Inc., Chicago, IL). Values were given as mean±SE. Statistical analysis was performed by using analysis of variance with repeated measures and Mann-Whitney-u test for comparing groups. Categorical data were analyzed by chi-square test. A p value <0.05 was considered statistically significant.

**RESULTS**

Table I presents the demographic data of the groups. There were significant differences between the groups with respect to sex and duration of the anesthesia (p<0.05).

There was no significant difference between the groups with respect to heart rates measured in the preoperative period, intraoperative period and after the extubation. (p>0.05).

The evaluation of the control group in itself revealed that heart rate recorded in the preoperative period was lower than that recorded in the 1 minute after the intubation. Heart rate for the same period was higher in the dexmedetomidine group (p>0.05). In both

| Table I. Patient Characteristics and Duration of Anesthesia and Surgery in Groups C and D. Values are the Mean±SE, Except For Gender. |
|---------------------------------|-----------------|-----------------|
|                                | Group D (n=30)  | Group C (n=27)  |
| Age (yr)                       | 45.1 ±9.5       | 49.6 ± 8.7      |
| Weight (kg)                    | 68.4 ±2.8       | 69.5 ± 2.3      |
| Duration of surgery (min)      | 105.1 ± 11.7    | 84.7 ±8.4       |
| Duration of anesthesia (min)   | 112.1 ± 12.5    | 95.3 ± 7*       |
| Gender (F/M)                   | 22 / 8          | 26 / 1*         |
| ASA I/II                       | 29 / 1          | 26 / 1          |

*: p<0.05 vs Group D
groups, heart rates recorded in the preoperative period and in the 1 minute after the intubation were higher than those recorded in the intraoperative period (p<0.05). In the control group, heart rate, which increased after the extubation, started to fall after the 10th minute (p<0.05). In the dexmedetomidine group, heart rates did not exceed those recorded in the preoperative period (Figure 1).

The comparison of the control and the dexmedetomidine groups with respect to MAP revealed that the MAP values of the control group in the 20 and 60 minutes after the intubation were higher than those of the dexmedetomidine group (p<0.05).

In the control group, MAP was higher in the 1st minute following the intubation than that measured in the preoperative period. On the other hand, the same value measured for the dexmedetomidine group was lower than that measured in the preoperative period. In the control group, MAP fell below the preoperative value at the 5th minute but began to surpass the preoperative value at the 15th minute (p<0.05). In the dexmedetomidine group, it did not surpass the preoperative value in the intraoperative period (p<0.05). After the extubation, MAP values in both groups continued to be higher than those in the preoperative period (Figure 2). Peripheral oxygen saturation did not reduce below 96% throughout the study period in any patient.

The comparison of the control and dexmedetomidine groups showed no difference with respect to norepinephrine measurements. In the control group, plasma norepinephrine levels increased progressively. On the contrary, in the dexmedetomidine group, the norepinephrine levels measured 1 minute after the incision were lower than those measured 1 hour before the induction. Plasma norepinephrine level in the dexmedetomidine group surpassed the initial value 30 minutes after the incision (p<0.05, Table II).

There were differences between the two groups with respect to cortisol and glucose measurements. Values related with these measurements increased progressively in both groups (Table III, IV).

The comparison of the two groups with regard to the use of opioid in the induction indicates that the requirement for opioid in the induction was less in the dexmedetomidine group than that in the control group (p<0.05, Table V).

There was no difference between the control and dexmedetomidine groups with regard to the intraoperative and postoperative complications (p>0.05).

Erythema was observed on one patient

![Figure 1. Heart rate values of groups C and D (mean±SD).](image-url)
bradycardia responding to 0.5 mg atropine and hypotension responding to 5 mg ephedrine emerged in two patients and in one patient respectively.

In the postoperative period, one patient had nausea and another patient had tremor in
the control group. These, however, did not require any intervention. In the dexmedetomidine group, on the other hand, two patients had nausea and vomited subsequently. One of these patients was treated with metoclopramide. Another patient had bradycardia responding to 0.5 mg atropine. One of the patients also suffered from tremor.

**DISCUSSION**

In this study, the effects of dexmedetomidine on the heart rates and on the blood pressures were correlated. The increase in the heart rate and blood pressure emerging from intubation was not observed in the dexmedetomidine group. Similarly, heart rate and blood pressure for the dexmedetomidine group were lower during the surgery than those measured for the control group.

The effect of dexmedetomidine on the respiratory system is at minimum\(^{11}\). In our study, patients in both groups did not have any \(\text{SpO}_2\) value lower than the initial values and the lowest \(\text{SpO}_2\) value was 98%.

Dexmedetomidine can reduce plasma norepinephrine concentration up to 90% depending on the dosage\(^{12}\). Dexmedetomidine should affect at least 4% of all \(\alpha_2\) receptors in order to suppress central norepinephrine transformation.

In a study by Aantaa\(^{13}\) 1 µg kg\(^{-1}\) im dexmedetomidine, 0.08 mg kg\(^{-1}\) im midazolam and placebo were used. The study was conducted from 9:00 a.m. to 13:00 a.m. In this study, dexmedetomidine reduced mean arterial pressure 20% at maximum. In our study, mean arterial pressure decreased 12% in the dexmedetomidine group. Similarly, heart rate decreased 15% at maximum in Aantaa’s study and our dexmedetomidine group experienced a 14.4% decrease.

Dexmedetomidine reduced plasma norepinephrine concentration 50% at maximum in Aantaa’s study\(^{13}\). In our study, dexmedetomidine reduced plasma norepinephrine concentration 15.5% at maximum.

In a study by Scheinin\(^{14}\), pharmacokinetics and pharmacodynamics of dexmedetomidine given intramuscularly were examined. The results of the study showed that dexmedetomidine suppressed blood pressure and heart rate moderately and plasma norepinephrine level 89% at maximum depending on the dosage.

In our study, norepinephrine level decreased 16.4% in the 1 minute after incision in the dexmedetomidine group and at the end of the surgery, norepinephrine level increased 10% over the preoperative value.

In the control group, norepinephrine level increased 16.3% in the 1st minute after the incision and this increase continued throughout the surgery and it finally reached 142% at the end of the surgery.

Studies have reported either that dexmedetomidine did not affect cortisol levels or that the increase in the cortisol observed after the surgery did not exceed placebo\(^{15-17}\).

A total of 30 ASA I-II patients for whom radical cystectomy had been planned were included in a study by Nagla\(^{18}\). Fifteen patients were intramuscularly injected with 2.5 µg kg\(^{-1}\) dexmedetomidine 45-60 minutes prior to the surgery. The remaining 15 patients were given only placebo. All medication was administered from 7:00 a.m. to 8:00 a.m. in order to minimize the differences between the values, which may have emerged due to circadian rhythm of cortisol. This study revealed no significant difference between the two groups with respect to blood cortisol levels.

In spite of the fact that the cortisol level in the dexmedetomidine group was lower in the blood sample drawn 1 minute after the incision in comparison with that measured in the preoperative period, it started to increase parallel to the increase in the control group in subsequent periods.

Dexmedetomidine administered intravenously in the postoperative period decreased visceral pain and opioid requirement as it increased tendency towards sedation and bradycardia\(^{17}\).

The number of patients using meperidine in the postoperative period decreased in our study. Meperidine was used by 66.7% of the patients in the control group and by 46.7% of the patients in the dexmedetomidine group. The number of patients using opioid in induction decreased in our study. Of all patients enrolled
in the control group, 63% used narcotics; while, only 6.7% of those listed in the dexmedetomidine group required narcotics (p<0.05).

The evaluation of dexmedetomidine with respect to its side effect profile reveals that it is well tolerated in in vivo studies. Exhaustion, dry mouth, nausea, discomfort and agitation are rare side effects observed after dexmedetomidine\textsuperscript{(19–21)}. In our study, bradycardia, hypotension and nausea were observed.

CONCLUSION
The use of 1 μg kg\textsuperscript{-1} dexmedetomidine administered intramuscularly as premedication decreased the need for opioid in induction and postoperative period and, enabled the suppression of increase in norepinephrine concentrations which emerged as a response against anesthetic and surgical stress. Moreover, there was no statistically significant side effect. In the light of all this information, we believe that 1 μg kg\textsuperscript{-1} dexmedetomidine administered intramuscularly can be an alternative to other agents in premedication.

REFERENCES


