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Hemodynamic and Anesthetic Advantages of Dexmedetomidine, an α2-Agonist, for Surgery in Prone Position

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OZKOSE, Z., DEMIR, F.S., PAMPAL, K. and YARDIM, S. *Hemodynamic and Anesthetic Advantages of Dexmedetomidine, an α2-Agonist, for Surgery in Prone Position.* Tohoku J. Exp. Med., 2006, **210** (2), 153-160 —— The α2-agonist dexmedetomidine (Dex), a sedative and analgesic, reduces heart rate (HR) and blood pressure, and has been used in the practice of anesthesia. In this study, we aimed to evaluate the effects of Dex on hemodynamic variables, anesthetic sparing effects, and recovery profiles in patients who underwent surgery in prone position. The prone position itself can cause a decrease in the systemic blood pressure. Forty patients who undergo lumbar discectomy were randomly assigned to receive either Dex (a loading dose 1 μg/ kg in 10 minutes followed by an infusion rate of 0.2 μg/ kg/ hr) or saline. In both groups, the anesthesia was induced with fentanyl, thiopental and rocuronium, and maintained with desflurane in 50% N_2O. Mean arterial blood pressure (MAP), HR, cardiac output (CO), and level of anesthesia were monitored. Recovery times and analgesic requirements were also recorded. As a response to endotracheal intubation, a significant increase in MAP and HR was observed in the control group compared to the Dex group, but no difference in CO. The recovery times were significantly shorter in the Dex group compared to the control group. Anesthetic and analgesic requirements of the Dex group were lower than controls. Thus, the use of Dex caused no detrimental effects on the hemodynamic variables in prone position. In addition, Dex decreased pressure response to intubation, and anesthetic and analgesic requirements, shortened recovery times, and decreased postoperative pain level. Dex may be an alternative to currently used adjunctive anesthetic agents in lumbar discectomy operations. ———— anesthesia; dexmedetomidine; NICO; cardiac output; lumbar discectomy
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Dexmedetomidine (Dex) is a potent, highly specific and selective α2-adrenoceptor agonist. The sedative-hypnotic effects of Dex have been well documented in various clinical and experimental studies (Bekker and Sturaitis 2005; Paris and Tonner 2005). The major problem with dexmedetomidine is its hemodynamic side effects. Bradycardia and hypotension are the most common side-effects. Increasing concentrations of Dex are also have been reported to increase pre-

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load and afterload, and decrease cardiac output (CO) (Bloor et al. 1992; Ebert et al. 2000).

There are limited numbers of studies in which hemodynamic effects of prone position during general anesthesia (Yokoyama et al. 1991; Toyota and Amaki 1998). Under general anesthesia, the prone position causes hemodynamic changes such as decreased blood pressure. It was shown that turning a healthy patient into prone position leads to a clinically significant reduction in CO, the change being greater during maintenance of anesthesia with propofol, compared to isoflurane (Sudheer et al. 2006). However, there is no data available regarding the effects of Dex together with desflurane on hemodynamic parameters and CO of the patients operated in prone position.

Since Dex has been increasingly used in the practice of anesthesia, we aimed to investigate the effects of Dex on hemodynamic variables, anesthetic requirements, and recovery parameters in patients who underwent lumbar discectomy in prone position.

Materials and Methods

Patient selection

The study protocol was approved by the ethical Committee of Gazi University Faculty of Medicine, and written informed consent was obtained from all patients. Forty American Society of Anesthesiologists (ASA) I-II adult patients who underwent elective surgery for lumbar disc disease were enrolled in the study. Emergency cases and patients with valvular heart disease, intracardiac shunts, severe pulmonary, hepatic or renal disease, pregnancy, chronic alcoholism, drug abuse or morbid obesity (Body Mass Index [BMI] > 35) were excluded. None of the patients was using beta-blockers or α2-agonists, and there existed no history of exposure to Dex.

In this double blind study, the patients were allocated randomly to receive either dexmedetomidine (Dex group, n = 20) or saline (Control group, n = 20) using a computer based program. Dexmedetomidine was diluted with 0.9% NaCl to a concentration of 4 μg/ml in 50 ml. Dexmedetomidine or saline was prepared by one of the authors who was blinded to the recorded data, and administered by using a syringe pump (Life Care 5000 Infusion System, Abbott, Ireland). Before induction of anesthesia, the patients in the Dex group received a loading dose of 1 μg/kg Dex over a period of 10 min, which was followed by an intravenous (I.V.) infusion of Dex 0.2 μg/kg/hr until closure of the surgical incision. The same amount of saline was given to the patients in control group.

Induction and maintenance

No sedative premedication was given. When the patients arrived in the operation room, an I.V. catheter was inserted, and 5 ml/kg Ringer's lactate solution was given prior to the induction of anesthesia. The anesthesia was standard for all patients, and induction was performed with thiopental sodium (5-7 mg/kg I.V.) and fentanyl (2 μg/kg I.V.). Muscle relaxation was achieved with 0.6 mg/kg rocuronium. The lungs were ventilated by maintaining a tidal volume of 7-10 ml/kg, respiratory rate of 8-12 per minute, and an end-tidal CO_2 concentration of 35-40 mmHg. Desflurane was delivered in 4 l/min fresh gas flow that was combined with 50% N_2O in oxygen for the maintenance of anesthesia. The desflurane vaporizer was initially set to deliver a concentration of 6%, and titrated to an intraoperative BIS range of 40 to 60 throughout the surgery. The patients were turned to a prone position on the standard operation table, and a pair of chest rolls was placed between the chest of the patient and the table. Vaporiser settings were recorded every 5 minutes, and the time of each change was noted. Muscle paralysis was maintained with intermittent boluses of 5-10 mg I.V. rocuronium. Desflurane was stopped upon initiation of skin closure while Dex or saline infusion was continued until the surgical dressing was applied. At the end of the surgery, neuromuscular blockade was reversed with 0.05 mg/kg neostigmine and 0.02 mg/kg atropine.

Monitoring procedures and hemodynamic control

Standard monitoring consisted of electrocardiogram, noninvasive blood pressure measurement, and pulse oximetry with Taema Artema MM-206 monitors (Artema Medical AB, Sundbyberg, Sweden). The bispectral index (BIS) monitor (Aspect® Medical Systems, Newton, MA, USA) was used to measure the level of anesthesia. After intubation, a NICO (non invasive cardiac output) sensor was placed between the endotracheal tube and "Y" piece of the breathing circuit, and then connected to the NICO monitor (Novametrix Medical Systems, Wallingford, CT, USA). NICO measures the cardiac output depending on changes in respiratory carbon dioxide (CO_2) concentration caused by a brief period of par-

tial rebreathing (50 sec every 3 min) according to Fick principle (Tachibana et al. 2002).

Mean arterial pressure, HR and BIS values were recorded by the second investigator (F.S.) 1 min before infusion of Dex or saline (baseline); 5 min after completion of either solution; just before induction of anesthesia; 1 min after endotracheal intubation; and every 3 min during the operation period. Cardiac output was measured 3 min after the intubation and every 3 min during the surgery. The mean end-tidal concentration of desflurane was recorded at 5 min intervals from the beginning of anesthesia until extubation. Duration of anesthesia (from the induction of anesthesia until discontinuation of desflurane) and surgery (from incision until the placement of the surgical dressing) were also recorded. After discontinuation of desflurane, the times to eye opening, extubation, and following commands were assessed at 1 min intervals by a third investigator (K.P.), who was blinded to the groups.

Intraoperative side effects including bradycardia (HR < 45 beats/min), hypotension (systolic blood pressure decrease more than 20% from the baseline and/or < 80 mmHg), and hypertension (systolic blood pressures increase more than 20% from baseline and/or > 150 mmHg) were also recorded. If hypertension or tachycardia developed during anesthesia while BIS was between 40 and 60, it was assumed to be due to insufficient analgesia and a bolus dose of 1 μg/kg fentanyl was given. Hypotension was treated initially with I.V. crystalloids and 50% decrements in infusion rates of the study drugs. Atropine 0.5 mg was administered in case of bradycardia. If the BIS became less than 40 for more than 30 sec, the concentration of desflurane was decreased by 25%. If BIS exceeded 60 for more than 30 sec, the concentration of desflurane was increased by 25%.

Recovery period

In the postanesthesia care unit (PACU), a blinded observer monitored the patients for 1 hr for nausea and vomiting, any side effects, analgesic requirement, and vital signs. Postoperative nausea and vomiting (PONV) was treated with 10 mg of I.V. metoclopramide. If PONV persisted after 10 min, 4 mg ondansetron was administered intravenously. Postoperative pain was evaluated at 5 min intervals using a 10 point verbal rating scale (VRS) (0: no pain; 10: severe pain). Rescue analgesia with 1 mg/kg meperidine was administered intramusculary after the operation in the presence of a pain score of ≧ 3 or if the patient requested analgesia during pain assessment. Total consumption of meperidine, metoclopramide, and ondansetron was noted. Patients were discharged to ward if (a) they stayed in the PACU for at least 60 min, (b) the modified Aldrete score was ≧ 9, and (c) the pain and nausea were controlled. Assessment for PACU discharge was made at 10-min intervals. The decision about discharge from the hospital was made by the surgeon.

Statistical analyses

Before initiating the study, a power analysis based on a pilot study suggested that a sample size of 15 patients for each group should be adequate to detect a 30% reduction in the times to awakening and extubation with a power of 0.8 (α = 0.05). Demographic data and operation characteristics were evaluated by descriptive statistics and one-way analysis of variance. Analysis of variance for repeated measures was used for scores obtained from the scales used in the study; post-hoc Newman-Keuls test was applied for significant results. Nonparametric variables were analyzed using the chi-square test with Yates' continuity correction, as appropriate. Data are expressed as mean values ± S.D., and p values less than 0.05 were considered statistically significant. Statistical tests were performed using the SPSS version 11.0.5 (Chicago, IL, USA).

Results

There were no significant differences between the groups regarding age, weight, height, ASA status, gender, and duration of anesthesia or surgery (Table 1). The amount of thiopentone used for induction of anesthesia was higher in the control group (385.22 ± 45.1 mg) compared with Dex group (210.19 ± 27.4 mg) ($p < 0.05$).

During the induction of anesthesia, MAP and HR remained stable in both groups. After 5 min of Dex loading period, MAP decrease in Dex group was higher than control group ($p < 0.05$) (Fig. 1). There were no significant differences between the groups regarding HR during this period (Fig. 2). In response to tracheal intubation, a significant increase was encountered in HR and MAP in control group compared to Dex group ($p < 0.05$). That increase was also significantly higher than the baseline value in control group ($p < 0.05$). After the skin incision, HR remained stable in both groups while MAP lower in the Dex

TABLE 1. Patient demographics, duration of anesthesia and surgery, and thiopentone requirements.

	Control group (n = 20)	Dex group (n = 20)
Age (yrs)	46.2 ± 11.3	47.8 ± 8.28
Gender (F/M)	11/9	9/11
Weight (kg)	72 ± 11.43	73.7 ± 12.06
Height (cm)	163.8 ± 8.53	168.6 ± 9.74
ASA physical status (I/II)	13/7	11/9
Duration of anesthesia (min)	114.8 ± 31.41	112 ± 21.71
Duration of surgery (min)	90.8 ± 20.2	98.35 ± 27.4
Thiopentone (mg)	385.2 ± 45.1	210.19 ± 27.4*

Values are presented as mean ± S.D. and number ; *$p < 0.05$ vs control group.
ASA, American Society of Anesthesiologists.

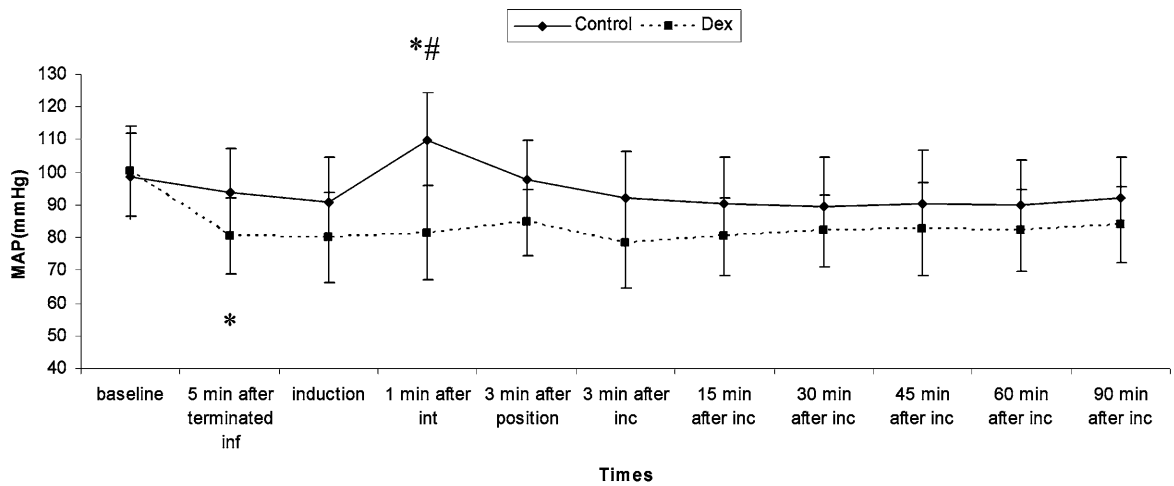

Fig. 1. Mean arterial pressure values in both groups. Values are mean ± S.D. *$p < 0.05$ vs baseline, #$p < 0.05$ vs other group.
MAP, mean arterial pressure; inf, either Dex or saline infusion at the pre-induction of anesthesia; ind, 1 min after anesthesia induction; int, tracheal intubation; position, after turning prone position; inc, surgical incision.

group than in the control group in same period ($p < 0.05$).

Changes occurred in cardiac output are shown in Fig. 3. Although the CO was lower in Dex group than in control group, it was within the physological range in both groups, and there was no statistically significant difference between the groups. In addition, none of the values were significantly different than the baseline values in both groups.

End-tidal desflurane concentration required to maintain the target BIS level (40-60) was lower in Dex group than control group ($p < 0.05$). The dose of the muscle relaxant required during operation was similar in both groups. BIS values of both groups were also similar during the perioperation. Ephedrine was not required both after administration of the study drug and during anesthesia. However, atropine was required for bradycardia in 4 and 2 patients in Dex and control groups, respectively.

The time spent untill eye opening, extubation

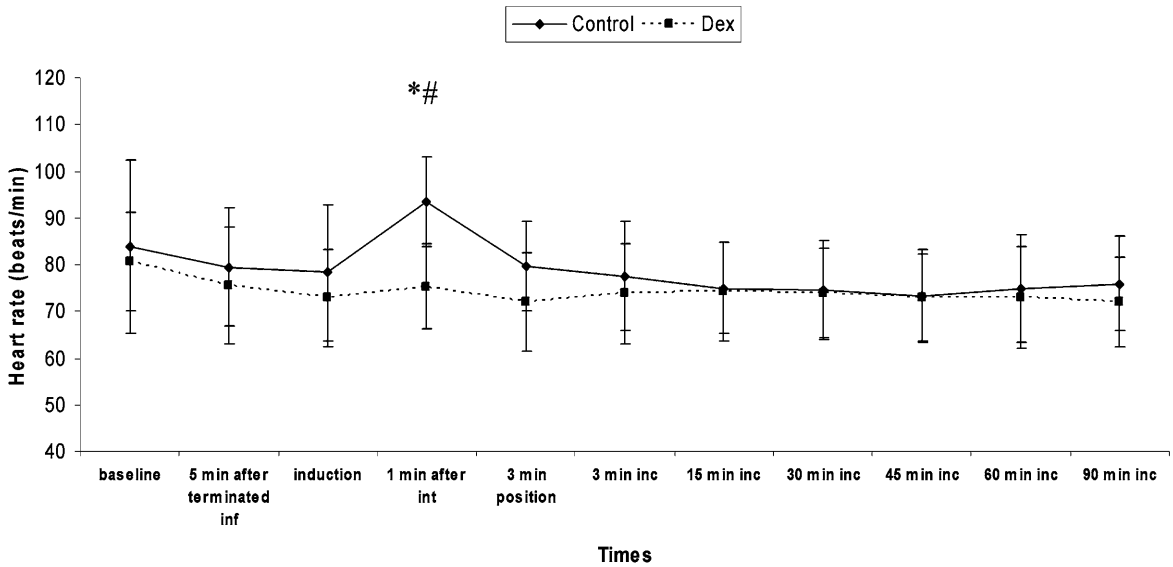

Fig. 2. Heart rate values in both groups. Values are mean ± S.D. $^{*}p < 0.05$ vs baseline, $\#p < 0.05$ vs other group. inf, either Dex or saline infusion at the pre-induction of anesthesia; ind, 1 min after anesthesia induction; int, tracheal intubation; position, after turning prone position; inc, surgical incision.

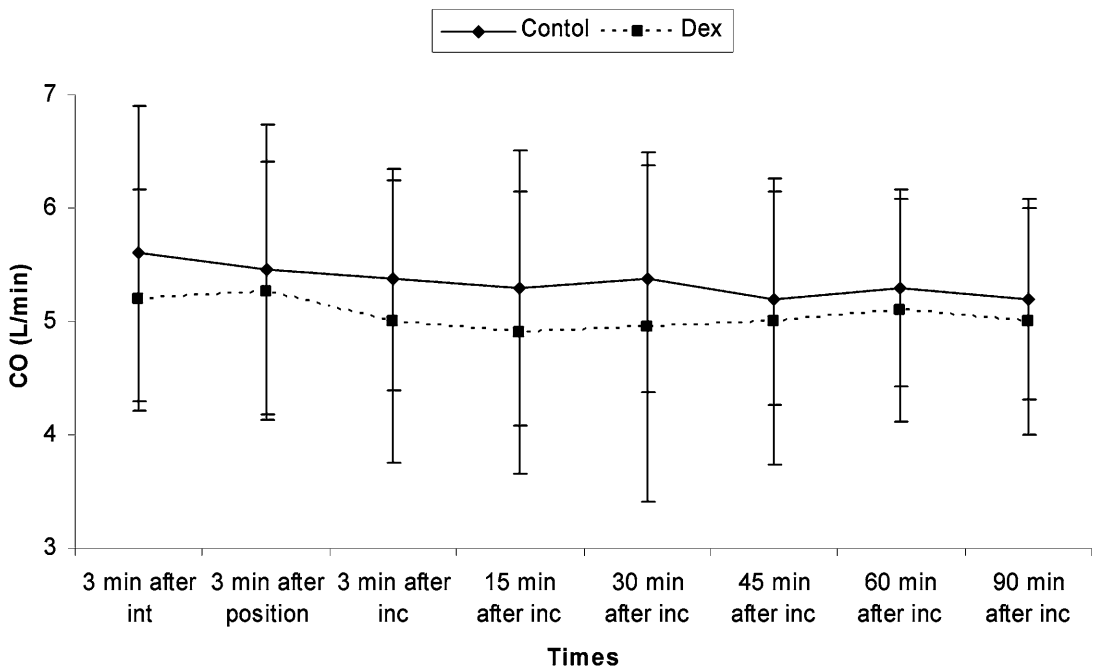

Fig. 3. Cardiac output values in both groups. Values are mean ± S.D.
CO, cardiac output; int, tracheal intubation; inc, surgical incision.

and following commands were consistently shorter in Dex group than control group ($p < 0.05$). There was no significant difference between the groups regarding the incidence of PONV. The antiemetic drug was not required in both groups. Postoperative pain scores at 30 and 60 min. were

TABLE 2. Recovery profiles among the groups.

	Control group ($n = 20$)	DEX group ($n = 20$)
Spontaneous eye opening time (min)	6.9 ± 2.5	3.8 ± 1.6*
Extubation time (min)	7 ± 1.8	3.9 ± 1.5*
Response to verbal commands (min)	7.5 ± 2.1	4.2 ± 1.3*
Aldrete Score at 10 min	8.8 ± 2.7	9.2 ± 2.1
Patients with PONV (n)	3	2
VRS at 30 min	5.5 ± 2.4	1.9 ± 2*
VRS at 60 min	5.6 ± 2.5	1.4 ± 2.1*
Patients received analgesic (n)	11	2*

Values are presented as mean ± S.D., and number ; *$p < 0.05$ vs control group.
PONV, postoperative nausea and vomiting; VRS, verbal rating scale.

significantly lower in Dex group than control group ($p < 0.05$). Eleven of 20 patients in the control group and two of 20 patients in Dex group required meperidine during the first hour in postoperative period ($p < 0.05$) (Table 2). No allergic phenomenon was observed.

DISCUSSION

According to the results of this study, loading followed by continuous perioperative infusion of 0.2 μg/kg/hr Dex reduced the requirements for thiopentone and desflurane, preserved CO, improved hemodynamic stability and shortened the duration of recovery in the patients who underwent lumbar discectomy.

Dexmedetomidine is a relatively new drug which has potent sympatholytic, analgesic, and sedative properties mediated through $\alpha 2$-adrenoceptors in the central and peripheral nervous systems (Bekker and Sturaitis 2005; Paris and Tonner 2005). It has become increasingly popular among anesthesiologists and intensive care physicians as an adjuvant to the classical regimen of anesthesia techniques (Paris and Tonner 2005). Also, it has been shown to reduce the anesthetic and analgesic requirements in animals and humans (Khan et al. 1999; Dutta et al. 2001). The anesthetic-sparing activity of Dex was demonstrated almost exclusively using hemodynamic criteria to assess anesthetic depth in many studies. However, as in our study, the hemodynamic parameters may be inadequate to assess anesthesia depth properly when drugs with direct cardiovascular effects are used as part of the anesthetic regimen. The use of cerebral monitors to minimize the administration of anesthetic drugs and expedite the recovery process raised concerns regarding the potentially deleterious effects of increased autonomic activity (e.g., myocardial ischemia) as well as the possibility of intraoperative awareness (Drummond 2000). Therefore in this study, BIS monitoring was used in order to solve this dilemma, and we observed that Dex reduced requirements of thiopentone for induction and desflurane for maintenance.

$\alpha 2$-agonists decrease blood pressure by centrally mediated sympatholytic effects and by decreasing norepinephrine release via peripheral presynaptic $\alpha 2$-receptors (Flacke 1992). In addition, $\alpha 2$-agonists induce peripheral vasoconstriction by directly activating vascular smooth muscle $\alpha 2$-receptors (Chen et al. 1988). The hemodynamic effects of $\alpha 2$-agonists are therefore thought to be a combination of their central sympatholytic and peripheral vasoconstrictive effects. As expected from the pharmacologic profile, bradycardia and hypotension are the most common side effects of Dex, and can be described as an adverse exaggeration of its clinical advantages (Lawrence and De Lange 1997; Talke et al. 2000). Dexmedetomidine, like other $\alpha 2$-agonists, displays a biphasic, dose-dependent blood pressure

response. High doses initially results in a transient increase of the blood pressure and a reflex decrease in heart rate. The initial response lasts for 5 to 10 min, and is followed by a decrease in blood pressure. It has been shown that a higher (2 μg/kg) dose infusion of Dex produced a transient increase in blood pressure with a concommitant decrease in HR and CO, and then a longer lasting decrease in MAP (Bloor et al. 1992). In the same study, where thoracic bioimpedance method was used, a reduction in CO was observed with infusion of 0.5, 1 and 2 μg/kg Dex whereas no reduction was seen with infusion of a dose of 0.25 μg/kg. Talke et al. (2000) demonstrated that Dex (plasma concentrations ranging from 0.18 to 0.35 ng/ml) attenuates the increases in HR and plasma norepinephrine levels observed during emergence from anesthesia. Furthermore, within the plasma concentrations mentioned, Dex did not increase the incidence of either hypotension or bradycardia. It was reported that the initial effect of blood pressure rise might be closely related to the speed of injection of the drug (Lawrence and De Lange 1997). We preferred a loading dose of 1 μg/kg of Dex in 10 min, and did not observe the expected biphasic effect on blood pressure. The Dex package insert recommends a maintenance infusion of 0.2 to 0.7 μg/kg/hr. We started with the lowest recommended dose (0.2 μg/kg/hr) to avoid untoward hemodynamic effects. However, it was reported that when Dex was used as a total intravenous anesthetic agent (up to 10 μg/kg/hr), hypotension or severe bradycardia would not be observed (Ramsay and Luterman 2004).

Maintenance of an optimal CO results in improved outcomes, and therefore is an important goal of intraoperative hemodynamic management. Recently, a noninvasive CO monitor (NICO™) that uses partial rebreathing of CO_2 and determines CO via the Fick principle has been developed. Compared to the conventional methods, the partial CO_2 rebreathing technique is non-invasive, and can easily be automated, and provide real-time and continuous CO monitoring (Kotake et al. 2003). There is no study about the effects of Dex on CO when it was used during the perioperative period. In the present study, NICO™ was used for CO monitoring, and we observed that Dex did not cause a decrease in CO. However, it was shown in most of the studies that Dex reduced the CO, and the mechanisms of this effect are controversial (Housmans 1990; Gregoretti et al. 1992; Ebert et al. 2000). The reasons for the lack of decrease in CO in the present study could be the absence of significant bradycardia episodes, the use of the lowest infusion dose and the sufficient preoperative fluid loading.

Detoriorative effects of the prone position on CO during lumbar disectomy have been explored recently by Sudheer et al. (2006). They demonstrated that when patients are turned into the prone position, the cardiac index is reduced due to a reduction in venous return and ventricular compliance, with a secondary rise in SVRI maintaining the mean arterial blood pressure. This study also showed that the decrease in cardiac index was significantly greater if propofol was used instead of isoflurane. We preferred desflurane as an inhalation agent due to its hemodynamic stabilizing effect which was demonstrated in numerous studies (Pagel et al. 1991; Weiskopf et al. 1991).

Perioperative use of Dex provides stable hemodynamics, and blunts the sympathetic response during critical moments such as laryngoscopy, intubation and surgical incision (Lawrence and De Lange 1997; Grant et al. 2004). In the present study, HR and MAP increased significantly after intubation in the control group. The patients who received Dex did not show tachycardia and/or hypertension at these time points. These findings showed that Dex attenuated the sympathetic response to endotracheal intubation.

Postoperative neurological assessment of a patient after spinal surgery is critical in terms of the possibility of additional neurological deficits. Therefore, appropriate anesthetic procedure should provide early extubation and recovery of cognitive functions. In the present study, Dex given patients emerged rapidly from the anesthesia. The reason for this early recovery is probably due to less desflurane requirement because of intraoperative Dex suppplementation for the maintenance of anesthesia.

The analgesic effects of Dex have been demonstrated in numerous studies (Aho et al. 1991; Venn et al. 1999). After major abdominal surgeries, Dex loading followed by infusion resulted in a 66% reduction in morphine consumption in the PACU with no significant change in the respiratory parameters (Arain et al. 2004). Similarly, in the present study, Dex reduced the meperidine requirement without respiratory depression.

Consequently, combination of preoperative loading and intraoperative I.V. infusion of Dex blunted the pressure response to intubation and surgery, decreased the desflurane requirements, shortened recovery times, improved hemodynamic stability, and decreased postoperative pain level and meperidine requirement in patients who underwent lumbar discectomy under desflurane anesthesia. Thus, Dex may provide an alternative to currently used adjunctive anesthetic agent in lumbar surgery, especially in the treatment of intraoperative hypertension and when a severe postoperative pain is expected.

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