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Remifentanil versus dexmedtomidine for posterior spinal fusion surgery

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Abstract

Background: Controlling the hemodynamic situation of patients who have spinal operation is of prime importance, and maintaining the heart rate and blood pressure in normal or low- normal levels in these patients can reduce their bleeding loss. One of the commonly used drugs for this purpose is remifentanil. Another sedative-hypnotic-analgesic drug, with acceptable effects is dexmedetomidine. The aim of this study was to compare the effect of dexmedetomidine with remifentanil in spinal operation.

Methods: In a double blind randomized clinical trial, using random sampling method, 60 patients with the age range of 15-65 years who were candidates for posterior spinal fusion operation were included. Induction of anesthesia was performed, and both groups received isoflurane 1% during the surgery. Remifentanil was injected via infusion pump in one group. The patients in the trial group received dexmedetomidine. As trial outcomes, heart rate and blood pressure were measured before, after induction and during the operation. Pain score, sedation score and the need to analgesic therapy were recorded in the recovery room and the ward. Independent sample t-test and chi-square were used for statistical analysis.

Results: Dexmedetomidine had a significant lowering impact on intraoperative blood pressure and heart rate compared to remifentanil ($p<0.001$). The mean of sedation scores after extubation in patients who received dexmedetomidine was significantly higher than the sedation scores in patients who received remifentanil ($p<0.001$). The mean of post-extubation and recovery pain score in patients taking remifentanil was significantly higher than patients taking dexmedetomidine ($p<0.05$).

Conclusion: Dexmedetomidine in patients with spinal operation is associated with lower postoperative pain score and intraoperative bleeding. Hemodynamic effects are significantly better in patients received dexmedetomidine.

Keywords: Dexmedetomidine, Hemodynamic, Spinal fusion, Remifentanil.

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Introduction

Hemodynamic monitoring and maintaining the heartbeat and blood pressure of patients undergoing spinal surgery is of prime importance. It leads to better control of bleeding in the surgical field, particularly in congested, small and limited areas such as spine. Considering the nature of the spinal fusion surgery as a major surgery with a possibility of bleeding and the fact that this surgery is performed on the elderly or traumatic patients in many circumstances, the goal is to choose a drug with appropriate hemodynamic effects while providing good anesthetic depth and short recovery state. Using a potent and short acting opioid

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such as remifentanil follows this rule. Remifentanil has been used successfully as an analgesic-sedative drug in the recent years. We chose remifentanil because it is an ultra-rapid opiod with safe and convenient tapering effects. On the other hand, this drug is as potent as fentanyl. Another sedative-hypnotic-analgesic drug with an acceptable effect is dexmedetomidine (DEX). DEX has been known as a highly selective α2-adrenoreceptor agonist and has been used as a sedative agent in some operative and clinical situations (1-3). Some investigators reported that DEX could reduce the propofol requirement in remifentanil-based anesthesia for faster postoperative recovery and more stable intraoperative hemodynamics (4, 5). However, the exact propofol sparing impact of DEX during remifentanil-based anesthesia has not been well investigated.

Previous studies have found that DEX had complex vasodilative and vasoconstrictive hemodynamic effects on pre and postsynaptic α2 -receptors. The effect of DEX in a lower dose was vasodilation and its vasoconstriction effects have been presented in higher doses. Reduction of blood pressure and heart rate decreased after long-term DEX usage (6, 7).

Controlling hemodynamic state of patients who have spinal operation is very important, and maintaining their heart rate and blood pressure in normal or low- normal levels can reduce their bleeding loss. To increase anesthesia depth and minimize serious side effects, it is necessary to carefully choose and use appropriate drugs during the operation. This study was designed to compare the effect of DEX as an analgesic and sedative drug with remifentanil as an adjuvant drug in anesthesia regiment in spinal operation.

Methods

Patients

In the present randomized clinical trial with a parallel design, 60 patients in the age range of 15-65 years who were candidates for posterior spinal fusion operation were included. This study was approved in the Research Ethical Committee of Iran University of Medical Sciences; written informed consent was obtained from all the participants. The clinical trial was registered in the Iranian Clinical Trial Registry System as IRCT2012081410336N3. A pilot study of pain reported by patients after spinal fusion surgery revealed that the average VAS score for pain was 3 with a standard deviation of 1.4. The sample-size calculation was based on a maximum allowable difference of 1 in VAS scores. Inclusion of 30 patients in each group provided a power of 0.80 when alpha was set at 0.05. Samples were gathered using random sampling method and sample size was calculated based on the following formula:

$$2N = \frac{4(Z\propto+Z\beta)^2\sigma^2}{\delta^2}$$

Considering alpha= 0.05, beta= 20% and the calculation power 80%; the sample size was 60 patients. Eligibility criteria for the patients included in the trial were: patients with ASA class I or II, candidates for posterior spinal fusion surgery in maximum 3 levels, surgical time between 2-5 hours, participation agreement, and without cardiovascular, pulmonary, neurological, nephrology and coagulopathy abnormality in their history and physical examination. All the operations were performed in Rasool-Akram hospital complex affiliated to Iran University of Medical Sciences.

Patients were randomized using block randomization method and were equally divided into two trial groups with 30 patients. They were monitored in the operation room. The monitoring device was Massimo (SAADAT Company, Iran) and we also used electrocardiography, pulsoxymetry, NIBP and capnograph for these patients. Therefore, the blood pressure was monitored in a non-invasive way. Induction of anesthesia was performed for all the patients using fentanyl 3 microgram/ kilogram, midazolam 0.1 milligram/kilogram as premedication and was continued with

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0.2 milligram/kilogram cis-atracurium and sodium thiopental 5 milligram/kilogram. This study was double blinded and patients and their surgeons were both blind to the intervention and an unknown person of research team prepared encrypted codes separately. Both groups received isoflurane 1% during the surgery as a maintenance regiment. It has been observed that DEX can decrease the heart rate and induce bradycardia in special doses; propofol has this effect as well. So we chose isoflurane which does not have this effect and was a suitable inhalation anesthetic agent for this study.

As an intervention in one group, remifentanil (Ultiva, Abbott, CA) was injected firstly using infusion pump with a dose of 1 microgram/kilogram in 15 minutes and then injected with continuous infusion with a dose of 0.2 microgram/kilogram/min. In the other group, patients received DEX (Precedex, Hospira, USA) firstly via infusion pump with a dose of 1 microgram/kilogram in 15 minutes continued followed by an infusion of 0.5 microgram/kilogram/hour. DEX was prepared as 4 microgram/milliliters in 0.9% sodium chloride infusion. For the postoperative pain control, an infusion pump containing 1000 micrograms of fentanyl was used in the first day followed by a rate of four milliliters per hour.

As trial outcomes, heart rate and mean arterial blood pressure (MAP) was measured before and after induction and every 15 minutes during the surgery. In patients with bradycardia (heart rate<40 bits/minute) and MAP<50 mmhg, five milligrams of ephedrine was injected and recorded; and in non-responded cases, patients were excluded from the trial. In patients with increased or decreased blood pressure, 10% increase or decrease in **isoflurane** dosage was used. If blood pressure or heart rate were still elevated, fentanyl 50 microgram was used. In hypertensive patients who were non-responder to isoflourane or fentanyl, nitroglycerine infusion was used and they were then excluded from the study. At the end of the surgery, all the drugs were discontinued and patients were extubated and transferred to the recovery room. In order to provide a similar condition, 50 microgram of fentanyl was injected for patients at the end of operation just after anesthetic drug cessation. Awakening time after anesthetic drugs cessation, time of discharge from recovery, surgeon satisfaction score from surgical field (good, moderate, poor) and bleeding loss were recorded. Time of discharge from recovery was estimated according to Aldrete score.

Pain score, sedation score and the need to analgesic therapy were recorded in first 30, 60,120 and 360 minutes after entrance to the recovery room; so patients were evaluated in the ward. In case of analgesic need (VAS>4) in the recovery and ward, 15 mg intravenous ketorolac was injected and recorded in the prepared questionnaire.

Statistical analysis

Data were analyzed using SPSS (IBM statistics) 20.0 software. Data remained blinded until all data were collected. Quantitative variables were presented as mean ± standard deviation, and qualitative variables were presented as count and percentages. Independent sample t-test and chi-square were used for statistical analysis to compare numerical and categorical data, respectively between the two groups if they had a normal distribution. Data without normal distribution were analyzed through nonparametric equivalents of the mentioned tests. Repeated-measures analysis of variance (ANOVA) was used to review the results at different time points. All results of statistical tests lower than 0.05 were assumed as significant.

Results

In this study, baseline variables such as age, gender, body mass index, having diabetes mellitus and hypertension were significantly different between the two trial groups. Female/male ratio in the remifentanil group was 9/21, and it was 12/18 (p=0.401) in the DEX group.

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Table 1. Descriptive statistics of demographic variables

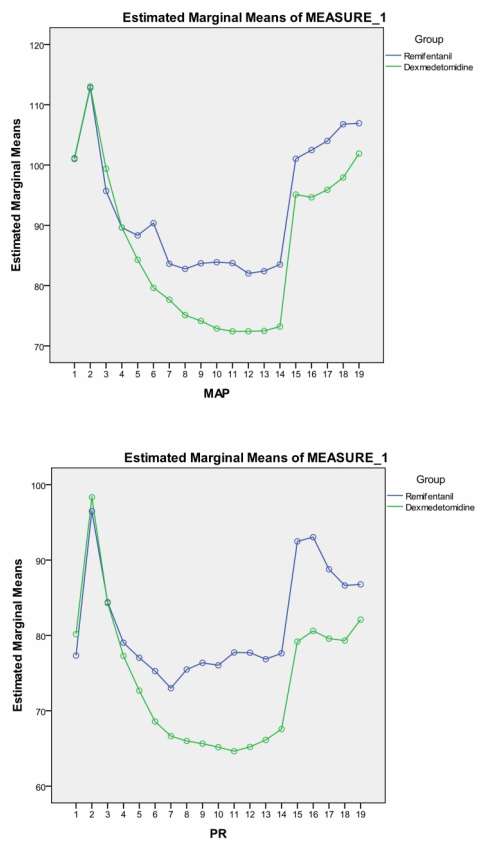
Parameters	Remifentanil (n=30) (Mean±SD)	Deoxmedtomidine(n=30) (Mean±SD)	p
Age	54±7.65	55.57±8.95	0.480
BMI (Mean±SD)	25.88±2.37	26.50±2.86	0.420
Awakening time (min)	15.7±3.10	32.9±4.90	<0.001
Discharge time from recovery (min)	33.3±3.80	48.5±5.40	<0.001

Four patients in the remifentanil group, and 2 patients in the DEX group had diabetes (p= 0.890), and 5 patients had hypertension (p<0.001). Details of comparison between the two groups were presented in Table 1.

The mean of blood pressure (p = 0.005) and heart rate (p<0.001) had significant changes in patients who received remifentanil and DEX as study intervention compared to the baseline time. In the study patients, DEX had a significant lowering impact on intraoperative blood pressure and heart rate compared to remifentanil (p<0.01).

The mean of sedation scores after extubation in patients who received DEX was significantly higher than sedation scores in patients who received remifentanil (p<0.01).

Awakening time in patients of the remifentanil group was significantly lower than patients of DEX group (3.11±15.75 vs. 4.89±32.93; p<0.001). There was a significant difference between the two groups in term of need to Fentanyl at 105 minutes during the operation (p= 0.010). In other measured times during operation, the need to fentanyl injection had no significant difference between the patients of the two groups. In the first 30 and 60 minutes of entrance to the recovery room, the need to analgesic therapy in the remifentanil group was significantly higher than the DEX group (p<0.05); but there were no significant differences between the two groups in the other measured times in recovery. Discharge time in patients of the remifentanil group was significantly lower than the patients in the DEX group (3.39±33.25 vs. 5.36±48.54; p<0.001). The mean of post-extubation pain score of patients in the remifentanil group was significantly higher than the patients in the DEX group (0.4±2.1 vs. 0.3±1.8; p=0.03). The mean pain scores one and two hours after entering the recovery ward in was significantly higher in the remifentanil group comparing the DEX group (p<0.001). Six hours after extubation, the mean pain score was not significantly different between the two groups (0.4±2.9 vs. 0.8±2.7; p=0.2). Surgeons were more satisfied with the observed outcomes in patients of the DEX group compared to the patients of the remifentanil group (100% vs. 78.6%; p=0.01). Bleeding loss during operation was significantly lower in patients in the DEX group. (p<0.05)



Graph1- Time series of Mean Arterial Pressure (MAP) and Pulse rate (PR) among study participants

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Table 2. Descriptive statistics of blood pressure and heart rate between two trial groups

Time		Remifentanil	Dexmedtomidine
Before induction	MAP	100.96 ± 16.57	80.18 ± 8.44
	HR	77.96 ± 10.91	80.18 ± 8.44
After intubation	MAP	112.89 ± 22.23	98.32 ± 7.05
	HR	96.96 ± 9.03	98.32 ± 7.05
15 minutes after operation	MAP	95.32 ± 15.54	84.29 ± 8.58
begin	HR	84.25 ± 5.76	84.29 ± 8.57
30 minutes after operation	MAP	89.64 ± 14.96	77.29 ± 6.15
begin	HR	79.25 ± 4.39	72.29 ± 6.15
45 minutes after operation	MAP	88.04 ± 13.08	72.68 ± 7.01
begin	HR	77.14 ± 4.12	68.57 ± 10.08
60 minutes after operation	MAP	90.0 ± 22.60	68.57 ± 10.08
begin	HR	75.43 ± 4.07	68.58 ± 7.01
75 minutes after operation	MAP	83.50 ± 8.88	66.64 ± 10.08
begin	HR	73.07 ± 13.76	66.64 ± 10.01
90 minutes after operation	MAP	82.50 ± 9.08	66 ± 10.11
begin	HR	75.29 ± 5.69	66 ± 10.10
105 minutes after operation	MAP	83.21 ± 10.29	65.64 ± 10.41
begin	HR	76.14 ± 7.46	65.64 ± 10.40
120 minutes after operation	MAP	83.57 ± 7.56	65.18 ± 9.01
begin	HR	76.0 ± 6.84	65.18 ± 9.02
150 minutes after operation	MAP	83.61 ± 5.67	64.64 ± 9.11
begin	HR	77.64 ± 7.95	64.64 ± 9.11
180 minutes after operation	MAP	81.89 ± 6.02	65.21 ± 9.05
begin	HR	77.43 ± 7.02	65.21 ± 9.05
210 minutes after operation	MAP	82.14 ± 6.45	66.14 ± 10.12
begin	HR	76.61 ± 6.43	66.14 ± 10.12
240 minutes after operation	MAP	83.52 ± 5.69	67.57 ± 10.03
begin	HR	77.63 ± 6.03	67.57 ± 10.03
p		<0.001	<0.001

Table 3. Mean of sedation scores between patients of both trial groups

Study group Sedation score	Remifentanil (Mean±sd)	Deoxythymidine (Mean±sd)	p
After extubation	2.9±0.36	3.11±0.32	< 0.001
30 minutes later	1.0±0.01	2.96±0.19	< 0.001
60 minutes later	1.18±0.39	2.61±0.57	< 0.001
120 minutes later	2.0±0.01	1.96±0.19	< 0.001
360 minutes later	2.0±0.01	2±0.01	< 0.001

Discussion

Although in this present study the mean blood pressure (BP) and heart rate (HR) revealed significant difference in both drugs, DEX had a significant lowering impact on intra-operative BP and HR compared to remifentanil. Sedation after extubation was significantly higher in patients who received DEX compared to patients who received remifentanil. In addition, in the DEX group lower need to analgesic was observed in some intra-operative times and more specifically in postoperative period. Some previous studies found relatively similar trial findings and reported that DEX can make 30-50% reduction in the propofol requirement in concomitant use of DEX in adolescent patients and healthy volunteers (1, 2). It seems that the sedative impact of DEX in patients is mediated by locus ceruleus in the brain stem. In this region, DEX decreases sympathetic and increases parasympathetic outflow (8, 9).

Laryngoscope insertion and endotracheal intubation can induce the sympathetic nervous system and cause severe tachycardia, hypertension or arrhythmia (10). Several studies had been performed on the reduction of these cardiovascular responses. DEX is a very effective alpha-2 agonist and has more impact on stabilizing cardiovascular system after intubation and reduces the need to analgesic and sedative drugs preoperatively (11). Some investigators such as Segal et al. reported a decrease in requirement for halothane, and Aho et al.

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reported a decrease in a requirement for isoflurane up to 90% (12, 13). Moreover, in one study, the dosage of thiopental sodium was significantly decreased after using DEX in anesthesia (14). DEX can decline the serum level of catecholamine and norepinephrine against some of the stressful stimuli such as intubation (15).

Some other studies reported that DEX have complex of vasodilation and vasoconstriction impacts, by activating pre-synaptic α2-receptors on sympathetic and post-synaptic α2 -receptors of the central nervous system medicates vasodilation, and by effects on post-synaptic α2 -receptors on vascular smooth muscle cells can mediate vasoconstriction impacts (16-18). Some previous studies reported a biphasic and dose-dependent impact for DEX on the blood pressure and heart rate of patients (17, 18). On the other hand, DEX increases BP in the short-term usage and decreases BP in patients in the long time usage. DEX in low dosage (plasma concentrations, 0.7-1.2 ng/ml) causes reduction in the release of norepinephrine release and an inhibition of sympathetic neurotransmission by activating α2A receptors (6, 8, 19). The high dosage of DEX (i.e., plasma concentrations, >1.9 ng/ml) produces α2B receptor-mediated vasoconstriction (6, 8). Most previous studies confirmed cardiovascular depressive effects of DEX and reported an increase in the incidence of hypotension and bradycardia (7, 14, 19). The propofol-sparing effect of DEX may be beneficial for the reduction of the propofol dosage and may avoid the adverse effects such as myocardial depression, metabolic acidosis, impaired platelet aggregation and extended recovery caused by prolonged and large-dose administration of propofol (20-24).

This study had some limitations that should be considered for the future studies in this filed. Firstly, our study was performed in one hospital and with patients with one type of operation. Conducting multicenter studies with patients of different operation types is recommended. Secondly, some of the disease characters in spinal regions might have effects on their hemodynamic changes. For the future studies, it is recommended to match the study variables and randomly select the participants while excluding patients with previous history of hemodynamic changes.

Conclusion

Dexmedetomidine in patients with spinal operation is associated with lower postoperative pain score and intraoperative bleeding; Hemodynamic effects are also significantly better in the DEX group.

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