

Effects of Dexmedetomidine on Serum Interleukin-6, Hemodynamic Stability, and Postoperative Pain Relief in Elderly Patients under Spinal Anesthesia

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The beneficial effects of dexmedetomidine (DEX) have not been extensively investigated in elderly patients receiving spinal anesthesia. This study evaluated the effects of intravenous DEX infusion on stress and hemodynamic response, as well as on postoperative analgesia in elderly patients undergoing total knee arthroplasty (TKA). We randomly allocated 45 adult patients to 3 patient groups (n = 15 each): uni-saline group patients underwent unilateral TKA with saline administration, uni-DEX group patients underwent unilateral TKA with DEX administration, and bilateral-DEX group patients underwent bilateral TKA with DEX administration. Serum interleukin-6 (IL-6) levels were significantly lower in the bilateral-DEX group than in the uni-saline group 6 and 24h postoperatively, and were negatively correlated with total DEX dosage 24h postoperatively. Bradycardia occurred more frequently in the uni-DEX and bilateral-DEX groups than in the uni-saline group. The total dose of required supplementary analgesics was significantly higher in the uni-saline group than in the uni-DEX and bilateral-DEX groups 6h postoperatively. The results indicate that perioperative intravenous DEX administration decreases postoperative serum IL-6 levels in patients undergoing bilateral TKA, and has a postoperative analgesic effect in patients undergoing unilateral or bilateral TKA.

Key words: analgesic effect, dexmedetomidine, hemodynamic response, stress response

Unlike previously employed sedatives such as midazolam and propofol, which are primarily inhibitors of γ -aminobutyric acid (GABA) receptors, dexmedetomidine (DEX) acts on α_2 -adrenergic receptors and induces adequate sedation without respiratory depression [1-3]. The US Food and Drug Administration (FDA) approved the use of DEX in humans at the end of 1999 as a short-term (less than 24h) analgesic and sedation medication in the intensive care unit [4]. This sedative also produces analgesia by affecting the central nervous system, and thereby reduces

opioid requirements during and after surgery [5, 6]. It has been reported that DEX decreases the release of stress response biomarkers [7], and suppresses the sympathetic tone in a dose-dependent manner, resulting in a considerable decrease in heart rate, systemic blood pressure, and cardiac output [8-10].

Previous studies have reported that intravenous DEX administration extends the duration of spinal anesthesia, and can provide postoperative analgesia [11, 12]. However, no study has evaluated the maintenance of hemodynamic stability and the postoperative stress response in elderly patients receiving spinal

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anesthesia. This study was conducted to assess the hemodynamic changes and the extent of sedation associated with DEX administration in elderly patients undergoing total knee arthroplasty (TKA). In addition, we aimed to determine the beneficial effects of the use of intraoperative DEX during postoperative recovery, by examining its effects on the reduction of stress response and induction of analgesia.

Methods

After obtaining approval from the Institutional Review Board, we designed and conducted a randomized prospective, controlled clinical study between June 2013 and April 2014 IRB of Jeju National University Hospital (IRB No. 2013-05-012).

Patients. Written informed consent was obtained from all patients. Forty-five adult patients with physical status I and II according to the American Society of Anesthesiologists (ASA) who underwent TKA under spinal anesthesia were evaluated. Patients with a history of diabetes, severe cardiovascular disease, steroid use, renal or hepatic dysfunction, mental retardation, pregnancy, and preoperative hypotension or hypovolemia were excluded.

Group assessment. Patients were randomly assigned to 3 groups: a uni-saline group ($n = 15$; unilateral TKA with saline administration); uni-DEX group ($n = 15$; unilateral TKA with DEX administration of $0.4\text{--}0.8\mu\text{g}/\text{kg}/\text{h}$); or bilateral-DEX group ($n = 15$; bilateral TKA with DEX administration of $0.4\text{--}0.8\mu\text{g}/\text{kg}/\text{h}$).

Anesthetic regimen. All patients were admitted to the operating room without premedication; they underwent noninvasive blood pressure monitoring, electrocardiography, and pulse oximetry. Hemodynamic parameters were recorded intraoperatively at 5 min intervals. After measuring the initial vital signs, uni-DEX and bilateral-DEX group patients were administered an intravenous injection of DEX at $0.4\mu\text{g}/\text{kg}/\text{h}$ to a maximum of $0.8\mu\text{g}/\text{kg}/\text{h}$ (without a loading dose), together with oxygen at $5\text{L}/\text{min}$ through a mask. DEX was injected until the surgical tourniquet was removed from the leg. A similar protocol was carried out for saline group patients, with the administration of saline and oxygen. The dose of intraoperative DEX was adjusted to maintain a Ramsay sedation score of 3 [13].

Spinal anesthesia was induced at the L4-5 or L3-4

intervertebral spaces using $100\mu\text{g}$ epinephrine and added to 10mg bupivacaine HCl (AstraZeneca, Australia). Surgery was started when a bilateral sensory blockade was achieved up to the T10 dermatome. No additional sedatives or analgesics were used during anesthesia or surgery.

Once patients were confirmed as stable following anesthetic induction, the end-tidal carbon dioxide (EtCO_2) was monitored. Apnea was suspected when EtCO_2 was not detected for 20 sec or more during sedation. Systolic blood pressure (SBP) was maintained within 20% of baseline; when SBP was equal to or less than 90mmHg , 5mg ephedrine was administered intravenously. Bradycardia was defined as a heart rate of $50\text{beats}/\text{min}$ or less; in cases of bradycardia, 0.5mg atropine was administered intravenously.

Postoperative pain was managed using a patient-controlled analgesia (PCA) device containing $10\mu\text{g}/\text{kg}$ fentanyl and 300mg ketorolac mixed with 30mg ramotetron to a total volume of 100mL ($1\text{mL}/\text{h}$ basal, 1mL bolus, and lockout time 15min , intravenously). Pain was assessed using the visual analogue scale; when the score was 5 or more, 50mg tramadol was administered intravenously at the ward.

Measurements. Electrocardiogram, non-invasive blood pressure, peripheral capillary oxygen saturation, and EtCO_2 were monitored continuously during surgery at 5 min intervals. Postoperative pain was evaluated based on the total PCA volume administered 6 and 24 h postoperatively and the supplementary analgesics administered within 6 h postoperatively. Hormonal stress response was evaluated and compared by measuring serum concentrations of interleukin-6 (IL-6); serum samples were collected preoperatively as well as at 6 and 24 h postoperatively.

Analysis. In a previous study, the mean serum concentration of IL-6 was shown to increase by a mean of $34.75 \pm 11.97\text{pg}/\text{mL}$ at 6 h postoperatively in the control group, but was unchanged in the DEX-treated group at this time point [7]. IL-6 is a stress indicator that peaks 4-6 h postoperatively. Assuming that the observed increase at 6 h postoperatively in the present study was similar to the trend observed in the aforementioned study, when comparing the time-dependent responses in the treatment group, the required sample size for an alpha error of 0.05 and a beta error of 0.2 would be 15 subjects per group.

All data were analyzed using SPSS software (IBM SPSS statistics 21 for Windows). Among the continuous categorical data, normally distributed data were expressed as the mean \pm standard deviation, and non-normally distributed data as the median value [25th–75th percentile]. Continuous data between groups were compared using Mann–Whitney U and Kruskal–Wallis tests. Non-continuous data between groups were analyzed using Fisher's exact test. A Wilcoxon test was used to analyze values that changed from baseline, and repeated measures analysis of variance (rANOVA) was used to analyze time-dependent hemodynamic variables and stress response values. Values of $p < 0.05$ were considered statistically significant.

Results

Demographic and clinical data were similar among the three groups. The mean patient age was 70 years or older. The median surgical and anesthetic durations were significantly longer in the bilateral-DEX group than in the other groups. The total dose of DEX administered was significantly higher in the bilateral-DEX group compared to the uni-DEX group (Table 1). When anesthesia was below dermatome T10, patients were allowed to leave the recovery room. There were no significant differences in recovery time among groups.

In all groups, the concentration of the stress response biomarker IL-6 was significantly different from the preoperative baseline value within groups. The differences between the 3 groups became statistically significant over time (Table 2). Serum IL-6

Table 1 Demographic distribution and perioperative parameters

	Uni-saline group (n = 15)	Uni-DEX group (n = 15)	Bilateral-DEX group (n = 15)
Age (years)	73.9 \pm 3.8	72.5 \pm 6.4	69.9 \pm 3.9
Height (cm)	150.9 \pm 6.3	152.2 \pm 5.7	153.9 \pm 6.7
Weight (kg)	62.6 \pm 8.8	64.5 \pm 6.2	61.3 \pm 7.4
HTN, n (%)	11 (73.3)	11 (73.3)	7 (46.7)
SBP (mmHg)	128.8 \pm 16.4	132.0 \pm 10.1	132.1 \pm 14.3
DBP (mmHg)	75.7 \pm 7.6	79.5 \pm 8.4	78.1 \pm 8.5
HR (beats/min)	64.2 \pm 5.9	67.1 \pm 7.8	65.7 \pm 8.7
IL-6 (pg/mL)	1.0 \pm 1.0	0.9 \pm 1.2	0.5 \pm 0.8
Duration of surgery (min), median [IQR]	69.0 [63.0–78.0]	65.0 [59.0–70.0]	155.0 [143.0–168.0] ^{*†}
Duration of anesthesia (min), median [IQR]	110.0 [100.0–115.0]	95.0 [90.0–110.0]	205.0 [180.0–215.0] ^{*†}
Total dose of DEX (μ g)	0	40.3 \pm 10.5 [*]	99.7 \pm 19.0 ^{*†}

Uni-saline group: unilateral total knee arthroplasty with saline administration. Uni-DEX group: unilateral total knee arthroplasty with dexmedetomidine administration. Bilateral-DEX group: bilateral total knee arthroplasty with dexmedetomidine administration. HTN, hypertension; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; IL-6, interleukin-6; IQR, interquartile range; DEX, dexmedetomidine. Data are presented as the mean \pm SD or median [IQR]. ^{*} $p < 0.05$ vs. the Uni-saline group; [†] $p < 0.05$ vs. the Uni-DEX group.

Table 2 Comparison of serum interleukin-6 levels among the 3 groups

	Uni-saline group (n = 15)	Uni-DEX group (n = 15)	Bilateral-DEX group (n = 15)
Interleukin-6 (pg/mL)			
Basal	1.0 \pm 1.0	0.9 \pm 1.2	0.5 \pm 0.8
PO 6h	52.5 \pm 23.5	47.4 \pm 11.8	35.8 \pm 22.7 [*]
PO 24h	84.1 \pm 32.2	78.5 \pm 17.1	50.7 \pm 25.3 [*]

Uni-saline group: unilateral total knee arthroplasty with saline administration. Uni-DEX group: unilateral total knee arthroplasty with dexmedetomidine administration. Bilateral-DEX group: bilateral total knee arthroplasty with dexmedetomidine administration. Basal: preoperative serum level; PO 6h and 24h: 6h and 24h postoperatively. Data are presented as the mean \pm SD. ^{*} $p < 0.05$ vs. the Uni-saline group.

levels were significantly lower in the bilateral-DEX group than in the uni-saline group at 6 and 24 h postoperatively ($p=0.010$, 0.005 , respectively). When the association between changes in the total DEX dose and serum IL-6 concentration was examined, a significant negative correlation was observed in the values obtained 24 h postoperatively ($p=0.008$, Fig. 1). This relation is expressed by the following equation:

$$[\text{IL-6}] = -0.46 \times (\text{total DEX dosage}) + 97.75.$$

The lowest mean SBP was maintained in the uni-saline group. Intraoperatively, the heart rate in the uni-DEX and bilateral-DEX groups remained lower than that in the uni-saline group; the differences between groups were not significant (Fig. 2). Apnea did not occur in either group as a secondary effect to drug administration. Two cases of hypotension were observed in each group, and no significant differences were observed among the 3 groups. Bradycardia occurred more frequently in the uni-DEX and bilateral-DEX groups than in the uni-saline group ($p=0.048$, 0.014 , respectively; Table 3).

To determine the analgesic effect of DEX, total PCA volume administered postoperatively as well as supplementary analgesic requirements were compared

among groups. There were no significant differences among the 3 groups in total PCA volume. However, supplementary analgesic requirements 6 h after surgery due to a pain score higher than 5 were significantly higher in the uni-saline group than in the uni-DEX and bilateral-DEX groups ($p=0.048$, 0.042 , respectively; Table 4).

Discussion

In this study, a significant negative correlation was observed between the serum IL-6 concentration, which is a stress response biomarker, and total DEX dose 24 h postoperatively. There was no significant decrease of SBP, even when the duration of DEX administration was increased from its minimum rate of $0.4 \mu\text{g}/\text{kg}/\text{h}$ to a maximum of $0.8 \mu\text{g}/\text{kg}/\text{h}$. Perioperative intravenous DEX administration produced a postoperative analgesic effect, without serious complications.

To determine whether the stress response was decreased, IL-6 concentrations were measured postoperatively and compared to baseline levels in the 3 groups. IL-6 is an immune mediator that can be detected 60 min after injury; it peaks after 4–6 h, and can be continuously detected up to 10 days [14].

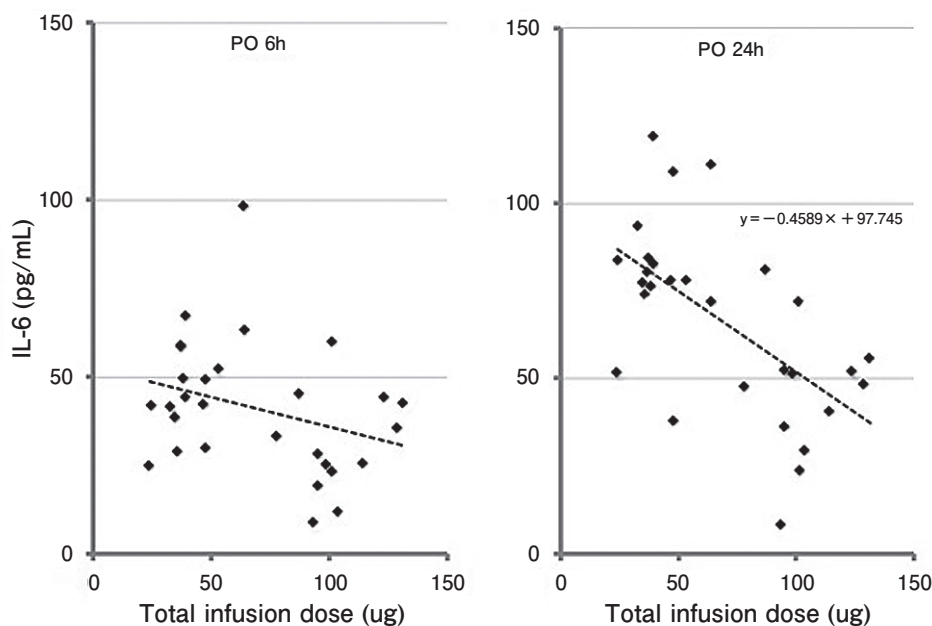


Fig. 1 Serum interleukin-6 concentration in relation to total dexmedetomidine dose in patients administered dexmedetomidine. A significant negative correlation was observed between the total infusion dose of dexmedetomidine and serum interleukin-6 levels 24 h postoperatively ($r = -0.46$, $p = 0.008$). PO 6h and 24h: 6h and 24h postoperatively in the group administered dexmedetomidine.

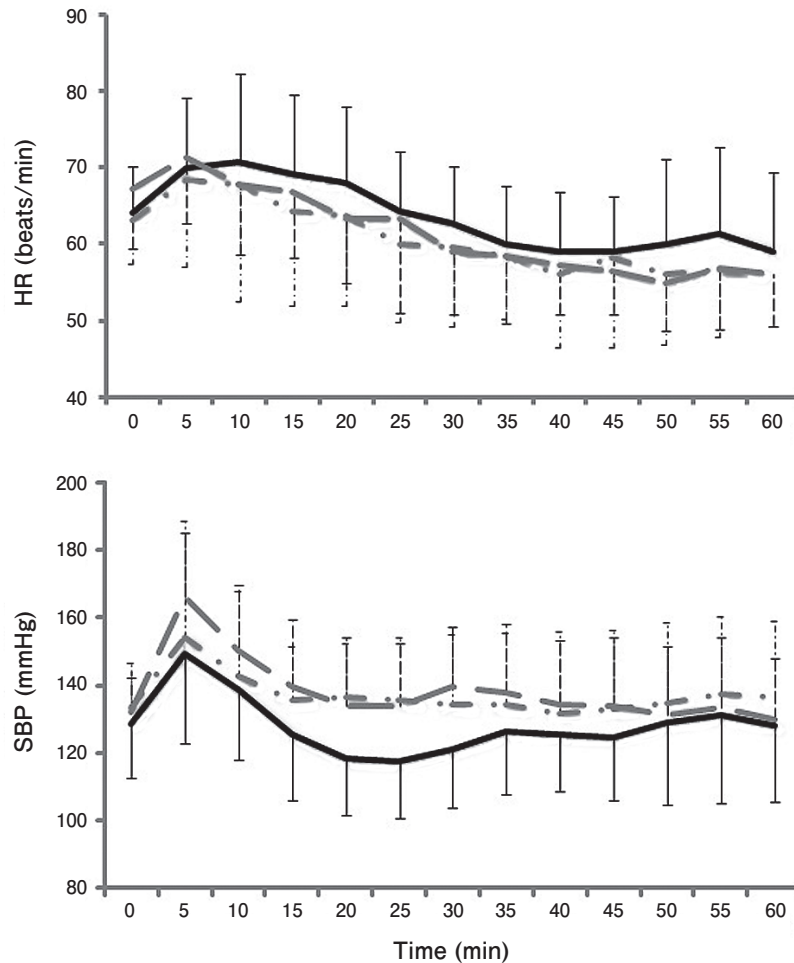


Fig. 2 Intraoperative changes (5 min intervals) in heart rate and systolic blood pressure after intravenous infusion of dexmedetomidine. Uni-saline group (black line —): unilateral total knee arthroplasty with saline administration. Uni-DEX group (gray line - -): unilateral total knee arthroplasty with dexmedetomidine administration. Bilateral-DEX group (gray dotted line ····): bilateral total knee arthroplasty with dexmedetomidine administration. Data are presented as the mean ± SD.

Table 3 Distribution of side effects

Uni-saline group (n = 15)	Uni-DEX group (n = 15)	Bilateral-DEX group (n = 15)
0 (0)	0 (0)	0 (0)
2 (13.3)	2 (13.3)	2 (13.3)
1 (6.7)	5 (33.3)*	8 (53.3)*

Uni-saline group: unilateral total knee arthroplasty with saline administration. Uni-DEX group: unilateral total knee arthroplasty with dexmedetomidine administration. Bilateral-DEX group: bilateral total knee arthroplasty with dexmedetomidine administration. Data are presented as the number of patients (percentage). * $p < 0.05$ vs. the Uni-saline group.

Levels of the cytokine IL-6 increase in response to acute psychological stress even in healthy adults, and its circulating levels have been positively correlated with feelings of anger and anxiety [15-17]. In a previous study, unlike in the DEX group, IL-6 levels in the saline group increased two-fold compared to baseline at 1d postoperatively [7]. In contrast, other studies reported no significant differences [18, 19]. In this study, the IL-6 concentrations at 6 and 24h postoperatively differed significantly between the bilateral-DEX and uni-saline groups (Table 2). Because the total dose of DEX administered differed between these groups, IL-6 changes associated with the total DEX dose were analyzed. A negative correlation was

Table 4 Comparison of analgesic effect among the 3 groups

	Uni-saline group (n = 15)	Uni-DEX group (n = 15)	Bilateral-DEX group (n = 15)
Tramadol, n (%)	5 (33.3)	0 (0)*	1 (6.7)*
PCA 6 h (ml)	10.2 ± 6.4	11.3 ± 4.4	6.5 ± 4.6
PCA 24 h (ml)	32.9 ± 12.4	33.7 ± 13.9	30.3 ± 15.8

Uni-saline group: unilateral total knee arthroplasty with saline administration. Uni-DEX group: unilateral total knee arthroplasty with dexmedetomidine administration. Bilateral-DEX group: bilateral total knee arthroplasty with dexmedetomidine administration. PCA 6h and 24h: total volume infused via patient-controlled analgesia at 6h and 24h postoperatively, respectively. Data are presented as the mean ± SD. * $p < 0.05$ vs. the Uni-saline group.

observed, suggesting a decreased stress response (Fig. 1).

The sedative DEX targets the presynaptic α_2 -adrenergic receptor, and through negative feedback controls the secretion of epinephrine, inhibiting sympathetic activity and decreasing blood pressure and heart rate [4, 8, 20]. In contrast to a previous study [21] that reported a dose-dependent decline in blood pressure, in the present study, no patient showed a decrease in blood pressure, even when the dose of DEX was increased to a maximum of $0.8 \mu\text{g}/\text{kg}/\text{h}$. However, bradycardia occurred in both the uni-DEX and bilateral-DEX groups, which is consistent with the results of previous studies.

The activation of dorsal horn α_2 -adrenergic receptors reduces the secretion of the nociceptive neurotransmitter substance P, producing primary analgesia [22]. The locus ceruleus is the origin of the descending medullo-spinal noradrenergic pathway, which plays an important role in the regulation of analgesia. DEX is known to extend the time to the first postoperative analgesic request [12, 23, 24]. This analgesic effect is not dose-dependent, and a ceiling effect occurs at a dose higher than $0.5 \mu\text{g}/\text{kg}$ [25]. Our study compared the requirements for supplementary analgesia within 6h postoperatively. In the uni-DEX and bilateral-DEX groups, postoperative pain was managed solely with PCA, except in the case of one subject. Five subjects in the control group required additional analgesia, which was a statistically significant difference (Table 4).

This study had some limitations. The sample size was small, and the experimental bilateral-DEX group lacked an appropriate saline group, which would include subjects undergoing bilateral TKA with saline administration. However, because bilateral TKA requires more than 2h of surgery, a sedative agent

(e.g., midazolam or propofol) is usually given to reduce patient discomfort. In addition, this study used the recommended continuous infusion dose without a loading dose. However, administration of DEX may cause hemodynamic instability. In elderly patients who are susceptible to blood pressure changes, the initial loading dose may increase the risk of hemodynamic complications; therefore, future research must focus on a continuous infusion protocol without a loading dose [20, 26].

In those undergoing TKA under spinal anesthesia, DEX resulted in a low incidence of adverse effects such as apnea or hypotension, while maintaining adequate sedation.

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