Comparing intravenous dexmedetomidine and clonidine in hemodynamic changes and block following spinal anesthesia with ropivacaine in lower limb orthopedic surgery: a randomized clinical trial

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Abstract

Dexmedetomidine (DEX) can prolong duration of anesthesia and shorten onset of sensory and motor block relative to clonidine. This study attempted to compare the efficacy of intravenous DEX and clonidine for hemodynamic changes and block after spinal anesthesia with ropivacaine in lower limb orthopedic surgery. In a double-blind randomized clinical trial, 120 patients undergoing spinal anesthesia in lower limb orthopedic surgery were recruited and divided into three groups using balanced block randomization: DEX group (n = 40; intravenous DEX 0.2 µg/kg), clonidine group (n = 40; intravenous clonidine 0.4 µg/kg), and placebo group (n = 40; intravenous normal saline 10 mL) in which pain scores were assessed using visual analogue scales (at recovery, and 2, 4, 6, and 12 hours after surgery) and time to achieve and onset of sensory and motor block. Statistically significant differences were found in mean arterial pressure among the groups at all times except baseline (P = 0.001), with a less mean arterial pressure and a prolonged duration of sensory and motor block (P = 0.001) in the DEX group where pain relieved in patients immediately after surgery and at above mentioned time points (P = 0.001). Simultaneous administration of intravenous DEX with ropivacaine for spinal anesthesia prolongs the duration of sensory and motor block and relieves postoperative pain, and however, can decrease blood pressure. Although intravenous DEX as an adjuvant can be helpful during spinal anesthesia with ropivacaine, it should be taken with caution owing to a lowering of mean arterial pressure in patients especially in the older adults. This study was approved by Ethical Committee of Arak University of Medical Sciences (No. IR.Aراكmu.Rec.1395.450) in March, 2017, and the trial was registered and approved by the Iranian Registry of Clinical Trials (IRCT No. IRCT2017092020258N60) in 2017.

Key words: dexmedetomidine; intravenous clonidine; ropivacaine; spinal anesthesia; pain; visual analog scale; mean arterial pressure; motor block; sensory block

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INTRODUCTION

Regional anesthesia is a common anesthetic procedure in which only one body part considered for surgery is required to be anesthetized.1,2 Subarachnoid spinal anesthesia (SA) is accompanied by local anesthetic injection, being firstly introduced in 1898 by Bier,3 and having enormous advantages, such as the fast onset of action, patient comfort, less adjuvant required, and desirable sensory and motor block.1 α2 adrenergic receptor agonists are found in the spinal cord and positively affect postoperative pain by agonist stimulation, among which dexmedetomidine (DEX) and clonidine (CLO) are included, with different drug administration including oral, spinal, and epidural.1,4,5

DEX, as reported by Agarwal et al.,7 is more effective than CLO, and can prolong duration of anesthesia, while having a shorter onset of sensory and motor block by infusion of DEX. Anderson et al.3 did also show a prolonged durations of post-operative analgesia and sensory and motor block with minimal side effects in DEX, if used. Besides, several have documented the effects of adding DEX to ropivacaine (ROP),6,11 reporting that it prolongs the duration of the sensory and motor block and hastens the onset. ROP is fast-acting, with an onset of action as short as that of lidocaine, however, the latter’s side effects, such as cauda equine syndrome have not been seen in ROP. Hence, the enthusiasm for its use is clearly growing. Its onset of action shorter than bupivacaine (BUP) then is highly significant in anesthesia.1

Since no study has so far been reported to compare the effects of these adjuvants for hemodynamic changes and block characteristics in spinal anesthesics with ROP and previous studies are performed with BUP,7 patients can benefit enormously from pain relief and from stable conditions achieved during anesthesia in the operating room, if an adjuvant can be found with minimal hemodynamic changes and a prolonged duration of postoperative analgesia, given the results of the project. While by adding an adjuvant to ROP, we aim to achieve a faster onset of action, as well as a proper duration, to provide highly effective analgesia for patients and, hence, decide to launch a study aimed at comparing DEX and CLO for hemodynamic changes and block after ROP SA in lower limb orthopedic surgery (LLOS).
Subjects and Methods
Design
This was a double-blind, placebo-controlled clinical trial, parallel study conducted in 2017, Arak, Iran. The trial was registered and approved by the Iranian Registry of Clinical Trials (IRCT No. IRCT2017092020258N60) in 2017. The writing and editing of the article was performed in accordance with the CONsolidated Standards Of Reporting Trials (CONSORT) Statement (Figure 1).

Subjects
Enrolled in a double-blind trial, 120 patients undergoing SA in LLOS were recruited after obtaining written informed consent and verification of inclusion and exclusion criteria at Valiasr Hospital, Arak, Iran.

Inclusion criteria
Inclusion criteria included age 18–60 years, American Society of Anesthesiologist status I–II, selecting patients of both genders, and patients undergoing LLOS. Some patients were not included in this study such as; patient refusal of SA, failure in SA, body mass index > 30 kg/m², history of taking β-blockers and α2 agonists and calcium channel blockers, cardiovascular problems, pregnancy, coagulation disorders, local infection in the patient’s back and waist, history of allergy to DEX, CLO, and ROP, arrhythmias, psychological problems and peripheral and central neuropathy.

Exclusion criteria
Exclusion criteria included failure in SA and the use of alternative methods of anesthesia. All patients were hospitalized at least a day before surgery and had nothing by mouth for 8 hours.

Intervention and outcomes
After demographic data was recorded, two intravenous lines were inserted in different areas, first to inject the adjuvants studied, and second for the administration of serum and other drugs. Before the procedure, we measured and recorded baseline heart rate (HR) and mean arterial pressure (MAP) (assessed by non-invasive monitoring), as well as arterial oxygen saturation (SaO₂). All participants were administered crystalloid (Ringer lactate) 10 mL/kg in the supine position on arrival in the operating room. After receiving serum and recording baseline vital signs, the patients were assigned into three groups using balanced block randomization: DEX group (intravenous DEX bolus 0.2 µg/kg, Hospira Inc., IL, USA), CLO group (intravenous CLO 0.4 µg/kg, Devlife Co., Mumbai, India) and placebo (PBO) group (intravenous normal saline 10 mL).

The volume of adjuvant needed for each group was calculated and adjusted to 10 mL with distilled water, then administered intravenously, and SA was performed with a 25–26-gauge Quincke needle at the L3/L4 or L4/L5 intervertebral space. All subjects were used 3–4 mL (15–20 mg) of ROP 0.5% (L. Molteni & C. dei F.Iii Alitti Societa di Esercizio

Figure 1: Patients recruitment flowchart.
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was unaware of the nature of drug in each syringe. While an anesthesiologist resident, having performed the SA, adjuvants was performed in each group by anesthesiologist, without any awareness of the patient group. Preparation of was measured and recorded by an anesthesiologist resident. Severe side effects. To conduct a double-blind study, the data and Bromage score of 0/1 was recorded.

Time to achieve sensory block at T12 and L1 dermatomes lasted for a long time, appropriate treatment was performed (oxygen administration by a nasal mask). If these conditions started surgery.

After the sensory and motor block was assessed, the surgeon measured and recorded in each group by an anesthesiologist resident: The sensory and motor block were evaluated with a needle (pin prick method) every 1 minute after anesthesia, and by the Bromage scale, every 5 minutes, respectively. After the sensory and motor block was assessed, the surgeon started surgery.

Pain scores were recorded using visual analogue scales (VAS) at recovery and 2, 4, 6, and 12 hours postoperation by an anesthesiologist resident. Zero and 10 represent the lowest and highest values in the scale, respectively. If VAS score > 3, pethidine (meperidine) 0.5 mg/kg was given intramuscularly to patients, at any time postoperatively. The time to achieve sensory block at T12 and L1 dermatomes and Bromage score of 0/1 was recorded.

Side effects, such as nausea and vomiting, bradycardia, hypotension and dizziness, if occurred, were recorded and appropriate remedial action was taken in case of any mentioned severe side effects. To conduct a double-blind study, the data was measured and recorded by an anesthesiologist resident, without any awareness of the patient group. Preparation of adjuvants was performed in each group by anesthesiologist resident, while an anesthesiologist resident, having performed the SA, was unaware of the nature of drug in each syringe.

**Table 1: Baseline characteristics of included patients in lower limb orthopedic surgery patients of dexmedetomidine, clonidine, and placebo groups**

| Item                      | Dexmedetomidine (n = 40) | Clonidine (n = 40) | Placebo (n = 40) | P-value |
|---------------------------|--------------------------|--------------------|------------------|---------|
| Age (yr)                  | 35.2±4.55                | 34.85±5.62         | 34.75±5.14       | 0.205   |
| Body mass index (kg/m²)   | 24.62±2.26              | 24.42±2.71         | 23.85±2.17       | 0.672   |
| Male                      | 20 (50)                 | 20 (50)            | 20 (50)          | 0.999   |
| Mean arterial pressure (mmHg) | 101.2±10.68   | 105.2±12.99        | 114±11.18        | 0.189   |
| Heart rate (beats/min)    | 87.9±7.35               | 89.37±8.76         | 85.1±8.76        | 0.721   |
| Oxygen saturation (mmHg)  | 97.82±0.74              | 97.87±0.64         | 97.85±0.57       | 0.753   |

Note: Data are expressed as the mean ± standard deviation (SD) or frequency (percentage). Likelihood ratio chi-square test, one way analysis of variance, post hoc Tukey test, repeated-measure analysis of variance and linear mixed model in Stata 13 (StataCorp. LLc., College Station, TX, USA) were used to compare the groups. P less than 0.05 was considered as statistically significance level.

**Results**

In this study, 40 patients in the DEX group, 40 patients in the CLO group and 40 patients in the placebo group were analyzed to compare DEX and CLO for hemodynamic changes and block after ROP SA in LLOS (Figure 1). Baseline characteristics of participants were compared in Table 1. Based on the Table 1, no statistically significant difference was seen in age, body mass index, sex, MAP, HR and SaO₂.

As can be seen in the Table 2, MAP has a significant difference between the three groups with lowest level in the DEX group. The first (DEX) and the second (CLO) groups received infusions of DEX 0.1 μg/kg per hour and CLO 0.2 μg/kg per hour, respectively, until the end of surgery. Finally, the third group (PBO) received normal saline 50 mL/h during the same time. It should be noted that the prescribed dosage needed for patients was calculated each hour, while the volume was adjusted to 50 mL.

At the end of each hour, if the surgery continued, the needed infusion was recalculated, and the volume was adjusted to 50 mL, i.e., a new syringe was used for each patient and this continued thereafter. Anesthesia resident recorded MAP, HR, and SaO₂ in both groups every 5 minutes in the first 15 minutes after SA, and then every 15 to 180 minutes at recovery until the end of surgery. Hypotension and bradycardia were defined as a decrease in pressure by more than 20% of baseline and a decrease in HR < 45 beats/min, respectively, and a decrease in SaO₂ by less than 92% (despite a 4 L/min oxygen administration by a nasal mask). If these conditions lasted for a long time, appropriate treatment was performed and recorded.

The sensory and motor block (up to T8 dermatome) were measured and recorded in each group by an anesthesiologist resident: The sensory and motor block were evaluated with a needle (pin prick method) every 1 minute after anesthesia, and by the Bromage scale, every 5 minutes, respectively. After the sensory and motor block was assessed, the surgeon started surgery.

Pain scores were recorded using visual analogue scales (VAS) at recovery and 2, 4, 6, and 12 hours postoperation by an anesthesiologist resident. Zero and 10 represent the lowest and highest values in the scale, respectively. If VAS score > 3, pethidine (meperidine) 0.5 mg/kg was given intramuscularly to patients, at any time postoperatively. The time to achieve sensory block at T12 and L1 dermatomes and Bromage score of 0/1 was recorded.

Side effects, such as nausea and vomiting, bradycardia, hypotension and dizziness, if occurred, were recorded and appropriate remedial action was taken in case of any mentioned severe side effects. To conduct a double-blind study, the data was measured and recorded by an anesthesiologist resident, without any awareness of the patient group. Preparation of adjuvants was performed in each group by anesthesiologist resident, while an anesthesiologist resident, having performed the SA, was unaware of the nature of drug in each syringe.

**Sample size**

Regarding to that α2 agonist can increase the duration of analgesia by up to 20%, and taking into account α = 0.05 and the power of 85%, the sample size was calculated by 40 patients in each group.

**Randomization and sequence generation**

Balanced block randomization approach was used to allocate patients into three groups. In this method, six blocks were used. Because of the use of balanced block randomization, allocation concealment was addressed.

**Ethical consideration**

Written informed consent was obtained from all participants after describing the aim of study. This study was approved by Ethical Committee of Arak University of Medical Sciences in March, 2017 (No. IR.Arakmu.Rec.1395.450). Also, the principles of the Helsinki Declaration were considered at all phases of the study. All participants were permitted to leave the study.

**Blinding**

Participants and medical staff were blind towards allocating patients to intervention groups.

**Statistical analysis**

Data were analyzed using the intention to treat approach. Data were described as the mean ± standard deviation (SD) or frequency (percentage). Likelihood ratio chi-square test, one way analysis of variance, post hoc Tukey test, repeated-measure analysis of variance and linear mixed model in Stata 13 (StataCorp. LLC., College Station, TX, USA) were used to compare the groups. P less than 0.05 was considered as statistically significance level.

In this study, 40 patients in the DEX group, 40 patients in the CLO group and 40 patients in the placebo group were analyzed to compare DEX and CLO for hemodynamic changes and block after ROP SA in LLOS (Figure 1). Baseline characteristics of participants were compared in Table 1. Based on the Table 1, no statistically significant difference was seen in age, body mass index, sex, MAP, HR and SaO₂.

As can be seen in the Table 2, MAP has a significant difference between the three groups with lowest level in the DEX group.
### Table 2: Comparison of mean arterial pressure (mmHg), heart rate (beats/min) and oxygen saturation (mmHg) in lower limb orthopedic surgery patients of dexmedetomidine, clonidine, and placebo groups

|                          | Dexmedetomidine (n = 40) | Clonidine (n = 40) | Placebo (n = 40) |
|--------------------------|---------------------------|--------------------|-----------------|
| **Mean arterial pressure** |                           |                    |                 |
| Baseline (0 min)         | 101.18±10.68              | 105.03±12.99       | 114.38±11.19    |
| 5 min after spinal anesthesia | 99.25±10.97              | 103.40±12.81       | 113.53±10.96    |
| 10 min after spinal anesthesia | 97.75±11.46              | 102.05±12.69       | 112.83±10.82    |
| 15 min after spinal anesthesia | 95.38±11.59              | 100.68±12.55       | 111.90±10.96    |
| 30 min after spinal anesthesia | 94.03±11.63              | 99.98±12.77        | 111.23±10.86    |
| 45 min after spinal anesthesia | 92.93±11.74              | 98.78±12.77        | 110.88±10.76    |
| 60 min after spinal anesthesia | 92.43±11.65              | 98.25±13.03        | 110.80±11.08    |
| 75 min after spinal anesthesia | 92.33±11.73              | 98.20±13.24        | 110.38±11.73    |
| 90 min after spinal anesthesia | 92.13±11.46              | 98.18±13.34        | 110.33±11.43    |
| 105 min after spinal anesthesia | 91.95±11.59              | 98.35±13.60        | 111.20±11.58    |
| 120 min after spinal anesthesia | 92.10±11.76              | 98.83±13.58        | 111.75±11.94    |
| 135 min after spinal anesthesia | 92.08±11.66              | 99.28±13.58        | 111.63±11.92    |
| 150 min after spinal anesthesia | 92.13±11.31              | 99.18±13.92        | 111.50±11.53    |
| 165 min after spinal anesthesia | 92.38±11.23              | 99.68±14.20        | 111.45±11.42    |
| 180 min after spinal anesthesia | 92.88±10.67              | 99.90±14.33        | 111.33±11.13    |
| **Heart rate**           |                           |                    |                 |
| Baseline (0 min)         | 87.90±7.36                | 89.38±8.77         | 85.10±8.76      |
| 5 min after spinal anesthesia | 86.80±6.78                | 87.65±8.28         | 84.55±8.38      |
| 10 min after spinal anesthesia | 85.63±6.53                | 86.60±7.95         | 84.03±8.28      |
| 15 min after spinal anesthesia | 84.65±6.43                | 85.63±8.06         | 83.45±8.09      |
| 30 min after spinal anesthesia | 83.73±6.42                | 84.95±8.23         | 83.20±7.69      |
| 45 min after spinal anesthesia | 83.15±6.44                | 84.30±8.13         | 83.00±7.60      |
| 60 min after spinal anesthesia | 83.03±6.80                | 84.08±8.25         | 82.80±7.71      |
| 75 min after spinal anesthesia | 83.28±6.74                | 83.83±7.98         | 83.23±7.83      |
| 90 min after spinal anesthesia | 83.28±6.68                | 83.93±7.93         | 83.58±7.60      |
| 105 min after spinal anesthesia | 83.18±6.53                | 84.68±7.89         | 84.25±8.10      |
| 120 min after spinal anesthesia | 83.43±6.23                | 85.33±7.63         | 85.23±8.03      |
| 135 min after spinal anesthesia | 83.70±5.65                | 85.45±7.89         | 85.00±7.99      |
| 150 min after spinal anesthesia | 83.98±5.28                | 85.23±7.77         | 84.88±7.58      |
| 165 min after spinal anesthesia | 84.35±5.18                | 85.53±7.82         | 85.18±7.43      |
| 180 min after spinal anesthesia | 84.93±5.48                | 85.95±8.05         | 85.28±7.25      |
| **Oxygen saturation**    |                           |                    |                 |
| Baseline (0 min)         | 97.83±0.75                | 97.88±0.65         | 97.85±0.58      |
| 5 min after spinal anesthesia | 97.90±0.55                | 97.80±0.56         | 97.73±0.51      |
| 10 min after spinal anesthesia | 97.80±0.56                | 97.63±0.63         | 97.63±0.54      |
| 15 min after spinal anesthesia | 97.63±0.59                | 97.63±0.49         | 97.50±0.51      |
| 30 min after spinal anesthesia | 97.78±0.53                | 97.65±0.58         | 97.78±0.53      |
| 45 min after spinal anesthesia | 97.73±0.55                | 97.90±0.55         | 97.65±0.58      |
| 60 min after spinal anesthesia | 97.70±0.61                | 97.78±0.53         | 97.65±0.58      |
| 75 min after spinal anesthesia | 97.68±0.57                | 97.63±0.59         | 97.58±0.59      |
| 90 min after spinal anesthesia | 97.73±0.55                | 97.78±0.58         | 97.65±0.58      |
| 105 min after spinal anesthesia | 97.70±0.52                | 97.70±0.56         | 97.83±0.55      |
| 120 min after spinal anesthesia | 97.88±0.46                | 97.63±0.63         | 97.75±0.54      |
| 135 min after spinal anesthesia | 97.73±0.51                | 97.70±0.56         | 97.83±0.50      |
| 150 min after spinal anesthesia | 97.73±0.55                | 97.78±0.58         | 97.85±0.53      |
| 165 min after spinal anesthesia | 97.78±0.53                | 97.73±0.55         | 97.70±0.56      |
| 180 min after spinal anesthesia | 97.83±0.45                | 97.78±0.58         | 97.75±0.54      |

Note: Data are expressed as the mean ± SD, and were analyzed by analysis of variance followed by Bonferroni post hoc test.

group (P = 0.001) and was higher in the placebo group than the CLO group (coefficient r = 9.35, 95% confidence interval 4.07–14.62, P = 0.001) but there was no significant difference between DEX and CLO groups (coefficient r = −3.85, 95% confidence interval −9.13–1.42, P = 0.153). No statistically significant difference was found in HR among groups (P = 0.658) and also no statistically significant difference was found in SaO2 (Table 2) among the three groups (P = 0.531).
As it was shown in Table 3, statistically significant differences were observed in onset of sensory block after SA ($P = 0.001$), in time to achieve sensory block at T8 or higher (using pin prick test every 1 minute) ($P = 0.001$), and in time to achieve sensory block at T12 and L1 dermatomes and SA wearing off among the groups ($P = 0.001$). Statistically significant differences were found in onset of motor block after SA ($P = 0.001$), in time to achieve motor block at T8 or higher (Bromage Grade 3) ($P = 0.001$), and in time to achieve Bromage score of 0/1 and SA wearing off among them ($P = 0.001$). In all comparison of sensory and motor block among groups, there was a significant difference between DEX and CLO groups and also between DEX and CLO groups in compared to placebo group.

Statistically significant differences were found in pain (assessed by the VAS) among the three groups at recovery, and 2, 4, 6, and 12 hours postoperation ($P = 0.001$), with a lower score in the DEX group than others at all times. Based on the studies, VAS score > 4 was not observed in the three groups at all times (Table 4).

Based on the Table 5, no statistically significant difference was found in side effects such as hypotension, nausea and vomiting, dizziness and HR drop among the three groups. Statistically significant differences were seen in need for meperidine (pethidine) among the three groups ($P = 0.011$). In the placebo group (15%), the need for meperidine was greater than DEX group (0%) and CLO group (5%).

### Discussion

The main finding of this study showed that significant differences were seen in MAP among three groups, while MAP was lower in the DEX and CLO groups than placebo. Between the intervention groups, the DEX group had a lower MAP. No statistically significant difference was found in HR and SaO2 among groups. Statistically significant differences were seen in onset of sensory block after SA, in time to achieve sensory block at T8 or higher dermatome (using pin prick test every 1 minute), in time to achieve sensory block at T12 and L1 dermatomes and SA wearing off, in onset of motor block after SA, in time to achieve motor block at D8 or higher dormancy (Bromage Grade 3) and in time to achieve Bromage score of 0/1 and SA wearing off. Statistically significant differences were found in VAS among three groups whose score was lower in the DEX group. No statistically significant difference was seen in side effects. While statistically significant differences were observed in the need for meperidine among the three groups, the need for meperidine was greater in the placebo group.

Andersen et al.\(^8\) conducted a study on DEX’s mechanism of action when used as an adjuvant to ROP during peripheral nerve block, showing that DEX prolongs the duration of block, whose results were consistent with our study where the DEX group had prolonged duration and less pain score. Patel and Patel’s study,\(^15\) aimed to compare DEX and midazolam on sedative parameters and sensory, motor, and cardiovascular block and reduction of adjuvants in SA showed a significant decrease in HR observed in the DEX group and suggested that DEX has prolonged duration of postoperative analgesia and of sensory and motor blockade, with minimal side effects, whose results were supported mostly by our trial, except for DEX which reduced BP and did not affect HR in the study, while it dropped in the Patel study.

In Agarwal et al.’s study\(^7\) to compare characteristics of SA with 0.5% BUP vs. intravenous DEX and CLO, they showed a faster onset to achieve the highest block level and a shorter onset time of sensory and motor blocks in the DEX group. Bradycardia was observed in the DEX group (1 case) and in the CLO group (2 cases), while hypotension was in the DEX group (5 cases) and in the CLO group (7 cases). They reported a prolonged duration of postoperative anesthesia in the first group, stating that DEX has been found to be very effective, with results consistent with our trial, but BUP used in Agarwal study vs. ROP in ours.

Hu et al.\(^13\) conducted a study on adding DEX to a mix of lidocaine and ROP to prolong the duration of the block, showing adding DEX to lidocaine/ROP would prolong the duration of the sensory and motor block and hastens the onset. They were, moreover, supported by our findings where DEX added to ROP had prolonged the duration of block and relieved pain. A study by Sharma et al.\(^16\) on the effect of addition of DEX to ROP 0.2% for femoral nerve block showed a less pain score and a prolonged time to the first request for DEX ($P = 0.001$), as well as a decreased anesthetic consumption at 24 and 48 hours ($P = 0.001$) in the group, while no statistically

### Table 3: Comparison of sensory and motor block in lower limb orthopedic surgery patients of dexmedetomidine, clonidine, and placebo groups

| Item | Dexmedetomidine ($n = 40$) | Clonidine ($n = 40$) | Placebo ($n = 40$) | $P$-value |
|------|---------------------------|---------------------|-------------------|-----------|
| Onset of sensory block after spinal anesthesia (min) | 3.45±0.84* | 6.15±1.14* | 8.77±0.99 | 0.001 |
| Time to achieve sensory block at T8 or higher dermatome (using pin prick test every 1 min) (min) | 5.90±0.92* | 9.2±0.85* | 12.45±0.98 | 0.001 |
| Time to achieve sensory block at T12 and L1 dermatomes and spinal anesthesia wearing off (min) | 148.8±8.2* | 129.8±13.1* | 108.6±7.9* | 0.001 |
| Onset of motor block after spinal anesthesia (min) | 4.97±0.69* | 8.40±0.74* | 11.22±0.86 | 0.001 |
| Time to achieve motor block at D8 or higher dormancy (Bromage Grade 3) (min) | 6.52±0.87* | 10.42±1.03* | 13.8±0.88* | 0.001 |
| Time to achieve Bromage score of 0/1 and spinal anesthesia wearing off (min) | 168.55±8.5* | 149.9±15.3* | 122.2±8.9* | 0.001 |

Note: Data are expressed as the mean ± SD, and were analyzed by analysis of variance followed by Bonferroni post hoc test. *$P<0.05$, vs. placebo group; #*$P<0.05$, vs. dexametomidine group.
Table 4: Comparison of the frequency (%) of pain at different times in lower limb orthopedic surgery patients of dexmedetomidine, clonidine, and placebo groups

| Time                | Dexmedetomidine | Clonidine (n = 40) | Placebo (n = 40) | P-value |
|---------------------|----------------|--------------------|-----------------|---------|
|                     | (n = 40)       | (n = 40)           | (n = 40)        |         |
| Immediately after surgery | 26 (65)         | 7 (17.5)           | 2 (5)           | 0.001   |
| No pain             | 26 (65)         | 7 (17.5)           | 2 (5)           |         |
| Very mild           | 14 (35)         | 33 (82.5)          | 38 (95)         |         |
| Mild                | 0              | 0                  | 0               |         |
| Below moderate      | 0              | 0                  | 0               |         |
| Moderate            | 0              | 0                  | 0               |         |
| Recovery            | 18 (45)         | 5 (12.5)           | 2 (5)           | 0.001   |
| No pain             | 18 (45)         | 5 (12.5)           | 2 (5)           |         |
| Very mild           | 22 (55)         | 33 (82.5)          | 37 (92.5)       |         |
| Mild                | 0              | 2 (5)              | 1 (2.5)         |         |
| Below moderate      | 0              | 0                  | 0               |         |
| Moderate            | 0              | 0                  | 0               |         |
| 2 h after surgery   | 4 (10)          | 0                  | 0               | 0.001   |
| No pain             | 4 (10)          | 0                  | 0               |         |
| Very mild           | 36 (90)         | 33 (82.5)          | 6 (15)          |         |
| Mild                | 0              | 7 (17.5)           | 34 (85)         |         |
| Below moderate      | 0              | 0                  | 0               |         |
| Moderate            | 0              | 0                  | 0               |         |
| 4 h after surgery   | 2 (5)           | 0                  | 0               | 0.001   |
| No pain             | 2 (5)           | 0                  | 0               |         |
| Very mild           | 38 (95)         | 33 (82.5)          | 0               |         |
| Mild                | 0              | 7 (17.5)           | 32 (80)         |         |
| Below moderate      | 0              | 0                  | 8 (20)          |         |
| Moderate            | 0              | 0                  | 0               |         |
| 6 h after surgery   | 25 (62.5)       | 4 (10)             | 0               | 0.001   |
| No pain             | 25 (62.5)       | 4 (10)             | 0               |         |
| Very mild           | 15 (37.5)       | 36 (90)            | 4 (10)          |         |
| Mild                | 0              | 0                  | 30 (75)         |         |
| Below moderate      | 0              | 0                  | 6 (15)          |         |
| Moderate            | 0              | 0                  | 0               |         |
| 12 h after surgery  | 0              | 0                  | 0               | 0.001   |
| No pain             | 0              | 0                  | 0               |         |
| Very mild           | 25 (62.5)       | 0                  | 0               |         |
| Mild                | 15 (37.5)       | 15 (37.5)          | 0               |         |
| Below moderate      | 0              | 23 (57.5)          | 34 (85)         |         |
| Moderate            | 0              | 2 (5)              | 6 (15)          |         |

Note: Pain was assessed by visual analogue scales. Data are expressed as number (percentage), and were analyzed by likelihood ratio chi-square test.

Table 5: Comparison of the frequency of postoperative side effects in lower limb orthopedic surgery patients of dexmedetomidine, clonidine, and placebo groups

| Side effects               | Dexmedetomidine (n = 40) | Clonidine (n = 40) | Placebo (n = 40) | P-value |
|----------------------------|--------------------------|--------------------|-----------------|---------|
| Hypotension                | 0                        | 0                  | 0               |         |
| Yes                        | 0                        | 0                  | 0               |         |
| No                         | 40 (100)                 | 40 (100)           | 40 (100)        |         |
| Nausea and vomiting        | 0.577                    | 0.577              |                 |         |
| Yes                        | 2 (5)                    | 3 (7.5)            | 1 (2.5)         |         |
| No                         | 38 (95)                  | 37 (92.5)          | 39 (97.5)       |         |
| Dizziness                  | 0.577                    | 0.577              |                 |         |
| Yes                        | 2 (5)                    | 3 (7.5)            | 1 (2.5)         |         |
| No                         | 38 (95)                  | 37 (92.5)          | 39 (97.5)       |         |
| Heart rate drop            | –                        | –                  |                 |         |
| Yes                        | 0                        | 0                  | 0               |         |
| No                         | 40 (100)                 | 40 (100)           | 40 (100)        |         |

Note: Data are expressed as number (percentage), and were analyzed by likelihood ratio chi-square test.
significant difference was seen in hemodynamics between the two groups. They also suggested that adding DEX in their subjects prolonged the duration of postoperative analgesia and the duration of the block, whose results were consistent with ours, however, the latter trial, DEX reduced BP, compared to the others, when no difference was found in hemodynamic status in Sharma et al.’s study.

Fritsch et al.14 who launched a study on adding DEX during a brachial block, showed the first onset of sensory block and motor block in DEX, while a statistically significant difference was observed, having a lower HR and stable MAP in the group. They expressed that adding DEX prolongs the duration of the sensory and motor block and hastens the onset and whose results were consistent with ours: MAP was lower in the DEX group in our study. Elcicek et al.9 aimed to explore the effects of intravenous DEX on spinal hyperbaric ROP anesthesia, reporting a longer duration of block, and a higher sedation score and need for atropine in the DEX group. Although, they stated that DEX prolongs the duration of the block with less side effects and provides proper sedation levels for the patient, the anesthesiologist should be alert for bradycardia caused by DEX, once used. Their results were consistent with ours, however, HR in the DEX group was no different from the others, while had lower MAP in our study.

Though, DEX prolongs the duration of sensory and motor block and relieves postoperative pain, it besides reduces BP, caused by DEX, once used. Their results were consistent with the others, while had lower MAP in our study.

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Data sharing statement
The data could be shared if requested.
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Author contributions
MJ, AS, HM, AK, AA and AAH conceived the study. MJ and HM collected the data. All authors contributed equally to draft the manuscript. AAH and HM analyzed the data. All authors revised the manuscript and approved the final version.

Conflicts of interest
There is no conflict of interest.

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Institutional review board statement
This study was approved by Ethical Committee of Arak University of Medical Sciences (No. IR.Arakmu.Rec:1395.450) in March, 2017.

Declaration of patient consent
The authors certify that they have obtained patients consent forms. In the form, patients have given their consent for their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published.

Reporting statement
The writing and editing of the article were performed in accordance with the CONsolidated Standards of Reporting Trials (CONSORT) Statement.

Biostatistics statement
The statistical methods of this study were reviewed by the epidemiologist of Arak University of Medical Sciences, Iran.

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