Comparative analgesic, hemodynamic, pain and duration of sensory and motor block effects of dexmedetomidine, granisetron, and nitroglycerin added to ropivacaine in intravenous anesthesia for forearm surgeries: a randomized clinical study

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Abstract

This trial-based paper strives to address the comparative efficacy of some ropivacaine adjuvant options, comprising dexmedetomidine, granisetron, and nitroglycerin, on pain and hemodynamic changes in intravenous anesthesia for forearm surgeries. This double-blind, placebo-controlled study enrolled four block-randomized eligible groups with patients (overall, *n*=128) undergoing orthopedic forearm surgeries in the dexmedetomidine, nitroglycerin, granisetron, and placebo groups. Intra- and post-operative vital signs (mean arterial pressure/heart rate/oxygen saturation) were monitored at baseline and captured every 10 minutes until the end of the surgery, as well as the onset of sensory and motor block and length and duration of the block and mean opioid use within 24 hours. Lastly, pain was noted after tourniquet inflation (at 15, 30, and 45 minutes every 15 minutes until the end of surgery) and after deflation (every 30 minutes to 2 hours at 30, 60, 90, and 120 minutes), as well as 6, 12, and 24 hours after the tourniquet was deflated. The dexmedetomidine-sedated subjects appeared to demonstrate quicker onset and longer length and duration of sensory and motor block, plus less pain and opioid use at all scheduled times (both P = 0.0001). Dexmedetomidine is recommended as an adjuvant to regional anesthesia (Bier's block), while being coupled with the rapid onset and prolonged length and duration of sensory and motor blocks, in addition to soothed pain and diminished opioid use within postoperative 24 hours. The study was approved by Ethics Committee of Arak University of Medical Sciences (approval No. IR.ARAKMU.REC.1398.112) on July 21, 2019, and registered at Iranian Registry of Clinical Trials (registration number IRCT20141209020258N123) on November 2, 2019.

Key words: dexmedetomidine; forearm surgeries; granisetron; hemodynamic changes; intravenous anesthesia; nitroglycerin; pain; ropivacaine

doi: 10.4103/2045-9912.330690
How to cite this article: Moshiri E, Modir H, Kamali A, Azami M, Molouk M. Comparative analgesic, hemodynamic, pain and duration of sensory and motor block effects of dexmedetomidine, granisetron, and nitroglycerin added to ropivacaine in intravenous anesthesia for forearm surgeries: a randomized clinical study. Med Gas Res. 2022;12(3):77-82.
Funding: The study was supported by Arak University of Medical Sciences.

Introduction

As foremost pioneered by August Karl Bier in 1908, intravenous regional anesthesia (IVRA) is presently being to be regarded as a straightforward, reliable and safe technique for minor surgical procedures,[1] especially here on the hand and forearm, whilst having been demonstrated particularly suitable for outpatients owing to the rapid anesthesia onset, the low failure probability, the rapid recovery, and lastly the controllable anesthesia extent.[2] The demand toward safer techniques appears to be crucial given the upper limb injuries prevailed, the frequent anesthesia required, and general anesthesia-related complications. As one well-liked technique fitting for short-term orthopedic surgery, potential IVRA-derived benefits embrace the ease of use, acceptable muscle relaxation, and elevated success rate.[3,4] However, its focal limitation is on the onset and swift development of pain following tourniquet deflation, most notably once operations are prolonged.[3,5]

The toxicity reaction developed after unexpected, accidental tourniquet cuff release during surgery is blamed for being the most severe Bier block complication.[1,4] Because an increased peripheral nerve compression is reported to be accounted for by ischemia following tourniquet inflation, the role of a nerve fibers and non-myelin C-fibers was judged significantly contributory in causing tourniquet pain.[3,5] Varying studies were established to include drugs like morphine, meperidine, magnesium sulfate, fentanyl, sufentanil, clonidine, nitroglycerin, granisetron added to the local anesthetic solution to lengthen the analgesia duration.[5,6] Notwithstanding abundant papers on the analgesic effects of transdermal nitroglycerin,[7] evidence about the effect of intravenous nitroglycerin in IVRA is bounded to the study led by Sen et al.[8] who first appraised the effect in the surgical interventions for carpal tunnel, trigger finger, and tendon release, suggesting nitroglycerin-derived pain relief benefits. Likewise, another focused on the improved quality of IVRA when including intravenous nitroglycerin to the lidocaine dosing regimen.[9]

Nitroglycerin, once added to intravenous anesthesia, helps hasten the onset of sensory and motor block sans any complications, and tourniquet and postoperative

pains are alleviated.[9,10] Further, granisetron is a specific 5-hydroxytryptamine 3 receptor antagonist with prolonged duration of action, exhibiting superior efficacy than ondansetron, and being frequently applied to prevent chemotherapy-induced nausea and vomiting.[11,12] Many former studies have been contributed to fruitfully focus on granisetron use to stop propofol-induced pain.[11,13] This class of drugs, akin to topical anesthetics, has been verified for sodium channels blocked and for analgesic effect induced.[14]

5-Hydroxytryptamine 3 peripheral receptors are established to be involved in pain pathways, bind to the opioid receptor, and act as their agonists.[15,16] As an α-2 adrenoceptor agonist, dexmedetomidine produced antinociceptive, sedative, and hypotensive effects[17] and, if added to regional anesthetics, can be demonstrated extremely effective in extending the duration of the peripheral nerve block. Furthermore, numerous clinical studies have documented evidence of its efficacy in prolonging the duration of sensory and motor block and on alleviating pain.[18,19] Dexmedetomidine, granisetron, and nitroglycerin have been found by literature to be applied generally in combination with lidocaine and bupivacaine in most foregone studies, but not with ropivacaine, whereas no study has ever endeavored to contrast multiple drugs, as done in our work. The present authors did outline a randomized trial-based comparing the effectiveness of dexmedetomidine, granisetron, and neostigmine added to ropivacaine on pain and hemodynamic changes in intravenous anesthesia for forearm surgeries.

Subjects and Methods

Study setting

A double-blinded clinical trial recruited 128 patients undergoing forearm surgeries under IVRA, who were studied as the target population after signing informed consent and meeting inclusion/exclusion criteria for eligibility.

The study was approved by Ethics Committee of Arak University of Medical Sciences (approval No. IR.ARAKMU.REC.1398.112) on July 21, 2019, and registrated at Iranian Registry of Clinical Trials (registration number IRCT20141209020258N123) on November 2, 2019. The writing and editing of the study report was performed in accordance with the CONsolidated Standards Of Reporting Trials (CONSORT) statement.

Subjects

Inclusion criteria were both genders, 20–65 years, candidate for forearm surgery, American Society of Anaesthesiologists I and II, no Raynaud's disease, no sickle cell anemia, no history of sensitivity to the drugs included in the study, no cyanosis of the affected limb, no drug and psychotropic substances, no contraindications to intravenous anesthesia, no more than one fracture or surgery, no pregnancy, no chronic pain syndrome, absence of neurological disorders in the hand, no disease related to hypotension, cardiac arrhythmias, and heart failure. Exclusion criteria include the duration of surgery greater than 90 minutes, any reason on which the IVRA must terminate (become ineffective) intraoperatively, duration of surgery < 30 minutes, and dissatisfaction.

Intervention

After recording vital signs including oxygen saturation (SaO_2), two intravenous lines were placed; the first catheter into the dorsal vein of the hand which underwent surgery and the second into the other hand to receive crystalloid fluids. A double tourniquet was applied at 3–4 cm above the target elbow after 2 mg midazolam (Exir Co., Tehran, Iran) was initially given as premedication. The patient's hands are elevated to drain the blood for 2 minutes and an Esmarch bandage (Safateb Co., Esfahan, Iran) was next applied. Subsequently, the proximal cuff of the double-cuff tourniquet was inflated 100 mmHg above the patients' baseline systolic blood pressure (BP) or to 250 mmHg and the Esmarch bandage was removed.[20]

Patients were randomly allocated into four groups ($n = 30$ per group) after the absence of a pulse was verified, based on the pulse oximetry readings. Block random numbers were generated using rolling the dice. The subjects were randomly assigned to the target groups depending on the order of entry into the study. An anesthesiologist prepared interventional drugs, provided them with the resident, unaware of the groupings, analyzed the effects and noted the data. Accordingly, double-blinding was ensured owing to the lack of patient and evaluator's awareness of the order of the groups and interventions.

To induce IVRA, the dexmedetomidine (DEX), granisetron (GRN), and nitroglycerin (NTG) groups received 0.5 μg/kg dexmedetomidine (Exir Co.), 2 mg granisetron (Caspian Co., Tehran, Iran), and 200 μg nitroglycerin (Caspian Co.), respectively, with 2.0% ropivacaine (Ropivacaina Molteni, Molteni, Italy) with a volume of 35 mL (70 mg) in all groups, when the target adjuvant dose was diluted to 5 mL by distilled water. Finally, the overall volume of drug for IVRA was injected in a volume of 40 mL through the venous cannula for each patient in all groups. The placebo group received 5 mL normal saline plus 35 mL of ropivacaine 0.2% via the venous cannula while being topped up to a total volume of 40 mL. The onset of sensory block was assessed by pinprick test using a 22-gauge needle. Patient response was tested for the sensory dermatomes (medial and lateral antebrachial, ulnar, median, and radial nerves). The level of motor block was assessed by requesting to bend hand up and down at the wrist and fingers (flexion and extension). When the patient could not produce voluntary movement in the corresponding limbs, a complete motor block was developed. The onset of sensory block/motor block was considered as the time taken from the administration of study drugs to that of achieving a complete sensory block/motor block, respectively, in all the dermatomes involved. After the sensory and motor block completed, the lower tourniquet was inflated to 250 mmHg, the upper tourniquet was deflated, and subsequently, surgery was allowed to begin.

We recorded vital signs, including heart rate, BP, and SaO_2, (i) prior to using the tourniquet, (ii) at 5, 10, and 20 minutes and then every 10 minutes until the end of the surgery, (iii) after the tourniquet deflation, and (iv) in recovery. All cases of insufficient analgesia and treatment failure were recorded were besides noted and alternative technique was chosen for anesthesia and patient preparation for surgery. The tourniquet should not be deflated earlier than 35 minutes and not be in-

flated for more than 90 minutes. For surgery lasting greater than 90 minutes, the patient would receive general anesthesia and be excluded from the study. The tourniquet was deflated by the cyclic deflation technique after the surgery ended. We then recorded the sensory and motor recovery times and analgesic requirement time, which are considered as the time elapsed after tourniquet deflation until recovery of sensation in dermatomes by a 22-gauge needle, the time elapsed after tourniquet deflation until return of finger movement, and the time elapsed after tourniquet deflation until to first patient request to analgesic, respectively.

The severity of pain as the primary outcome was assessed using the visual analogue scale[21] after the tourniquet inflation, at 15, 30, and 45 minutes and then every 15 minutes until the end of surgery. For patients with visual analogue scale > 4, we intravenously administered 1 μg/kg of fentanyl, and subsequently, the time of receiving the first dose of fentanyl was recorded. Pain scores were noted every 30 minutes to 2 hours at 30, 60, 90, and 120 minutes, as well as 6, 12, and 24 hours after deflating the tourniquet. Postoperatively, if the visual analogue scale was greater than 4, the patient was similarly treated with 25 mg of intramuscular meperidine (Exir Co.).

Statistical analysis

The sample size was calculated by considering the study power 80% and confidence interval 95% and the minimum expected difference of pain score between intervention and placebo groups.

The chi-square test was used to compare gender distribution among four groups. Moreover, one-way analysis of variance was used to compare the mean of age, hemodynamic parameters, SaO_2, pain score among groups. In addition, analysis of variance for repeated data was used to compare trend of pain and hemodynamic parameters during times after operation. Tukey's *post hoc* test was used for future pairwise analysis. All analysis conducted using SPSS version 20 (IBM SPSS Inc., Chicago, IL, USA). The statistical methods of this study were conducted and reviewed by the biostatistician of Arak University of Medical Sciences, Iran.

Results

Baseline of orearm surgery patients with dexmedetomidine, granisetron, and neostigmine plus ropivacaine intravenous anesthesia

This double-blind trial enrolled four block-randomized eligible groups of patients (n = 128) undergoing orthopedic forearm surgeries at the Valiasr Hospital (Arak, Iran): the DEX, NTG, GRN, and placebo groups (**Figure 1**), with the minimum and maximum ages of 22 and 57 years; the overall mean age of 37.00 ± 10.14: 36.12 ± 8.84, 37.09 ± 11.52, 37.46 ± 10.35, and 38.34 ± 9.23, in each respectively ($P > 0.05$). Overall, half of patients were male. The duration of surgery did not differ significantly among the four groups ($P < 0.05$), whereas no side effects were observed ($P < 0.05$). Moreover, patients in 4 groups were similar statistically in terms of age and gender. In addition, no significant statistical difference was observed in heart rate and SaO_2 in all times among the four groups (data not shown) ($P < 0.05$).

Blood pressure of orearm surgery patients with dexmedetomidine, granisetron, and neostigmine plus ropivacaine intravenous anesthesia

According to **Table 1**, four groups were significantly different in terms of BP at 30, 40, 50 and 60 minutes after surgery ($P < 0.05$). Statistically significant differences were found among the three blood pressure intervention groups at all times ($P < 0.05$). Lower blood pressure was in the NTG group, and next in the DEX group. Based on the repeated measure test, statistically significant differences were seen among the groups ($P < 0.05$). However, BP was lower in the NTG group.

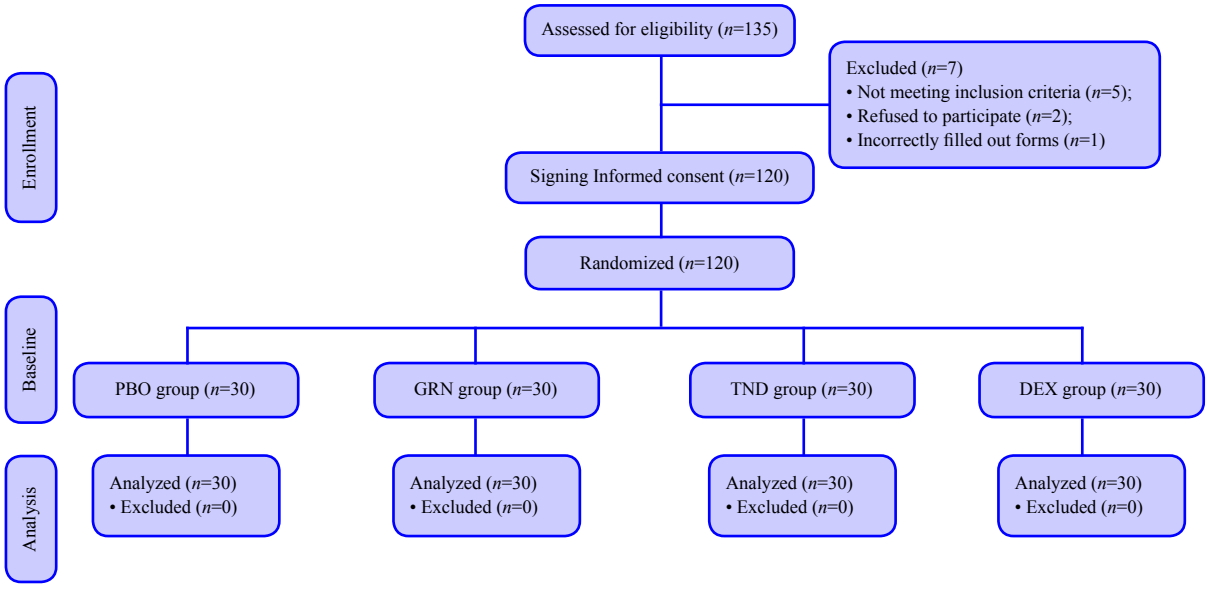

Figure 1: CONSORT diagram showing the flow of participants through each stage of a randomized trial.
Note: CONSORT: CONsolidated Standards Of Reporting Trials; DEX: dexmedetomidine; GRN: granisetron; PBO: placebo; TND: nitroglycerin.

Pain of orearm surgery patients with dexmedetomidine, granisetron, and neostigmine plus ropivacaine intravenous anesthesia

Table 2 shows statistically significant differences in pain among the four groups ($P = 0.0001$), whereas this was lower in the DEX group. Based on the repeated measure test, statistically significant differences were observed among the groups ($P < 0.05$) amongst which the DEX group showed lower pain score. Nevertheless, analysis of variance for repeated measurements showed that the lowest pain score was found in the DEX group.

Sensory block of orearm surgery patients with dexmedetomidine, granisetron, and neostigmine plus ropivacaine intravenous anesthesia

Table 3 shows a statistically significant difference observed in terms of the onset and duration of the sensory block ($P < 0.001$), while they were quicker and longer, respectively, in the DEX group. In addition, a statistically significant difference observed in terms of the onset and duration of motor block ($P < 0.001$), which were the same as those of sensory block in the DEX group. Opioid use during 24 hours was significantly different among the four groups ($P = 0.0001$) and the lowest mean use was observed in the DEX group.

Discussion

According to results significant statistical differences were observed in blood pressure among the four groups at 30, 40, and 50 minutes after the onset of surgery. Lower BP observed in the NTG group, and next in the DEX groups. Moreover, quicker onset and longer duration of sensory and motor block was in the DEX group, lower pain scores in the DEX group at all times and lower mean opioid use in the group. Dexmedetomidine was overall associated with the rapid onset of sensory block, and prolonged length and duration of sensory and motor block, alleviated pain, and reduced opioid use within postoperative 24 hours.

A clinical trial by Modir et al.[22] investigated the effect of

Table 1: Comparison of blood pressure in forearm surgery patients with dexmedetomidine, granisetron, and neostigmine plus ropivacaine intravenous anesthesia

Time point	Placebo	Dexmedetomidine	Nitroglycerin	Granisetron	*P*-value
Baseline (prior to using the tourniquet)	94.87±10.16	97.90±9.50	90.12±13.82	95.12±11.05	0.053
5 min after the onset of surgery	94.87±16.10	97.90±9.50	90.12±13.82	95.12±11.05	0.053
10 min after the onset of surgery	94.90±13.10	95.15±8.58	89.50±12.66	94.46±10.88	0.083
20 min after the onset of surgery	94.90±10.07	94.87±8.36	89.34±12.54	95.81±10.34	0.060
30 min after the onset of surgery	95.28±10.03	94.21±8.14	89.31±12.43	96.28±10.20	0.039
40 min after the onset of surgery	95.37±9.94	93.71±7.74	89.50±12.36	96.50±10.06	0.039
50 min after the onset of surgery	95.62±9.80	93.12±7.22	89.68±11.94	96.78±9.93	0.037
60 min after the onset of surgery	97.21±0.55	97.12±0.66	97.25±0.62	97.18±0.54	0.024
70 min after the onset of surgery	97.28±0.58	97.15±0.57	97.12±0.49	97.15±0.51	0.856
Tourniquet deflation	97.25±0.52	97.35±0.61	97.17±0.57	97.22±0.56	0.667
Recovery	97.15±0.51	97.25±0.62	97.21±0.55	97.18±0.54	0.918

Note: Data are expressed as the mean ± SD ($n = 30$), and were analyzed by one-way analysis of variance followed by Tukey's *post hoc* test.

Table 2: Comparison of visual analogue scale of forearm surgery patients with dexmedetomidine, granisetron, and neostigmine plus ropivacaine intravenous anesthesia

Time point	Placebo	Dexmedetomidine	Nitroglycerin	Granisetron	*P*-value
During tourniquet inflation	2.46±0.51	1.15±0.68	1.62±0.61	1.40±0.61	<0.001
15 min after inflation	2.28±0.46	1.15±0.68	1.62±0.61	1.41±0.61	<0.001
30 min after inflation	2.27±0.45	1.18±0.64	1.62±0.61	1.40±0.61	<0.001
45 min after inflation	2.46±0.51	1.21±0.61	1.61±0.60	1.41±0.60	<0.001
60 min after inflation	3.21±0.42	1.25±0.62	1.71±0.58	1.40±0.61	<0.001
75 min after inflation	4.09±0.30	1.37±0.66	1.78±0.55	1.50±0.62	<0.001
During tourniquet deflation	4.18±0.40	1.40±0.61	1.81±0.59	1.59±0.61	<0.001
30 min after deflation	4.34±0.48	1.50±0.62	1.84±0.57	1.81±0.82	<0.001
60 min after deflation	4.56±0.50	1.87±0.79	2.00±0.72	1.84±0.85	<0.001
90 min after deflation	4.50±0.51	2.18±0.64	2.12±0.87	2.60±1.18	<0.001
120 min after deflation	4.53±0.51	2.28±0.68	3.09±0.82	2.66±1.17	<0.001
6 h after deflation	4.51±0.51	2.51±0.67	4.04±0.74	2.91±0.96	<0.001
12 h after deflation	4.50±0.50	2.50±0.66	4.03±0.73	2.90±0.95	<0.001
24 h after deflation	4.59±0.50	3.50±0.67	4.65±0.48	4.37±0.53	<0.001

Note: Data are expressed as the mean ± SD ($n = 30$), and were analyzed by one-way analysis of variance followed by Tukey's *post hoc* test.

Table 3: Comparison of sensory block and motor block of forearm surgery patients with dexmedetomidine, granisetron, and neostigmine plus ropivacaine intravenous anesthesia

Variable	Placebo	Dexmedetomidine	Nitroglycerin	Granisetron	*P*-value
Time to onset of sensory block (min)	7.78±0.42	4.22±0.61	4.63±0.49	4.42±0.50	<0.001
Length and duration of sensory block (min)	74.38±4.71	99.84±8.93	86.25±8.23	97.66±9.75	<0.001
Time to onset of motor block (min)	13.22±1.07	8.13±0.61	8.50±0.51	8.25±0.62	<0.001
Length and duration of motor block (min)	63.59±5.27	88.75±8.61	70.16±8.28	81.88±10.83	<0.001
Opioid use (mg)	95.31±44.18	25.0±0.00	35.93±12.60	27.63±7.88	<0.001

Note: Data are expressed as the mean ± SD (n = 30), and were analyzed by one-way analysis of variance followed by Tukey's *post hoc* test.

analgesic mixtures with ropivacaine on pain, sensory and motor block, and hemodynamic changes in IVRA and reflected that dexmedetomidine had the least postoperative pain and opioid use, with the most rapid onset and the longest duration of sensory and motor block. Moreover, considering that no significant difference was observed in intra- and postoperative complications among the groups, this could be a potential adjuvant for IVRA.[22] Our results were consistent with theirs. Rabia et al.[23] in 2018 conducted a study comparing dexmedetomidine *vs*. magnesium sulfate as an adjuvant to ropivacaine for Bier block. Finally, the dexmedetomidine group was found to have less tourniquet pain and prolonged duration of sensory block and a more significant effect than magnesium sulfate, as they reported, whose results were in line with those we present herein.[24]

Besides, Modir et al.'s study[25] mirrored the comparative anesthesia effects of ketorolac-lidocaine vs. dexmedetomidine-lidocaine in IVRA, where pain score was reported to be less in the ketorolac group at all times after tourniquet release, reporting that this results in controlling postoperative and post-tourniquet deflation pains and thus appears to be beneficial and an effective alternative for pain control in patients undergoing IVRA, whereas pain and mean opioid use were lower in the DEX group of our study.

Modir et al.[26] explored the efficacy of different doses of granisetron combined with lidocaine on regional intravenous anesthesia, concluding that the use of granisetron could significantly soothe intra- and post-operative pain following forearm surgery. As shown in our study, granisetron was superior in reducing pain, but dexmedetomidine provided a more effective efficacy in pain reduction than the other three groups. Dekoninck et al.[27] accomplished a trial to compare ropivacaine and lidocaine in the Bier's block.

Barazandeh et al.[28] aimed at the effect of adding nitroglycerin to lidocaine on pain and hemodynamic changes in IVRA in upper extremity surgery. Nitroglycerin increases the effect of anesthetic without any significant increase in complications, especially hemodynamic effects. This relieved pain in patients in our study, compared to placebo, but dexmedetomidine had a greater effect on pain relief than the other three groups. A study by Sheth et al.[29] showed that dexamethasone causes more sedation, comparing the effects of dexmedetomidine and ketamine as adjuvants to lignocaine 0.5% 40 mL in IVRA. Both cause postoperative analgesia without side effects. Our results were consistent with theirs.

Similarly, other studies showed that the addition of nitroglycerin to lidocaine-meperidine, though, shortens the onset of sensory block, it does not change the quality of the intravenous block, postoperative analgesia and the need for opioid use in patients undergoing hand surgery.[30,31]

Our results were consistent with theirs. Nasr et al.[32] compared lidocaine-tramadol and lidocaine-dexmedetomidine in IVRA. Postoperative pain and postoperative opioid use were lower in the tramadol and dexmedetomidine groups than in the placebo group, while no difference was found between the dexmedetomidine and tramadol groups.[32] The difference between the Nasr study and ours could be due to the difference in the drug compared with dexmedetomidine which it compared with tramadol in their study versus with nitroglycerin, granisetron, and placebo in ours. A study on adding intravenous nitroglycerin to lidocaine was aimed to improve the quality of IVRA, concluding that the addition accelerates the onset of sensory and motor block without any complications, whereas it eases tourniquet and postoperative pain.[11] Dexmedetomidine had a greater modulatory effect on pain compared to the other three groups included in our study, while nitroglycerin alleviated pain, compared with the placebo.[11]

Sen et al.[8] explored the efficacy of nitroglycerin added to lidocaine on intravenous anesthesia and concluded that the mixture improves sensory and motor block and alleviates pain, without any side effects. While nitroglycerin relieved pain in patients in our study, compared to placebo, dexmedetomidine had a greater effect on pain relief than the others. Memiş et al.'s study[20] aimed at adding dexmedetomidine to lidocaine for intravenous anesthesia and suggested that the addition prolonged the duration of sensory and motor block and alleviated pain without side effects, resulting in results consistent with ours.

However, this study exposed to some limitations. First, pain is a subjective item and pain reporting in different subjects is related to different variables. Second, surgery type and gender effect were another limitation of this study. Third, long-time complications of intervention did not measure in this study and it is suggested for future studies with larger sample size.

Dexmedetomidine was associated with the rapid onset of sensory block, and prolonged length and duration of sensory and motor block, and alleviated pain, reduced opioid use within postoperative 24 hours, thus being suggested that it be an adjuvant to regional anesthesia (Bier's block), based on the results of this study.

Acknowledgements
We hereby would like to express our sincere gratitude to the Clinical Research Council of Valiasr Hospital for their guidance, and to the research deputy of Arak University of Medical Sciences for his help and support.

Author contributions
Study design: EM, HM, AK and MM; data acquisition and analysis: MA; data interpretation: EM, HM and MM. All authors approved the final version for publication.

Conflicts of interest
There is no conflict of interest.

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Date of submission: August 9, 2020
Date of decision: October 23, 2020
Date of acceptance: January 11, 2021
Date of web publication: November 29, 2021