Original Article

Access this article online
Website: www.ijciis.org
DOI: 10.4103/ijciis.ijciis_39_22
Quick Response Code:

Comparison of adjuvant therapy with midazolam, paracetamol, tramadol, or magnesium sulfate during intravenous regional anesthesia with ropivacaine: A randomized clinical trial

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ABSTRACT

Background: Intravenous (IV) regional anesthesia is an easy, safe, reliable, and efficient option for inducing anesthesia during surgeries but with tourniquet-related pain. This study aimed to evaluate midazolam, paracetamol, tramadol, and magnesium sulfate administration as adjuvants with ropivacaine on pain relief and hemodynamic changes in IV regional anesthesia.

Methods: A randomized, double-blind, placebo-controlled trial was conducted in subjects undergoing forearm surgery with IV regional anesthesia. The block randomization method was used to assign eligible participants to each of five study groups. Hemodynamic parameters were assessed before applying the tourniquet, at prespecified time points (5, 10, 15, and 20 min), then and every subsequent 10 min until surgery completion. A Visual Analog Scale was used to assess pain severity at baseline followed by every 15 min until completion of the surgery, and after tourniquet deflation every 30 min to 2 h, and at 6, 12, and 24 h postoperative. Data were analyzed using Chi-square and analysis of variance with repeated data testing.

Results: The shortest onset and the longest duration of sensory block were observed in the tramadol group and the shortest onset of motor block in the midazolam group ($P < 0.001$). Pain score was estimated to be significantly lower in the tramadol group at the time of tourniquet application and release, and 15 min to 12 h after tourniquet release ($P < 0.05$). In addition, the lowest dose of pethidine consumption was observed in the tramadol group ($P < 0.001$).

Conclusion: Tramadol appeared to be able to effectively relieve pain, shorten the onset of sensory block, prolong the duration of sensory block, and achieve the lowest consumption of pethidine.

Key Words: Intravenous anesthesia, pain, paracetamol, ropivacaine, tramadol

INTRODUCTION

Intravenous (IV) regional anesthesia is broadly recognized as an easy, safe, and reliable method for minor surgeries (especially on the hands and forearms) and as an efficient option for inducing anesthesia and for preventing bleeding complications during limb

Cite this article as: Modir H, Moshiri E, Khamene MP, Komijani D. Comparison of adjuvant therapy with midazolam, paracetamol, tramadol, or magnesium sulfate during intravenous regional anesthesia with ropivacaine: A randomized clinical trial. Int J Crit Illn Inj Sci 2023;13:11-7.

Received: 14.05.2022; Revision: 16.07.2022;
Accepted: 20.07.2022; Published: 24.03.2023

surgeries.[1] Based on our knowledge, its other huge benefit is perceived to include suitability, especially for outpatients, owing to the quick onset of anesthesia, the low probability of failure, the demonstrated fast recovery, and the easily controllable depth of anesthesia,[2] however, the limitations of the anesthesia, and most importantly, the development of tourniquet-related pain and the rapid development of posttourniquet release pain, especially in prolonged operations cannot be ignored.[3]

As evidenced by the literature, myelinated A (fibers and unmyelinated C) fibers play a central role in developing tourniquet-related pain, since the pressure caused by tourniquet inflation increases the ischemia of the peripheral nerves.[4] A major focus of clinical research has been to address the co-administration of potent agents such as morphine, meperidine, magnesium sulfate, fentanyl, sufentanil, clonidine, and ketamine as adjuvants with a local anesthetic solution to provide prolonged postoperative analgesia.[3,5-7]

Magnesium's analgesic effects are thought to be mediated through antagonism of the N-methyl-D-aspartate receptor. It is also known to block calcium channels, thereby inhibiting calcium influx and interfering with sensory processing which results in antinociception.[8] Midazolam is a benzodiazepine derivative, possesses analgesic effects mediated by gamma-aminobutyric acid (GABA), and reduces (A-delta) Aδ- and C-fiber-evoked activity,[9] being a commonly used benzodiazepine in anesthesia which affects the transmission of pain signals in the spinal cord due to the modulation of GABA receptors.[10]

Acetaminophen, also called paracetamol, is recognized as a p-aminophenol derivative and a synthetic nonopioid analgesic and antipyretic. IV acetaminophen is considered the nonopioid analgesic of choice for mild-to-moderate pain.[11] Moreover, an randomized controlled trial evaluating different doses of paracetamol added to lidocaine for Bier's block in patients undergoing hand surgery confirmed that the paracetamol adjuvant could improve the quality of IV regional anesthesia without any side effects.[12,13]

We found in literature, some studies have evaluated the efficacy of magnesium sulfate, tramadol, paracetamol, and midazolam in combination with lidocaine. Nevertheless, no study found that assess the ropivacaine in IV regional anesthesia, therefore, this study was set up as a four group comparative design to evaluate the efficacy of the adjuvants on pain relief and hemodynamic changes in IV regional anesthesia.

METHODS

Study setting and patients

A randomized, double-blind, placebo-controlled trial was conducted in the American Society of Anesthesiologists (ASA) Class I/II patients undergoing forearm surgery under IV regional anesthesia from July 1, 2021, to December 31, 2021, at the Arak's Valiasr Hospital. The study was approved by the institutional ethics committee, written informed consent was required for study participation, the study was registered at the Iranian Registry of Clinical Trials (IRCT20141209020258N168), and the manuscript adheres to the PRISMA guideline.

Patients were randomized using block randomization. The subjects were randomly divided into five groups [Figure 1] using blocks of 10 that were generated

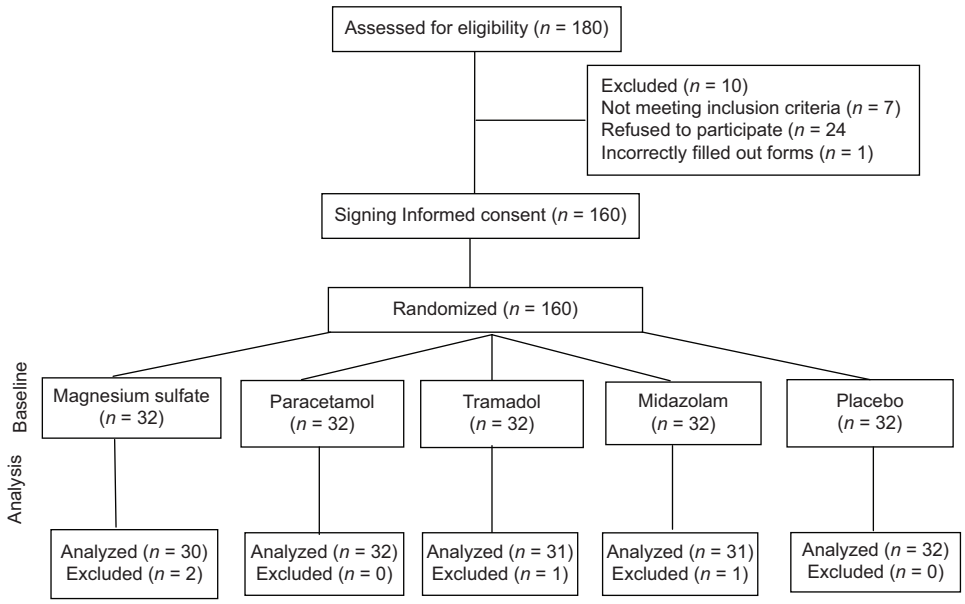

Figure 1: PRISMA flowchart diagram

using a random number table. Groups were labeled in a de-identified fashion (A, B, C, etc.) and concealment was maintained by study medications being similar in color, consistency, volume, and packaging. All study participants, investigators, clinical providers, and data abstractors remained blinded the group of randomization. The statistician worked from a de-identified data set and thus was also blind to the group of randomization for individual subjects.

Sample size calculation was conducted based on the results of our recent study[14] and by considering power 80%, confidence interval 95%, and the difference of pain score among groups. Therefore, 32 patients were selected for each group.

Inclusion criteria included patients aged 20–65 years, scheduled for forearm surgery, ASA Class I and II, no Raynaud's disease, no vascular disease, especially arterial disease, no sickle cell anemia, lack of sensitivity to medications used, no cyanosis of the affected limb, no history of drug/psychedelic substances abuse, no contraindications to IV anesthesia, no more than one fracture in the limb, no pregnancy, no chronic pain syndrome, and no hand neurological disorders. Exclusion criteria were duration of surgery >90 min and <30 min, any reason upon which the IV regional anesthesia is terminated (wearing off) intraoperatively, and finally, patient dissatisfaction.

Intervention

Two IV lines were placed, after arterial oxygen saturation, and other vital signs for patients were recorded: one IV catheter was inserted into a vein on the dorsum of the hand to be operated upon, and another into the other hand to deliver crystalloid IV fluids. Initially, 2 mg of midazolam was included as a premedication and a double-cuff tourniquet was placed at 3–4 cm above the elbow of the first hand which then was elevated for 2 min, and the arm was exsanguinated using an Esmarch bandage. Subsequently, the proximal cuff of the double-cuff tourniquet was inflated to a pressure of 100 mmHg above the patient's systolic blood pressure and the Esmarch bandage was removed.[15] The anesthesiologist prescribed intervention drugs and a medical student, unaware of the allocation of the groups, analyzed the effects and recorded the data. Thus, the double-blind was maintained due to the lack of patient and evaluator's awareness of the order of the groups and interventions.

To induce IV regional anesthesia, patients in the magnesium sulfate (S) group received 10 mg/kg of magnesium sulfate 50% (Shahid Ghazi Pharmaceutical Company, Tabriz, Iran) with ropivacaine 0.2%;[16] Patients in the paracetamol (P) group received 200 mg of paracetamol (Tehran Chemie Pharmaceutical Co., Iran) with ropivacaine 0.2%;[12] patients in the tramadol (T) group received 100 mg tramadol (Caspian Tamin Pharmaceutical Company, Rasht, Iran) with ropivacaine 0.2%;[17] and those in the midazolam (M) group received 50 μg/kg (Caspian Tamin Pharmaceutical Company) with ropivacaine 0.2%.[18] Ropivacaine (Molteni, Italy) was administered with a volume of 35 ml (70 mg) to each group and the target adjuvant dose was diluted to 5 ml by distilled water. Finally, the total amount of drug required for IV regional anesthesia was 40 mL and was delivered through a venous catheter, while each patient in the control (W) group was given 5 mL of normal saline as an adjuvant to 35 mL ropivacaine 0.2% with a total volume of 40 mL through a venous catheter. The level of sensory block was assessed by pinprick test with a 22G needle every 30 s.

Measurements

Patient response was evaluated in the dermatomal sensory distribution of the medial and lateral antebrachial cutaneous, ulnar, median, and radial nerves. The onset of motor block was assessed by asking the patient to flex and extend his/her wrist and fingers, while complete motor block was noted when no voluntary movement of the relevant limbs was possible. After sensory and motor blocks were achieved, the lower tourniquet was inflated to 250 mmHg and the upper tourniquet was deflated and the surgery was started.

Vital signs including heart rate, mean arterial blood pressure, and oxygen saturation were recorded before applying the tourniquet, at 5, 10, 15, and 20 min followed by every 10 min until surgery completion, after the tourniquet deflation, and during recovery. Moreover, all cases of inadequate analgesia and treatment failure were noted and patient anesthesia and preparation for surgery were made by another method: the tourniquet was not deflated earlier than 35 min and was not inflated for more than 90 min. If surgery took longer than 90 min, patients underwent general anesthesia and were excluded from the study.

The distal tourniquet was deflated by the cyclic deflation-inflation technique, once the surgery was done. The sensory and motor recovery times and analgesic requirement time were the time elapsed after tourniquet deflation until recovery of sensation in dermatomes using a 22G needle, that after tourniquet deflation until recovery of finger movement, and that after tourniquet deflation until to first request to analgesic, respectively. A numerical Visual Analog Scale (VAS) to evaluate pain severity was employed at 15, 30, and 45 min and every 15 min after tourniquet inflation to the end of surgery. This scale consists of scores from 0 to 10 with the far left being described as "no pain" and the far right described as "worst pain imaginable."[19] 1 μg/kg IV fentanyl was given intraoperatively if the VAS score was higher than 4. Then, the time of receiving medication was recorded.

Nevertheless, there was no patient complained of pain during the operation that fentanyl needed. On the other hand, since there was no need to administer fentanyl to patients during the operation and sufficient analgesia due to the adjuvant drugs with ropivacaine, we do not have any data for fentanyl administration.

Furthermore, after deflating the tourniquet, pain scores were recorded at 30, 60, 90, and 120 min every 30 min to 2 h. and at 6, 12, and 24 h. 25 mg of intramuscular pethidine was given postoperatively if VAS >4. Pethidine is used in some studies for prevention of postoperative pain in patients, and we used as an analgesic for control pain in patients with VAS >4 intramuscular due to better and longer effect.[20-22] Then, the time and amount of medication received were noted.

Statistical analysis

The gathered data were analyzed using a Chi-square test and analysis of variance with repeated data, whereas the software used in the analysis was IBM® SPSS® version 20 (IBM Corp., Armonk, New York, USA), with a significance level of 5%.

RESULTS

From all 180 eligible patients who were recruited in this study 20 patients excluded due to not meeting inclusion criteria or other cause and 160 patients assigned to study groups that finally 156 patients were analyzed as Figure 1. The mean age was 36.90 ± 6.49 years with minimum and maximum ages of 25 and 56 years. The mean of body mass index (BMI) was 22.54 ± 1.84 kg/m^2 and 91 (56.9%) were men and 69 (43.1%) women.

The study revealed no statistically significant intergroup difference in mean oxygen saturation, mean heart rate, mean arterial blood pressure, and duration of surgery ($P > 0.05$). Moreover, the groups were similar in age, gender, and BMI. Three cases of dizziness and confusion were observed in the tramadol group, but no side effects were seen in the other ($P = 0.016$).

The results in Table 1 demonstrated statistically significant intergroup differences in the onset time and duration of sensory block ($P < 0.001$) among which the tramadol group had the shortest onset and the longest duration of the block. In addition, the shortest onset of motor block was seen in the midazolam group and statistically significant intergroup differences were found in the onset of motor block ($P = 0.001$); the duration of motor block did not differ among the five groups ($P = 0.794$).

Based on results in Table 2, statistically significant intergroup differences were observed in pain score at the time of tourniquet inflation and release, and 15 min to 12 h after tourniquet release ($P < 0.05$), the score was lower in the tramadol group, followed by the paracetamol group than in all other groups. The repeated measure test [Figure 2] confirmed statistically significant differences in pain scores among the study groups ($P < 0.05$), whereas the score was lower in the tramadol group.

Pethidine consumption [Table 3] differed statistically significantly among the five groups ($P < 0.001$) and was the lowest in the tramadol group. Furthermore, statistically significant intergroup differences were observed in the consumption time at 12 h after tourniquet release ($P = 0.018$), while the lowest amount and need for pethidine were found in the tramadol group.

DISCUSSION

In our study, tramadol could relieve pain, shorten the onset of sensory block, and prolong the duration of sensory block, whereas the lowest consumption of pethidine was found in the group. Sahmeddini *et al.*'s study comparing magnesium sulfate and tramadol as adjuvants in IV regional anesthesia for upper extremity surgery suggested that tramadol helps reduce opioid

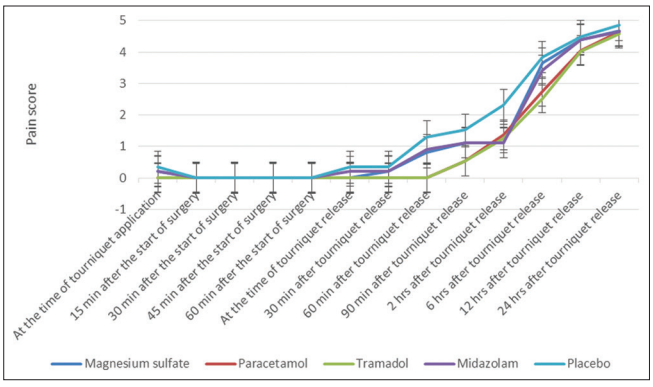

Figure 2: Intergroup comparison of mean pain score

Table 1: Intergroup comparison of mean and standard deviation of sensory block quality

Group / Sensory block (min)	Mean ± SD					*P*
	Magnesium sulfate	Paracetamol	Tramadol	Midazolam	Placebo	
Onset of sensory block	6.09 ± 0.69	5.37 ± 0.55	4.75 ± 0.57	6.06 ± 0.71	6.93 ± 0.62	<0.001
Duration of sensory block	138.87 ± 6.54	160.37 ± 6.13	162.71 ± 6.22	139.00 ± 6.51	125.75 ± 5.00	<0.001
Onset of motor block	8.15 ± 0.63	9.65 ± 0.48	9.71 ± 0.58	8.06 ± 0.72	11.96 ± 0.59	<0.001
Duration of motor block	127.50 ± 5.80	126.90 ± 5.77	126.84 ± 5.63	126.96 ± 5.63	125.75 ± 5.00	0.794

SD: Standard deviation

Table 2: Intergroup comparison of mean and standard deviation of pain score

Pain score	Mean ± SD					*P*
	Magnesium sulfate	Paracetamol	Tramadol	Midazolam	Placebo	
At time of tourniquet application	0.22 ± 0.42	0	0	0.22 ± 0.42	0.34 ± 0.48	0.001
15 min after the start of surgery	0	0	0	0	0	0.999
30 min after the start of surgery	0	0	0	0	0	0.999
45 min after the start of surgery	0	0	0	0	0	0.999
60 min after the start of surgery	0	0	0	0	0	0.999
At the time of tourniquet release	0.22 ± 0.42	0	0	0.21 ± 0.42	0.34 ± 0.48	0.001
30 min after tourniquet release	0.22 ± 0.42	0	0	0.22 ± 0.42	0.34 ± 0.48	0.001
60 min after tourniquet release	0.81 ± 0.64	0	0	0.91 ± 0.59	1.31 ± 0.47	0.001
90 min after tourniquet release	1.12 ± 0.66	0.53 ± 0.51	0.53 ± 0.51	1.12 ± 0.55	1.53 ± 0.51	0.001
2 h after tourniquet release	1.12 ± 0.66	1.37 ± 0.49	1.25 ± 0.44	1.12 ± 0.55	2.31 ± 0.47	0.001
6 h after tourniquet release	3.65 ± 0.65	2.75 ± 0.51	2.53 ± 0.57	3.43 ± 0.72	3.84 ± 0.67	0.001
12 h after tourniquet release	4.40 ± 0.49	4.06 ± 0.62	4.03 ± 0.54	4.40 ± 0.49	4.50 ± 0.51	0.001
24 h after tourniquet release	4.68 ± 0.47	4.65 ± 0.48	4.59 ± 0.49	4.65 ± 0.48	4.87 ± 0.34	0.143

SD: Standard deviation

Table 3: Intergroup comparison of frequency (percentage) of pethidine consumption per mg

Pethidine consumption	Magnesium sulfate, *n* (%)	Paracetamol, *n* (%)	Tramadol, *n* (%)	Midazolam, *n* (%)	Placebo, *n* (%)	*P*
No consumption	0	4 (12.5)	9 (28.12)	1 (3.125)	0	0.001
25 mg	26 (81.25)	87 (87.5)	22 (68.75)	28 (87.5)	18 (56.25)	
50 mg	6 (18.75)	0	1 (3.125)	3 (9.37)	11 (34.37)	
75 mg	0	0	0	0	3 (9.37)	

consumption and pain.[23] The results derived from the present study support their finding. In addition, Dubey *et al.*'s study comparing tramadol and fentanyl as adjuvants to lidocaine (also known as lignocaine) for IV regional anesthesia in forearm orthopedic surgery included 60 patients. The groups received 1 μg/kg fentanyl with 40 mL lidocaine 0.5% and 1 mg/kg tramadol with 40 mL lidocaine 0.5%. The onset of sensory block was faster in the tramadol group, and the duration of the block was longer in comparison to fentanyl. While no difference was found between the two groups in terms of motor block, the duration of anesthesia was longer in the tramadol group and tramadol improves block quality.[24] Their results were in line with ours. The mechanism of action of tramadol is two-fold; first, like other opioids (opium derivatives), it is a μ-receptor agonist, though the affinity of tramadol to μ receptors is relatively weak. Consequently, the analgesic potency of tramadol is about 10% of that of morphine. Tramadol exerts central-acting analgesic effects through binding to the μ-opioid receptors and inhibiting the norepinephrine and serotonin reuptake in the descending pathway of the spinal cord.[25,26] Alayurt *et al*. reported that tramadol shortened the onset of sensory block and reduced opioid consumption within 24 h.[17]

Midazolam showed a fast onset of motor block but lower duration of sensory block in comparison to the tramadol and paracetamol groups. Moreover, the pain score in the midazolam group was similar to the tramadol and paracetamol groups. It seems that the effects of acetaminophen and tramadol are not enough effective to cause analgesia. Another assumption is that the combination of these adjuvants with ropivacaine, which is the main local anesthetic drug used, creates the same results as combination of ropivacaine with midazolam as an effective and powerful analgesia. Similarly, as shown by one study on the efficacy of adding midazolam to lidocaine in upper extremity surgery (Honarmand *et al*., 2015), adding 50 μg/kg of midazolam to lidocaine can enhance block quality and relieve patients' pain.[18] The analgesic effects of intrathecal midazolam have been explored in numerous studies with different patients and clinical conditions[27] covering one case study confirming the effectiveness of IV administration of midazolam in relieving limb pain during spinal anesthesia.[28,29] In addition, another study showed midazolam has analgesic effects similar to opioids and it could be effective in relieving limb pain.[30] As confirmed by some evidence, including Honarmand *et al*.'s study exploring the efficacy of adding midazolam as an adjunct to lidocaine in upper limb orthopedic surgery, it was concluded that adding 50 μg/kg midazolam to lidocaine can help enhance block quality and relieve patients' pain.[18]

Tramadol in our study relieved pain, shortened the onset of sensory block, and prolonged the duration of sensory block. The lowest consumption of pethidine was seen in the tramadol group, and the shortest onset of motor block was found in the midazolam group.

Based on this study, the pain score was lower in the paracetamol group after tramadol groups than all other groups at the time of tourniquet application and release, and 15 min to 12 h after tourniquet release. Although there was no clinically significant difference in pain score among different groups and all treatments had good analgesia, sensory block time and pethidine

consumtion were different among groups. Another comparative clinical trial on assessing different doses of paracetamol added to lidocaine in Bier's block in patients undergoing hand surgery reported that paracetamol as an adjuvant can improve the analgesia quality of IV regional anesthesia without side effects.[31]

Our trial study showed that tramadol relieved pain, shortened the onset of sensory block, and prolonged the duration of sensory block. The tramadol group had the lowest consumption of pethidine. Moreover, another study compared the analgesic effects of paracetamol and magnesium sulfate. Paracetamol and magnesium sulfate were shown to have postoperative analgesic effects and reduce the quantity of narcotic use after surgery.[17] Nasr and Waly[32] conducted a study comparing lidocaine-tramadol versus lidocaine-dexmedetomidine in IV regional anesthesia. Their finding indicated lower postoperative pain and postoperative opioid consumption in the tramadol- and dexmedetomidine-treated patients than in the controls, with no difference found in this regard between both groups. Sensory and motor blocks developed faster and lasted longer in the tramadol and dexmedetomidine groups. Postoperative pain scores and postoperative drug consumption were lower in the groups than in the control group, while no difference was observed between the two groups.[32] Our results were consistent with those of Nasr and Waly.[32] Another study by Modir *et al*. concluded that dexmedetomidine could reduce pain and opioid consumption and have faster and longer onset of block in comparing different adjuvants to ropivacaine in IV regional anesthesia including dexmedetomidine, ketamine, neostigmine, and magnesium sulfate.[14] Furthermore, Alayurt *et al*. reported their study about the addition of sufentanil, tramadol, and clonidine to lidocaine (lignocaine) for IV regional anesthesia, concluding that the addition shortened the onset of sensory block and relieved tourniquet-related pain and reduced opioid consumption within 24 h but did not affect postoperative pain.[17]

CONCLUSION

Tramadol-treated patients had relieved pain, shortened onset of sensory block, prolonged duration of sensory block, and lowest consumption of pethidine and side effects of dizziness and confusion. Keeping in mind the trial's clinical findings, tramadol may be suggested as an adjuvant to the local anesthetic ropivacaine for IV regional anesthesia, but the possible complication of dizziness and confusion should also be considered.

Research quality and ethics statement

This study was approved by the Institutional Review Board/Ethics Committee at Arak Medical University (Approval #IR.ARAKMU.REC.1400.173; Approval Date October 10, 2021). The authors followed the applicable EQUATOR Network (http://www.equator-network.org/) guidelines, specifically the PRISMA guideline, during the conduct of this research project. The study was prospectively registered with the Iranian Registry of Clinical Trials (IRCT20141209020258N168).

Financial support and sponsorship

This study was financially supported by Arak University of Medical Sciences.

Conflicts of interest

There are no conflicts of interest.

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