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Original Article

The efficacy of different doses of Midazolam added to Lidocaine for upper extremity Bier block on the sensory and motor block characteristics and postoperative pain

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ABSTRACT

Objective: This study was designed to evaluate the effect of different doses of midazolam on anesthesia and analgesia quality when added to lidocaine during the intravenous regional anesthesia (IVRA).

Methods: One hundred and forty patients underwent hand surgery were randomly allocated into four groups to receive 3 mg/kg lidocaine 2% diluted with saline to a total volume of 40 mL in the control Group L-C (n = 35), 30 μg/kg midazolam plus 3 mg/kg lidocaine 2% diluted with saline to a total volume of 40 mL in the midazolam Group L-M_1 (n = 35), 40 μg/kg midazolam plus 3 mg/kg 2% lidocaine diluted with saline to a total volume of 40 mL in the midazolam Group L-M_2 (n = 35), and 50 μg/kg midazolam plus 3 mg/kg lidocaine 2% diluted with saline to a total volume of 40 mL in the midazolam Group L-M_3 (n = 35). Sensory and motor block and recovery times, tourniquet pain, intra-operative analgesic requirement, and visual analog scale (VAS) scores were recorded.

Findings: Onset time of sensory and motor block in L-M_3 Group was shorter than the L-M_2 and L-M_1 and L-C Groups (P < 0.001). Furthermore, prolonged sensory (P = 0.005) and motor recovery time (P = 0.001) in L-M_3 were longer than the other groups. Intra-operative VAS score and intra-operative fentanyl consumption in L-M_3 were lower than the other groups (P < 0.001). The numbers of patients needed to pethidine in Group L-M_3 were significantly less compared with the other groups (P = 0.035). VAS scores were significantly lower in Group L-M_3 in different time intervals in the postoperative period compared with the other groups (P < 0.001).

Conclusion: Addition of 50 μg/kg midazolam for IVRA (Group L-M_3) enhanced intra-operative analgesia and improved anesthesia quality better than other groups receiving lower midazolam doses as well as a control group.

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INTRODUCTION

Intravenous regional anesthesia (IVRA) is easy to administer, reliable, and cost-effective for short operative procedures of the extremities performed on an ambulatory basis.[1] IVRA has success rates of 94–98%.[2]

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Local anesthetic (LA) toxicity, poor muscle relaxation, slow onset, tourniquet pain, and minimal postoperative pain relief are the problems encountered with IVRA.[2,3] Various adjuvant drugs have been evaluated in conjunction with LA to improve IVRA block reality with variable results.[2] The ideal solution for IVRA should have rapid onset to reduce the dose of LA, lower prolong postdeflation analgesia, and decrease tourniquet pain. The additives such as muscle relaxants and opioids have been combined with LA to improve these problems.[4]

Midazolam, a benzodiazepine (BDZ) derivate has analgesic effects mediated by gamma amino butyric acid (GABA) midazolam reduced A-delta and C-fiber evoked activity.[5] One previous case report showed that intravenous (IV) administration of midazolam was effective in relieving severe phantom limb pain during the spinal anesthesia.[6]

Dickenson *et al*.[7] showed that midazolam, a BDZ agonist, has analgesic properties mediated via the spinal cord. Due to the antinociceptive effect of midazolam, it was known to augment the effect of opioids[8] and LA[9,10] when given intrathecally or epidurally. It has been reported[6] that IV administration of midazolam was effective in relieving severe phantom limb pain during spinal anesthesia. Midazolam a BDZ derivative has analgesic effects mediated by GABA-A, BDZ receptors in the spinal cord.[11]

GABA receptors have also been found in peripheral nerves[12,13] midazolam reduces A-delta and C-fiber evoked activity.[5] This study was designed to assess the effect of different dose of midazolam (30, 40, 50 μ/kg) and placebo when added to lidocaine in IVRA for elective hand surgery on the sensory and motor block onset and recovery time, and the quality of anesthesia, intra- and post-operative, hemodynamic variable, and pain.

METHODS

This is a double-blind clinical trial study conducted in Alzahra Hospital, Isfahan, Iran during 2013–2014. The target population were patients who the candidate for hand surgeries. Inclusion criteria were American Society of Anesthesiologists (ASA) grade I or II (ASA I = normal healthy patients; ASA II = patients with mild systemic disease), aged 20–50 years old scheduled for elective hand and forearm surgery (i.e., tendon carpal tunnel release). Patients with the history of any drug allergy, Reynaud disease, chronic pain syndromes, sickle cell anemia, psychological disorders, diabetes, epilepsy, leukemia, ingestion of any analgesic or sedative medication during 24 h before surgery or pregnant or breastfeeding women, were excluded. In the case of change in the type of surgery or technique of anesthesia and increase of operation time (above 2 h), the patient was excluded from the study.

The sample size for this study was estimated using the formula of estimating the sample size for comparing means, considering the 95% level of confidence ($Z_{1-a/2}$), 80% power (Z_{1-b}), 1.17 (D) for the standard deviation of postoperative pain[13] and 0.8 statistically difference between groups; accordingly, the sample size was calculated 35 patients for each group.

After Ethics Committee approval and improved written consent, 140 patients were allocated in 4 groups of 35 patients by block randomization method.

Injectable drugs were prepared by an anesthesia assistant who had not any role in the study. Preparing the patients for operation, they were premeditated with 1 mg midazolam administered IV, 30 min before the surgical procedure and were monitored for mean arterial blood pressure (MAP), oxygen saturation (SpO_2), and heart rate (HR); before beginning the anesthetic block, two IV Canola were inserted, one in dorsal vein of the operative hand and the other in the opposite hand for crystalloid infusion.

The operated arm was elevated for 2 min then exsanguinated with an esmarch bandage or pneumatic (double tourniquet) and then placed around the upper arm and the proximal Cuff was inflated 250 mmHg (at least 100 mmHg above the systolic blood pressure for all patients); circulatory isolation of the arm was confirmed by Peyton absence of radial pulse, and loss of pulse oximetry tracing in the ipsilateral index finger. IVRA was achieved with 3 mg/kg lidocaine 2% W/V diluted with normal saline to the total volume of 40 mL in the Control Group L-C (n = 35), or with 50 μg/kg midazolam plus 3 mg/kg lidocaine 2% W/V diluted with normal saline to a total volume of 40 mL in the midazolam Group L-M_1 (n = 35), or with 40 μg/kg midazolam plus 3 mg/kg lidocaine 2% W/V diluted with normal saline to a total volume of 40 mL in the midazolam Group L-M_2 (n = 35), or with 30 μg/kg midazolam plus 3 mg/kg lidocaine 2% W/V diluted with normal saline to a total volume of 40 mL in the midazolam Group L-M_3 (n = 35). The solutions were prepared by an anesthesiology assistant not involved in any other parts of the study. The solution was injected over 90 s by an anesthesiologist blinded to group assignments.

The sensory block was evaluated with pinprick testing every 30 s until the start of surgery with a 22 gauge needle in the median, ulnar, and radial nerve innervated areas of the hand and forearm. Motor function has been evaluated by examining the flexion

and extension of the patients' wrist and fingers, whereas complete motor block recorded when the voluntary movement was impossible. Sensory block onset time was defined as the time elapsed from injection of the drug to loss of pinprick sensation wall nerve distribution and onset of motor block (defined as the time elapsed from injection of the study drug to complex motor block). After completion of sensory and motor block, the distal Cuff was inflated to 250 mmHg and the proximal tourniquet was released. Thereafter, the operation was started.

MAP, SpO_2, visual analog scale (VAS) scores (from 0 = no pain, to 10 = the worst pain imaginable), and degree of sedation scale 1–5 (1 = complete awake; 2 = awake, but drowsy; 3 = asleep, but responsive to verbal command; 4 = asleep, but responsive to tactile stimulus; 5 = asleep and not responsive to any stimulus) were recorded before and after tourniquet inflation at 1, 5, l0, 15, and 30 min after injection of study drugs and at 1, 5, 10, 15, and 30 min after tourniquet release, and postoperatively at 1, 2, 6, and 12 h.

Boluses of fentanyl 1 μg/kg were administered intra-operatively for tourniquet pain treatment when VAS was more than 4, and it was repeated 5 min after if pain was not improved; the number of the patients requiring fentanyl was recorded. During surgery, 5 mg IV ephedrine was given for hypotension (systolic blood pressure <90 mmHg or 50 mmHg lower than normal value), 0.5 mg atropine was given for bradycardia defined as HR <50 min, and 4 mg IV ondansetron for nausea and vomiting.

Arterial SpO_2 <91% was treated with O_2 supplementation via a face mask and all of these complications were also considered with respect to time. No additional sedative drugs were given during the intra-operative period. Postoperatively, when VAS was more than 4, the boluses of pethidine 25 mg/kg were administered, whereas total pethidine consumption was recorded. The time elapsed after tourniquet release to the first patient request for pethidine was also recorded at the end of the operation. Patients were asked to qualify the operative conditions such as tourniquet pain or incisional pain, according to the following numeric scale: Excellent (4), no complaint from pain, good (3), minor complaint with no need for supplement analgesics, moderate (2), complaint that needed a supplemental analgesia and unsuccessful (1).[12] The patient was given general anesthesia at the end of the operation.

The surgeon who was blinded to group assignment was asked to qualify the operation conditions according to the following numeric scale: 0 = unsuccessful, 1 = poor, 2 = acceptable, 3 = good, 4 = excellent.[13] The tourniquet was not deflated before 30 min and was not inflated more than 90 min. At the end of surgery, the tourniquet deflation was completed by cyclic deflation technique. The tourniquet was deflated 3 times with fixed periods of deflation (10) separated by 1-min periods of reflation. Sensors recovery time was noted (time elapsed after tourniquet deflation up to the recovery of pain in all innervated areas determined by pinprick to test done in 30 s).

Motor block recovery time was noted (the time elapsed after tourniquet deflation up to movement of fingers) as well as the first analgesic requirement time (the time elapsed after tourniquet release to first patient request of analgesic). Through the study period, the patients were asked about any side effects (tinnitus, skin rash, gastric discomfort, nausea and other side effects) which were recorded if any. All evaluations were performed by an anesthesiology resident blinded to the study group assigned patients who were assessed for 12 h in the postsurgical ward for MAP, HR, SpO_2, VAS, and sedation. At 1, 6, and 12 h postoperatively, they were questioned for pain, and if VAS score was more than 4, pethidine 25 mg was given. Finally, the collected data entered to computer and analyzed by SPSS version 20 software (Chicago, IL, USA) and the One-way analysis of variance, Chi-square, Fisher exact tests, and Mann–Whitney test were used for data analysis.

RESULTS

All the groups were similar with regard to sex, age, weight, surgical procedure, ASA, duration of tourniquet, and duration of sensory [Table 1].

Table 1: Demographic and clinical characteristics of patients

Characteristics	Groups				*P*
	L-C	L-M1	L-M2	L-M3	
Age (year)	34.6±9.6	38.9±9.5	36.9±9.2	37.1±9.9	0.723
Weight (kg)	75.3±7.9	77.7±7.4	75.5±9.9	73.3±9.4	0.218
Sex (male/female)	27/8	28/7	26/9	25/10	0.855
ASA grade (I/II)	26/9	25/10	27/8	29/6	0.708
Operation time (min)	51.3±9.7	49.5±9.3	52.1±8.5	54.3±9.3	0.180
Type of surgery					0.784
Carpal tunnel syndrome	18	18	22	19	
Trigger finger	3	6	3	3	
Tendon repair	14	11	10	13	

Data are presented as mean±SD or number of patients, where applicable. Group L-C=40 mL lidocaine 0.5% added to normal saline, Group L-M_1=40 mL lidocaine 0.5% added to midazolam 30 μg/kg, Group L-M_2=40 mL lidocaine 0.5% added to midazolam 40 μg/kg, Group L-M_3=40 mL lidocaine 0.5% added to midazolam 50 μg/kg. ASA, sex, and operation type were analyzed by Chi-square test. Age, weight, operation time were analyzed by ANOVA. SD=standard deviation, ASA=American Society of Anesthesiologists

There was no significant difference between groups regarding SpO_2, MAP, and HR at any intra-operative or postoperative periods (data not presented).

All patients were able to complete the study and there were no exclusions in data analysis. There were no cases of respiratory depression, hypoxia, hypotension, bradycardia, or other side effects throughout the study. Anesthesia quality as determined by the surgeons and patients was significantly better in L-M_3 Group compared with other groups [Table 2].

Sensory and motor block onset times were significantly shorter in L-M_3 Group compared with other groups ($P < 0.001$) [Table 3]. Duration of sensory ($P = 0.005$) and motor block recovery time ($P = 0.001$) were significantly more prolonged in L-M_3 Group compared with other groups [Table 3]. No patients suffered from incisional pain during the intra-operative period in all groups. Patient in all groups received fentanyl once.

VAS scores of tourniquet pain were significantly lower at 5, 10, 15, and 30 min in L-M_3 and L-M_2 Groups compared with L-M_1 and L-C Groups [Table 4]. The numbers of patients needed to intra-operative fentanyl in L-M_3 were significantly lower than the other groups ($P < 0.001$) [Table 5].

The numbers of patients needed to pethidine were significantly less in L-M_3 Group compared with other groups ($P = 0.035$) [Table 5]. The postoperative VAS scores were also significantly lower at 1, 6, and 12 h in L-M_3 and at 1 h in L-M_2 Groups compared with L-C and L-M_1 Groups ($P < 0.001$).

Table 2: Quality of anesthesia assessed by patients and surgeons

Quality of anesthesia	Groups				*P*
	L-C	L-M1	L-M2	L-M3	
Assessed by surgeons					0.13
4	8 (22.9)	8 (22.9)	11 (31.4)	22 (44.9)*	
3	8 (22.9)	5 (14.3)	10 (28.6)	8 (22.9)*	
2	9 (25.7)	11 (31.4)	7 (20.0)	4 (11.4)*	
1	8 (22.9)	7 (20.0)	5 (14.3)	1 (2.9)*	
0	2 (5.7)	4 (11.4)	2 (5.7)	0 (0)*	
Assessed by patients					<0.001
4	3 (8.6)	5 (14.3)	3 (8.6)	16 (45.7)*	
3	7 (20)	8 (22.9)	10 (28.6)	13 (37.1)*	
2	10 (28.6)	9 (25.7)	14 (40)	5 (14.3)*	
1	9 (25.7)	10 (28.6)	7 (20)	1 (2.9)*	
0	6 (17.1)	3 (8.6)	1 (2.9)	0 (0)*	

*$P<0.05$ versus Groups L-C, L-M_1, and L-M_2. Data are presented as number (%) of patients. Group L-C=40 mL lidocaine 0.5% added to normal saline, Group L-M_1=40 mL lidocaine 0.5% added to midazolam 30 μg/kg, Group L-M_2=40 mL lidocaine 0.5% added to midazolam 40 μg/kg, Group L-M_3=40 mL lidocaine 0.5% added to midazolam 50 μg/kg. Quality of anesthesia: 0=Unsuccessful, 1=Poor, 2=Acceptable, 3=Good, 4=Excellent. Statistical analysis between four groups was done using Chi-square test. Statistical analysis between each two groups was performed by Mann-Whitney test

Table 3: Onset and recovery times of sensory and motor block in the studied patients

Time (min)	Groups				*P*
	L-C	L-M_1	L-M_2	L-M_3	
Sensory block onset	6.23±1.0	6.14±1.0	5.99±1.0	5.20±1.0*	<0.001
Motor block onset	6.74±1.0	6.69±1.0	6.39±1.0	5.60±1.0*	<0.001
Sensory block recovery	4.49±0.8	4.51±0.8	4.54±0.8	5.13±0.8*	0.005
Motor block recovery	4.58±1.0	4.72±1.0	4.65±1.0	5.52±1.0*	0.001

*$P<0.05$ versus Groups L-C, L-M_1, and L-M_2. Data are presented as mean±SD. Group L-C=40 mL lidocaine 0.5% added to normal saline, Group L-M_1=40 mL lidocaine 0.5% added to midazolam 30 μg/kg, Group L-M_2=40 mL lidocaine 0.5% added to midazolam 40 μg/kg, Group L-M_3=40 mL lidocaine 0.5% added to midazolam 50 μg/kg. *P* values are attributed to the comparison of Group L-M_3 with Groups L-C, L-M_1, and L-M_2 using ANOVA statistical analysis. SD=Standard deviation

DISCUSSION

In this study, it was revealed that the addition of 50 and 40 μ/kg midazolam to lidocaine for IVRA decreases tourniquet pain, and reduces intra-operative analgesic consumption without causing side effect and reduces the postoperative pain score. Shortens sensory and motor block onset times, prolongs sensory and motor block recovery times. This method decreases VAS scores intra-operatively and during the 12 h after the operation and prolonged delay between the IVRA administration and additional analgesic requirement. But adding 30 μ/kg midazolam to lidocaine for IVRA has not additional effect than placebo. The effect of midazolam on the GABAergic system might make it effective in alleviating neuropathic pain.[5-15]

Kontinen and Dickenson[5] demonstrated that midazolam reduced A-delta and C-fiber evoked activity and reversed cold and mechanical allodynia after spinal nerve ligation. There are different suggested sites for the action of IVRA. Raj *et al*.[16] described that the action of LAs is on major nerve trunks, perhaps reaching to the nerve trunk trough small venues inside the nerve core, while Rosenberg[18] afforded strong proof related to a peripheral site. It is currently believed that together, the nerve endings and trunk are affected;[18] it was possible that the analgesic effect of midazolam added to IVRA was due to its action on binding sites in the periphery. A variety of authors have also shown the existence of the GABA-A receptors in peripheral nerves.[19]

Midazolam-induced analgesia has also been linked to a μ opioid mechanism, possibly via κ opioid receptors.[20] Besides GABA effects, spinal midazolam stimulates the opioid system through delta or κ receptors.[21]

Table 4: Intra-operative and post-operative pain scores in the studied patients

Time period	Groups				*P*
	L-C	L-M_1	L-M_2	L-M_3	
Before tourniquet	3.73±1.4	3.93±1.3	3.64±1.2†	3.76±1.6	0.860
After tourniquet inflation	3.91±1.1	3.74±1.2	2.89±1.2†	2.66±1.1*	<0.001
5 min	3.61±1.3	3.51±1.4	2.54±1.2†	2.34±1.2*	
10 min	3.39±1.2	3.53±1.4	2.41±1.2†	2.45±1.0*	
15 min	3.13±1.0	3.26±1.3	2.34±1.0†	2.20±1.0*	
30 min	3.02±1.0	3.11±1.0	2.16±1.0†	2.19±1.0*	
After tourniquet release	3.65±1.0	3.56±1.2	2.51±1.0†	2.48±1.0*	<0.001
5 min	4.01±1.1	3.85±1.5	2.69±1.0†	2.57±1.3*	
10 min	4.41±1.2	4.14±1.5	2.92±1.0†	2.60±1.2*	
15 min	4.69±1.5	4.39±1.7	3.16±1.2†	2.69±1.4*	
30 min	4.90±1.5	4.53±1.7	3.30±1.3†	2.73±1.2*	
1 h	5.83±1.6	5.24±1.7	3.79±1.3†	2.90±1.1*	
6 h	3.88±1.3	3.41±1.3	3.23±1.0	2.23±1.0*	
12 h	3.06±1.2	3.21±1.0	2.99±1.0	2.01±1.0*	

*P<0.05 versus Group L-C, Group L-M_1, and Group L-M_2, †P<0.05 versus Group L-C, Group L-M_1. There was no significant difference between Group L-M_2 and L-M_3 (P>0.05). Data are presented as mean±SD. Group L-C=40 mL lidocaine 0.5% added to normal saline, Group L-M_1=40 mL lidocaine 0.5% added to midazolam 30 μg/kg, Group L-M_2=40 mL lidocaine 0.5% added to midazolam 40 μg/kg, Group L-M_3=40 mL lidocaine 0.5% added to midazolam 50 μg/kg. SD=Standard deviation

Table 5: Numbers of patients need the additional analgesics in four groups

Analgesic	Groups				*P*
	L-C	L-M_1	L-M_2	L-M_3	
Fentanyl	22 (62.9)	21 (60)	8 (22.9)*	6 (17.1)*	<0.001
Pethidine	15 (42.9)	15 (42.9)	13 (37.1)	5 (14.3)†	0.035

*P<0.05 versus Groups L-C and L-M_1, †P<0.05 versus Groups L-C, L-M_1, and L-M_2. Data are presented as numbwers (%) of the patients. Group L-C=40 mL lidocaine 0.5% added to normal saline, Group L-M_1=40 mL lidocaine 0.5% added to midazolam 30 μg/kg, Group L-M_2=40 mL lidocaine 0.5% added to midazolam 40 μg/kg, Group L-M_3=40 mL lidocaine 0.5% added to midazolam 50 μg/kg. *P* values are attributed to the comparison of Group L-M_3 with Groups L-C, L-M_1, and L-M_2 using Mann-Whitney test

In vitro studies have shown that midazolam displaced [3H] diprenorphine binding from cloned human κ and delta receptors, and this effect of midazolam was inhibited by selective κ and delta agonists.[22] Peripheral opioid receptors present in the peripheral wrist and hand tissue and their stimulation by midazolam can be responsible for IVRA analgesia.[23] Additionally coexistent local tissue inflammation may perhaps lead to up-regulation or activation of these opioid receptors. Stimulation of these opioid receptors by midazolam may be the responsible for its analgesic effect.

Midazolam exerts some antioxidant activity *in vitro* as measured their protection of fluorescence day of B-phycoerythrin.[24] Coderre *et al*.[25] advocated that antioxidant therapy such as N-acetyl cysteine may decrease experimental ischemic pain owing to oxidative damage. Antioxidant for pain treatment may reduce the dose of analgesics and inhibit the negative[26] influence of reactive oxygen spices on nociception.

Tourniquet pain is a common problem complication due to the use of a pneumatic tourniquet during surgical procedures involving the upper or lower limb.[27] Neuropathic pain produced by nerve compression plays an important role in the etiology of this discomfort.[28]

The role of A-delta fibers and unmyelinated C-fiber may be considered being involved in tourniquet pain.[29] The pneumatic tourniquet causes ischemia, which distort nerve penetration by oxidative stress and affects blood-nerve barrier.[30] BDZ tend to suppress afferent evoked excitation in the substantia gelatinosa and motor horn leading to an anti-nociceptive.[21,31] Batra *et al*.[5] Study showed that intra articular administration of midazolam decreases postoperative pain after arthroscopic knee surgery when compared with placebo, their investigation also proposed that midazolam may act as a peripheral site in the joint, to produce analgesia. The addition of midazolam to bupivacaine for brachial plexus block quickened the onset of sensory and motor blocks and improved postoperative analgesia. As manifested by lower pain scores, prolonged effect, and reduced requirements for rescue analgesics.[32,33]

Muscimol and isoguvacine, attenuate behavioral allodynia and hyperalgesia nerve injury.[34] Clinical studies have demonstrated an enhanced analgesic effect from midazolam when administered by the centro neuroaxial route in combination with bupivacaine. Naguib *et al*.[9] and Nishiyama and Hanaoka[35] showed that midazolam administration at doses of 0.05 mg/kg epidurally or 0.03 my/kg intrathecally produce significant analgesia in both animal and human studies ant nociceptive effect of neuraxial midazolam arise from agonism at the BDZ binding site on a subunit of pentameric GABA-A receptors, when operates paradoxically to reduce the transmitter release, from of presynaptic inhibition.[8-20]

Consist with this effect and from BDZ subunit expression in dorsal root ganglion and on spinal nerves BDZ have a prosperity in substantia gelatinosa and motor horn[20,36] leading to an anti-nociceptive effect Sajedi and Islami[37] showed that midazolam can improve the duration of sensory and motor blocks to lidocaine in a single epidural administration and demonstrated that the 5 mg dosage works better the 3 my dosage. In Su *et al*.[6] case, midazolam was effective

for relief of the pain, BDZ facilitates the inhibition of GABA binding sites in the CNS. The above-described mechanisms may possibly explain the efficacy of IV midazolam in relieving Intra- and post-operative pain when added to IVRA. It is possible that IVRA might not be a perfect model to differentiate peripheral versus central mechanisms of analgesia.

Chang *et al*.[38] demonstrated that midazolam produces vasodilation by endothelium-dependent and independent mechanisms. Endothelium-dependent vasodilatation produced by midazolam possibly is mediated by own release of NO. Endothelium in dependent vasodilatation appears to be related to inhibition of voltage-gate calcium channels. The beneficial effects of midazolam, which were showed in our study, probably will also depend on vasodilator effect that promotes distribution of lidocaine to nerves. This would explain the rapid onset sensory and motor block. There was no significant difference in side effects among groups. In our study, we have no cased of apnea. Respiratory depression, hypoxia, bradycardia, hypotension, or another side effect after tourniquet would be released till 12 h after surgery. Our study had some limitations. There is no possibility of patients follow-up in 48 h due to discharge in 12 h postoperation.

In conclusion, this study showed that the addition of 50 μ/kg midazolam to lidocaine for IVRA enhanced intra-operative analgesia and improved anesthesia quality; this could be explained by the peripheral effect of midazolam as the tourniquet placement prevents whole-body distribution of midazolam through the blood stream. The occurrence of sedation and enhanced postoperative analgesia after tourniquet deflation in the midazolam groups could be explained by the systemic effect of midazolam in addition to the peripheral analgesic effect.

AUTHORS' CONTRIBUTIONS

MRS has planned the study and finalized it; KN, AH, PO, and MRS did the statistical analysis and prepared the first version of the manuscript for publish. All authors read and approved the final manuscript.

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Conflicts of interest

There are no conflicts of interest.

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