Original Article

Effect of adding 8 milligrams ondansetron to lidocaine for Bier's block on post-operative pain

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Abstract

Background: Ondansetron has analgesic properties. The aim of the present study was to assess the analgesic effect of 8 mg ondansetron when added to lidocaine for intravenous regional anesthesia (IVRA).

Materials and Methods: Ninety patients undergoing hand surgery were randomly allocated to the three groups to receive 3 mg/kg 2% lidocaine diluted with saline to a total dose of 40 mL (Group L, $n = 30$) or 8 mg ondansetron plus 3 mg/kg 2% lidocaine diluted with saline to a total dose of 40 mL (group LO, $n = 30$) or 3 mg/kg 2% lidocaine diluted with saline to a total dose of 40 mL plus 8 mg ondansetron intravenously (Group IO, $n = 30$). Tourniquet pain and analgesic use were recorded before and after the tourniquet application.

Results: The sensory and motor block onset times were significantly shorter in Group LO compared with Group L and Group IO (4.2 ± 1.7 vs. 5.2 ± 0.8 and 5.1 ± 1.2 respectively, $P < 0.05$; 4.5 ± 1.4 vs. 5.8 ± 1.5 and 5.7 ± 1.4 respectively, $P < 0.05$). The sensory and motor block recovery times were significantly longer in Group LO compared with Group L and Group IO (6.1 ± 1.1 vs. 4.1 ± 1.3 and 4.5 ± 0.9 respectively, $P < 0.05$; 6.7 ± 1.4 vs. 4.4 ± 0.9 and 4.7 ± 0.7 respectively, $P < 0.05$). Post-operative VAS scores were significantly less in Group LO compared with Group L and Group IO till 24 h after tourniquet deflation ($P < 0.05$).

Conclusion: The addition of 8 mg ondansetron to lidocaine for IVRA reduced intraoperative and post-operative analgesic use till 24 h.

Key Words: Anesthetic techniques, intravenous regional, lidocaine, ondansetron, pain, post-operative

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INTRODUCTION

Intravenous regional anesthesia (IVRA) is a simple, reliable and cost-effective technique of regional anesthesia that used for short operative procedures of extremities.[1,2] There are some disadvantages related to the IVRG that include: Toxicity of local anesthetic (LA), slow onset of sensory and motor block, poor muscle relaxation, tourniquet pain, and short duration of post-operative analgesia.[3,4]

For improving block quality, prolonging post-operative analgesia, and decreasing tourniquet pain different additives combined with LA. These additives include opioids, tramadol, muscle relaxants, dexmedetomidine and non-steroidal anti-inflammatory drugs.[1-5]

Ondansetron is a specific 5-Hydroxy tryptamine-3 (5-HT3) antagonist, which is used as an antiemetic drug

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while has no significant side effect.[6] It was shown by Glaum and colleagues[7] that 5-HT3 antagonists interfere with peripheral effects of serotonin on nociception. Also, as Ye *et al*.,[8] showed, ondansetron has local anesthetic effects. Ondansetron can bind to the opioid mμ receptors in human and acts as an agonist.[9]

In a study that was performed by Farouk *et al*.,[10] it was shown that adding ondansetron 4 mg to the lidocaine for IVRA can decrease intraoperative and post-operative analgesic uses while improved sensory and motor block. The analgesic effect of this combination was limited to the first 4 h after tourniquet deflation. It was not clear that if higher dose of ondansetron (for example 8 mg) was used for this purpose, it could be prolonged the analgesic effect of lidocaine use for IVRG. The analgesic effect of ondansetron which showed in Farouk *et al*., study might be due to its peripheral local anesthetic effect on the nerve ending or its effect on the pain control center in the brain. This important point was not investigated in Farouk and colleagues study.

So, we designed the present study to evaluate the effect of adding ondansetron 8 mg to the lidocaine for IVRG on sensory and motor block onset and recovery time, intraoperative and post-operative pain, tourniquet pain, the quality of anesthesia, intraoperative and post-operative hemodynamic variables, and the side effects. We compared the effect of 8 mg ondansetron added to IVRG with another group which received 8 mg ondansetron intravenously to show that the analgesic effect of ondansetron was peripheral or central effect.

MATERIALS AND METHODS

After obtaining institutional approval from Ethic committee of our university and written informed consent from the patients, ninety American Society of Anesthesiologist (ASA) physical status I-II patients, aged 18-65 years old, scheduled for elective hand or forearm surgery gave written informed consent to participate in this randomized prospective double-blind study. Other inclusion criteria were patients without Reynaud disease, without sickle cell anemia or who had no history of allergy to any drug used. All surgeries were tendon repair following soft tissue injury to the forearm and hand.

Two 18 gauge intravenous cannula were inserted; one in a dorsal vein of the operative hand and the other in the opposite hand for infusion of crystalloid before beginning the anesthetic block. After exsanguinations of operating arm with an Esmarch bandage, it was elevated for 3 min. After that, a 10 cm pneumatic padded double-tourniquet was placed around the upper arm and proximal cuff was inflated to 250 mmHg.

After generation of a randomization list, an anesthesiologist who was blinded to the study prepared identical syringes. Another anesthesiologist blinded to the group allocation administered concealed syringes and recorded all data. IVRA was administered in three groups. In the first group, IVRA begins in hand injury with 3 mg/kg 2% lidocaine diluted with saline (Group L, $n = 30$) to a total dose of 40 mL and in the other hand with 3 mL normal saline intravenously. In second group, IVRA begins in hand injury with 8 mg ondansetron plus 3 mg/kg 2% lidocaine diluted with saline to a total dose of 40 mL (Group LO respectively; $n = 30$) and in the other hand with 3 mL normal saline intravenously. In third group, IVRA begins in hand injury with 3 mg/kg 2% lidocaine diluted with saline (Group IO, $n = 30$) to a total dose of 40 mL and in the other hand with 8 mg ondansetron in volume of 3 mL intravenously.

An anesthesiologist that did not involve in data collection prepared study drug solution in similar syringe in equal volume and coded them. The administration of coded study drugs was done by resident of anesthesiologist. Data collection was performed by resident of anesthesiologist who was not aware from the study group. The sensory block was evaluated continuously at 30 seconds intervals by a pinprick performed with a 22 gauge short beveled needle. The response of patient was evaluated in the dermatomal sensory distribution of the medial and lateral antebrachial cutaneous, ulnar, median, and radial nerves. Motor function was evaluated by asking the patient to flex and extend his/her wrist and fingers, and complete motor block was considered when voluntary movement was impossible.

Onset of sensory block (defined as the time elapsed from injection of study drug to sensory block achieved in all dermatomes), and onset of motor block (defined as the time elapsed from injection of study drug to complete motor block) were also recorded. After completion of sensory and motor block, the distal cuff was inflated to 250 mmHg, and the proximal tourniquet was released. After that the surgery was begun.

MAP, HR, Spo2, visual analog scale (VAS) scores (0 = no pain and 10 = worst pain imaginable) and degree of sedation (scale 1-5, 1 = completely awake, 2 = awake but drowsy, 3 = asleep but responsive to verbal commands, 4 = asleep but responsive to tactile stimulus, 5 = asleep and not responsive to any stimulus)[11] were recorded before and just after

tourniquet inflation, at 1, 5, 10, 15, 30 min after the injection of study drugs and at 1, 5, 10, 15, 30 min after tourniquet release.

If patients developed tourniquet pain with VAS more than 3 during operation, boluses of fentanyl 1 μg/kg were administered for tourniquet pain and total fentanyl usage was recorded. The time elapsed after tourniquet inflation to the first patient request for fentanyl was also recorded. Tourniquet duration was defined as time from initial proximal tourniquet inflation until deflation of the distal tourniquet at the end of operation. The VAS and hemodynamic parameters were recorded at 2, 4, 8, 12, and 24 h after operation.

During post-operative periods, if VAS was more than 3, 75 mg of suppository diclofenac were administered and total dose diclofenac usage was recorded. The time elapsed after tourniquet release to the first patient request for diclofenac was also recorded. All evaluations were done by an anesthesia resident blinded to the study group assignment.

Qualification of surgical condition such as disturbing movement of the arm and too much bleeding was assessed by the surgeon who did not know group allocation according to the following numeric scale: 0 = unsuccessful, 1 = poor, 2 = acceptable and 3 = perfect. In addition, the patients was asked to qualify the operative conditions according to following numeric scale: 4 (excellent) = no complaint from patient, 3 (good) = minor complaint with no need for supplemental analgesics, 2 (moderate) = complaint that required supplemental analgesics, and 1 (unsuccessful) = patient given general anesthesia at post-operative period.[12]

Sensory recovery time (defined as the time elapsed after tourniquet deflation up to recovery of pain in all dermatomes determined by pinprick test) was recorded. Motor block recovery time (defined as the time elapsed after tourniquet deflation up to movement of fingers) was also recorded.

The statistical analysis was performed by the SPSS 16 statistical software package. A sample size of 30, in each group had 80% power to detect a difference in means amount of intraoperative fentanyl requirement of 17.9 μg assuming that standard deviation (SD) in Group L and Group LO was 13.3 and 25.6 respectively using a 0.050 two-sided significance level.

Statistical comparisons for quantitative variables were done by using two-way ANOVA, followed by unpaired *t*-tests with Bonferroni's correction nominal or categorical data were analyzed and compared using the Chi-square test and Fisher's exact test, when it was appropriate. Sedation score and the quality of the anesthesia between the four groups were compared using the Kruskal–Wallis test. $P < 0.05$ was considered statistically significant.

RESULTS

Ninety patients were included in the present study. No patient was excluded from the study due to any problem. Flow diagram of randomized patients was shown in Figure 1. No significant difference was noted among three groups with respect to demographic data, duration of surgery and tourniquet time [Table 1].

Hear rate, mean arterial pressure and SpO_2 recorded at different time intervals was not significantly different between three groups ($P > 0.05$). The sensory and motor block onset times were significantly shorter in Group LO compared with Group L and Group IO ($P < 0.05$) [Table 2]. The sensory and motor block recovery times were significantly longer in Group LO compared with Group L and Group IO ($P < 0.05$) [Table 2]. No significant difference was noted between Group L with Group IO regarding the above variables.

Median sedation level was no significantly difference at any intraoperative and post-operative period between three groups. The VAS scores for tourniquet pain during the intraoperative period were significantly less in Group LO compared with Group L and Group IO at 5, 10, 20, and 30 min after tourniquet inflation ($P < 0.05$) [Figure 2]. There was no significant difference between Group L with Group IO in this regards.

The first time for initiation of tourniquet pain was significantly longer in Group LO compared with Group L and Group IO ($P < 0.05$) [Table 2]. The total dosage of fentanyl used for relieving tourniquet pain was significantly less in Group LO compared with Group L and Group IO ($P < 0.05$) [Table 2]. No significant difference was noted between Group L with Group IO regarding these variables.

The post-operative VAS scores were significantly less in Group LO compared with Group L and Group IO at 1, 3, 5, 10, 15, and 30 min after tourniquet deflation in ($P < 0.05$) [Figure 3]. There was no significant difference between Group L with Group IO in this regards. Also, post-operative VAS scores were significantly less in Group LO compared with Group L and Group IO at 2, 4, 8, 12, and 24 h after tourniquet deflation ($P < 0.05$) [Figure 4]. No significant difference was noted between Group L with Group IO in this regards.

The first time for rescue analgesic was significantly longer in Group LO compared with Group L and

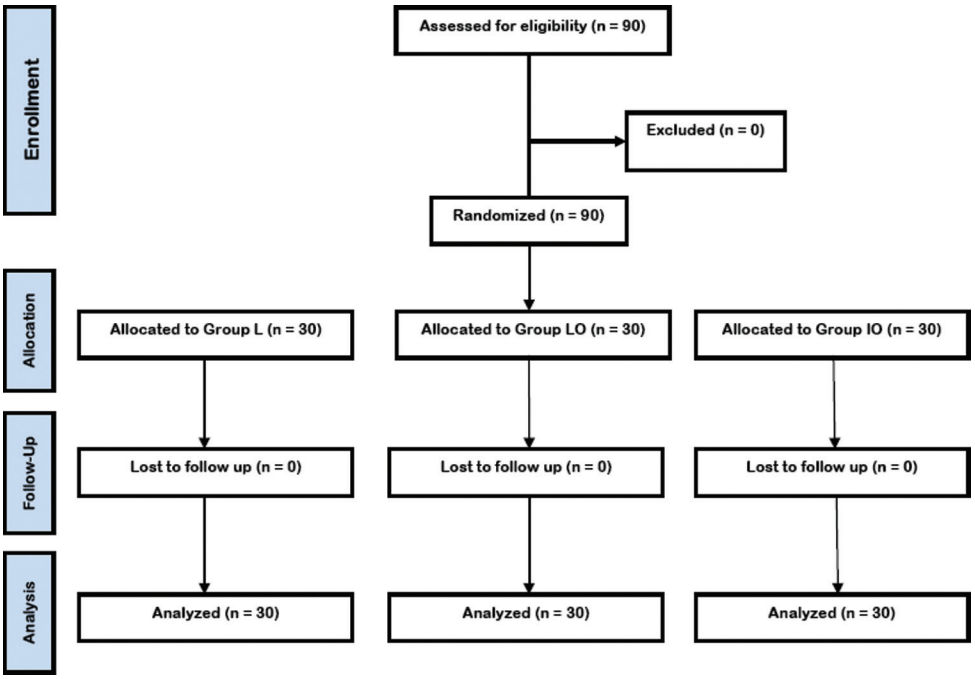

Figure 1: Flow diagram of randomized patients

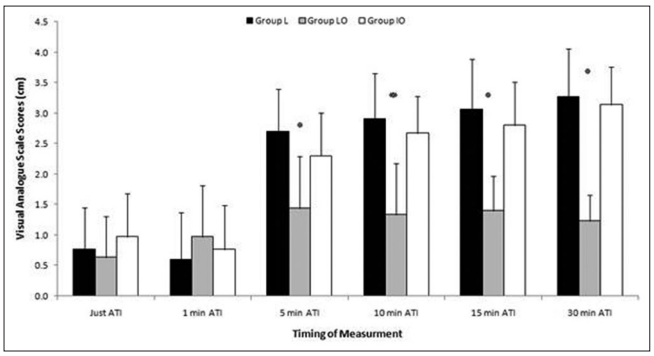

Figure 2: Intraoperative (tourniquet pain) visual analogue scale scores. Data are presented as mean±SD. Group L=Lidocaine group; Group LO=Lidocaine-ondansetron group; Group IO=Intravenous ondansetron group. ATI=After tourniquet inflation. **P*< 0.05 vs. Group L and Group IO

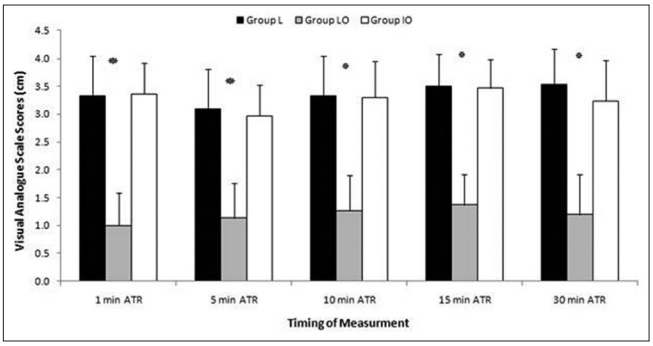

Figure 3: Post-operative visual analogue scale scores at 1, 3, 5, 10, 15, and 30 min after tourniquet release. Data are presented as mean ± SD. Group L=Lidocaine group; Group LO=Lidocaine-ondansetron group; Group IO=Intravenous ondansetron group. ATR=After tourniquet release. **P*<0.05 vs. Group L and Group IO

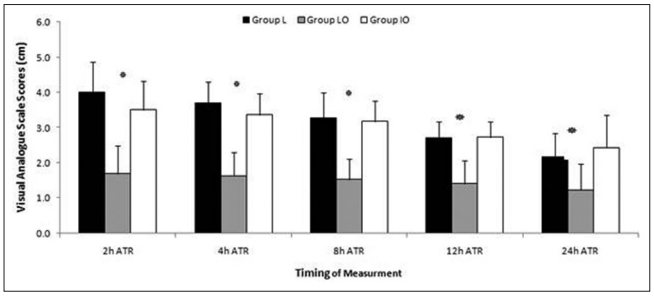

Figure 4: Post-operative visual analogue scale scores at 2, 4, 8, 12, and 24 h after tourniquet release. Data are presented as mean ± SD. Group L=Lidocaine group; Group LO=Lidocaine-ondansetron group; Group IO=Intravenous ondansetron group. ATR=After tourniquet release. **P*<0.05 versus Group L and Group IO

Group IO ($P < 0.05$) [Table 2]. The total dosage of analgesic used for relieving post-operative pain was

Table 1: Patients' demographic data, duration of surgery and tourniquet inflation in three groups

Variable	Group L (*n*=30)	Group LO (*n*=30)	Group IO (*n*=30)
Age (yr)	30.4±12.8	29.1±5.2	31.8±14.3
Gender (F/M)	6/24	4/26	3/27
Weight (Kg)	65.2±14.5	63.1±13.9	61.6±11.3
ASA (I/II)	23/7	22/8	21/9
Duration of surgery (min)	53.3±8.8	52.4±7.4	56.4±7.2
Tourniquet time (min)	66.6±9.4	68.4±8.4	67.4±10.5

significantly less in Group LO compared with Group L and Group IO ($P < 0.05$) [Table 2]. No significant difference was noted between Group L with Group IO regarding these variables.

Quality of anesthesia which assessed by the patients

Table 2: Onset and recovery times of sensory and motor block, initial time of tourniquet and post-operative pain, and the amount of intraoperative and post-operative analgesic needs in three groups

Variable	Group L (*n*=30)	Group LO (*n*=30)	Group IO (*n*=30)	*P* value
Sensory block onset time (min)	5.2±0.8	4.2±1.7*	5.1±1.2	0.007
Sensory block recovery time (min)	4.1±1.3	6.1±1.1*	4.5±0.9	0.000
Motor block onset time (min)	5.8±1.5	4.5±1.4*	5.7±1.4	0.001
Motor block recovery time (min)	4.4±0.9	6.7±1.4*	4.7±0.7	0.000
The first time of tourniquet pain (min)	13.6±8.2	31.2±8.6*	16.8±7.9	0.000
Intraoperative fentanyl requirement (μg)	126.2±53.9	66.7±25.8*	133.8±52.2	0.024
The first time of post-operative pain (min)	105.3±38.6	252.0±50.2*	111.5±36.7	0.000
Post-operative diclofenac requirement (mg)	106.3±28.3	60.0±22.4*	103.8±32.0	0.011

Values are presented as mean±SD. Group L: Lidocaine group; Group LO: lidocaine-ondansetron group; Group IO: Intravenous ondansetron group; *P<0.05 versus Group L and Group IO

Table 3: Quality of anesthesia evaluated by patients and surgeon

Variable	Group L (*n*=30)	Group LO (*n*=30)	Group IO (*n*=30)	*P* value
Quality of anesthesia (Patient)	3 (2-4)	1 (1-3)*	3 (2-4)	0.000
Quality of anesthesia (Surgeon)	3 (2-4)	1 (1-3)*	3 (2-4)	0.000

Values are presented as median (range). Group L: Lidocaine group; Group LO: Lidocaine-ondansetron group; Group IO=Intravenous ondansetron group; *P<0.05 versus Group L and Group IO

and the surgeon was significantly more in Group LO compared with Group L and Group IO ($P < 0.05$) [Table 3]. No significant difference was noted between Group L with Group IO in this regards. No adverse effect was noted in any patient throughout the study period.

DISCUSSION

The results of our study showed that addition of ondansetron 8 mg to lidocaine for IVRG significantly improved the onset time and duration of sensory and motor block, decreased tourniquet pain, decreased intra-operative and post-operative analgesic use till 24 h compared with Group L and Group IO without causing important side effects. The quality of anesthesia was also significantly better in Group LO compared with Group L and Group IO.

In one previous study, which was performed by Farouk,[9] it showed that the addition of ondansetron 4 mg to lidocaine for IVRG significantly improved the quality of anesthesia, shortened onset time and duration of sensory and motor block, lessened tourniquet pain, decreased intraoperative and post-operative analgesic use for the first 4 h after surgery. It was not clear that addition higher dose of ondansetron prolonged duration of analgesia beyond 4 h after surgery or not. Our study showed that addition of higher dose of ondansetron (8 mg) prolonged duration of postoperative analgesia till 24 h without causing significant side effects.

Ondansetron is an antagonist of 5-hydroxytryptamine-3, which used commonly for prevention or treatment of postoperative nausea and vomiting.[13] Also, it was shown by Ye *et al.*,[8] that ondansetron could block sodium channels similar to local anesthetics and had anti-nociceptive effect. It was demonstrated that peripheral 5-hydroxytryptamine-3 receptors were participated in the pathway of nociception. These peripheral receptors could bind to the opioid receptor and show agonist activity.[9] Gregory *et al.*,[9] showed that ondansetron may be effective in preventing pain following injection of propofol by binding to the opioid receptors. Ambesh *et al.*,[14] found that pain during injection of propofol can successfully prevent by administration of 4 mg ondansetron. Also, in another study performed by Reddy and colleagues,[15] it was shown that ondansetron 4 mg could reduce significantly pain during injection of rocuronium and propofol.

Ye and *et al.* colleagues[8] showed that ondansetron, as a local anesthetic, seems to be approximately fifteen times more potent than lidocaine because 0.1 percent ondansetron produced local anesthetic effect similar to that 1.5% lidocaine. They concluded that ondansetron's local anesthetic properties may contribute to its antiemetic effects. It was shown that there is receptors similar to enteric neuron 5-HT3 on the nociceptive primary afferent fibers (PAF) not only on the peripheral free terminal but also centrally on their spinal terminal.[16,17] These receptors are present on the neurons of the superficial lamina of the dorsal horn also.[16,17]

Fassoulaki *et al.*,[18] showed that ondansetron could antagonize the sensory block produced by intrathecal injection of lidocaine. Cui and colleagues[19] concluded that stimulation of periaqueductal gray matter could increase release of 5-HT in dorsal horns of spinal cord that consequently might inhibit the nociception of dorsal horn neurons. Arcionic *et al.*,[20] showed that ondansetron was administered by continuous infusion for prevention of post-operative nausea and

vomiting could reduce the analgesic effect of tramadol, which probably was due to blocking of spinal 5-HT3 receptors. The 5-HT3 receptors, which are present on PAF (from the nociceptors up to the dorsal horn) mediate pronociceptive action while those receptors located postsynaptically in relation to PAF mediate the antinociceptive effect of endogenous (5-HT) or administered agonist.[21,22]

It was showed by the Zeitz *et al*.,[23] that peripheral 5-HT3 receptors acts as a novel complement for the primary afferent nociceptors. As tourniquet inflation prevent whole body distribution of ondansetron. Our study may be useful model for investigating mechanism of peripheral action of ondansetron. Stratz and colleagues[24] showed that 5-HT3 receptor antagonists had anti-inflammatory effects and due to this property they could have a role in decreasing pain following surgical incision pain. Also, they founded that 5-HT3 receptor antagonists could acted as supplement or replacement for local administration of corticosteroids. Not only ondansetron but the other 5-HT3 antagonists such as tropisetron and alosetron have analgesic effect.[25-27]

Färber and *et al.* colleagues[25] showed that tropisetron have analgesic effect in patients with fibromyalgia pain. Also, the analgesic effect of alosetron in female patients with diarrhea predominant irritable bowel syndrome was reported by Camilleri *et al*.,[27] and Muller *et al*.,[28] showed that local administration of 5-HT3 antagonists had rapid analgesic effect in various rheumatic diseases. It was reported that this local anesthetic effect lasts significantly longer compared with local anesthetics but was comparable with local injection of local anesthetics combined with corticosteroids.

One of important limiting factor in duration of IVRA is tourniquet pain. Neuropathic pain caused by nerve compression is considered as an important etiology for tourniquet pain.[29] Pain due to nerve compression is mediated by unmyelinated, slow conduction C-fiber.[29] It was shown by Mc clean *et al*.,[30] that ondansetron as a 5 HT3 receptor antagonist has potential benefit in neuropathic pain. 5-HT3 receptor antagonists decrease serotonin-induced release of substance P from C-fiber.[31] It has been shown that when the drugs with local anesthetic properties such as meperidine,[32] clonidine[33] or nitroglycerine[34,35] added to the local anesthetic solution in IVRG, they can reduce tourniquet and postoperative pain. As it was shown by Ye J and colleagues,[8] ondansetron has potent local anesthetic properties. More studies must be de designed to evaluate the efficacy of different dosage of ondansetron and the other 5-HT3 receptor antagonists in various types of orthopedic surgeries with different techniques of regional anesthesia.

In conclusion, adding ondansetron 8 mg to lidocaine for IVRA reduced intraoperative and post-operative analgesic use till 24 h, decreased onset of sensory and motor block, increased duration of sensory and motor block, decreased tourniquet induced pain, prolonged the rescue time for analgesic use, and finally improved the patients' and surgeons' satisfaction without causing significant adverse effects. Our study showed that ondansetron has local anesthesia properties. As our results showed, it seems ondansetron has no systemic analgesic effect but further studies must be performed before final conclusion can be elucidated.

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This clinical trial study is registered in www.irct.ir with the code of: IRCT201207122410N10

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