Original Article

Effect of Addition of Ondansetron or Magnesium to Lidocaine on Duration of Analgesia of Intravenous Regional Anesthesia in Elective Upper Extremities Surgery: Comparative Study

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Abstract

Background: This study aimed at evaluating and comparing the effect of ondansetron and magnesium added to lidocaine on intravenous regional anesthesia (IVRA) in the surgery of upper extremity.

Methods and Materials: The current randomized, clinical trial was conducted on 45 patients considered as candidates for upper extremities surgery in Qazvin, Iran. The patients were randomly assigned into three groups. Group C only received 3 mg/kg lidocaine, group O lidocaine +4 mg/kg ondansetron, and group M lidocaine +7.5 mL magnesium sulfate 20%. Then, the sensory and motor blocks, tourniquet pain, the amount of administered extra fentanyl, pain intensity, and other parameters involved in analgesia were analyzed in the groups using the statistical tests.

Results: The time for onset of sensory and motor blocks in the M group was significantly shorter than the groups C and O ($p<0.05$). In terms of the recovery time of the sensory block, the time of group O was significantly longer than those of groups M and C ($p<0.05$). The amount of administered extra fentanyl and tourniquet pain after block in groups O and M were significantly lower than of group C ($p<0.05$). No significant difference was observed in postoperative pain and other features among the groups ($p>0.05$).

Conclusion: Magnesium had more rapid effectiveness and ondansetron had prolonged postoperative analgesia. Although the induced analgesia relatively improved the intensity of pain, it failed to maintain its supremacy in postoperative pain. To obtain more conclusive results, further studies are required.

Keywords: Bier Block, Ondansetron, Magnesium, Lidocaine

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Introduction

Intravenous regional anesthesia (IVRA) or Bier block is an anesthesia method in which the local anesthetic is intravenously injected into the extremity to induce analgesia for surgical purposes Lidocaine is a common drug to induce regional anesthesia (1). The prevalence of lidocaine drug toxicity is low among

other regional analgesics (2). In spite of the aforementioned advantages of lidocaine, it has slight prolongation; hence, this factor can affect tourniquet pain and analgesia during the surgery (3).

To improve the quality of blockade, prolong postoperative analgesia, and reduce tourniquet pain, different agents were added to lidocaine; for example, opioids, tramadol, muscular relaxants, dexmedetomidine, and non-steroidal anti-inflammatory drugs (NSAIDs) (4-7).

Ye et al., showed that ondansetron has regional anesthetic properties (8). A study showed that ondansetron has local anesthetic properties and can block sodium channels similar to that of local anesthetics and induce analgesia (9). Ondansetron also exerts its effect on pain receptors via peripheral effects of serotonin. This effect can be explained by binding to μ-opioid receptors and acting as an agonist (10, 11). In a study by Farouk et al., adding 4 mg ondansetron to lidocaine in order to induce Bier block reduced the number of sedatives administered during and after the surgery, in addition to the improvement of sensory and motor blocks (12).

On the other hand, some studies indicated that magnesium exerts vasodilatory effects via releasing nitric oxide from endothelium vessels. Nitric oxide activates guanylyl cyclase and increases cyclic guanosine monophosphate (cGMP) concentration, which results in soft muscles relaxation of the vessels (13, 14). Nitric oxide also is a strong inhibitor of binding neutrophils to endothelium vessels through which accelerates the release of regional anesthetics from vessels. It seems that the impact of magnesium on calcium channels and N-methyl-D-aspartat (NMDA) can play a significant role in analgesia (15). In a study by Bansal et al., adding magnesium sulfate to lidocaine activated the motor blockade, prolonged sensory and motor Blocks, and reduced postoperative pain without side effects (16).

According to the aforementioned findings, recent studies investigated the analgesic effects of ondansetron and magnesium as well as the lesser side effects of these drugs than opioids on tourniquet pain. However, since achieving rapid and adequate analgesia after the release of the tourniquet is of great importance, to make the best choice further investigations are required.

The current study aimed at evaluating and comparing the effect of ondansetron and magnesium added to lidocaine on intravenous regional anesthesia.

Methods

Selection of patients and randomization

The current randomized, double blind, controlled clinical trial design was conducted in Qazvin, Iran, on 45 patients who were candidates for elective surgery for the upper extremity. The inclusion criteria were the age range 20 to 60 years and physical status ASA I (healthy candidates) and II (patients with mild systemic diseases) (the American Society of Anesthesiologists Class I and II). The exclusion criteria were sickle cell anemia, history of allergy to the under study drugs, patients with Raynaud's disease, patients with poor cooperation due to mental retardation, NSAIDs, opioid consumption, and sildenafil consumption 24 hours prior to the surgery, as well as the patients who underwent surgery for at least 90 minutes, those with blockade failure, and intolerance to block. The current study was conducted in accordance with the research priorities of Qazvin University of Medical Sciences and the Ethics Committee of the university approved the study protocol (Code: IR.QUMS.REC.1394.138).

The patients were randomly allocated to three groups. Group C: 40mL local anesthetic solution containing 3 mg/kg lidocaine (lidocaine2% diluted with saline) Group O: the same amount lidocaine + 4 mg ondansetron; group M: the same amount lidocaine +7.5 mL magnesium sulfate 20%; the total volume in all the groups was 40 mL, that administered via the installed venous cannula within 90 seconds. Magnesium and ondansetron doses were selected based on previous studies. Selected doses of both drugs in the event of sudden and unexpected releasing of the tourniquet do not result in a specific complication in the patient (17, 18).

Anesthetic technique

Vital signs of the patients, including blood pressure and pulse rate, were recorded after admission to the operating room. A resident who was blind to the allocations performed preparation and premedication in all the patients. To induce analgesia, 1.5 μg/kg fentanyl + 0.02 mg/kg midazolam were administered. A second venous cannula was embedded in the back of

the other hand for surgery. Then, the blood of the organ was drained using an Esmarch bandage tight wrapped proximal the place of the cannula. Accordingly, a tourniquet wind-motor was bounded around the arm and then, its upper cuff pressure was adjusted 150 mmHg above the systolic blood pressure.

The sensory and motor blockades at surgical site were assessed by the pinprick and gripping force methods, respectively (19); all the procedures were performed by a resident who was blind to the random allocations. After induction and complete establishment of sensory and motor blockade, the lower tourniquet was inflated similar to the method applied to the upper cuff, and then the upper cuff was deflated and the surgery was started. The vital signs including blood pressure and pulse rate were recorded. Pain intensity was assessed based on the visual analog scale (VAS) (20). VAS is a 10-option scale on a line and the subject is required to determine the intensity of pain he or she experiences using this scale (18). The intensity of pain caused by tourniquet tightness at 5, 10, 15, 20, 25, and 30 minutes of installation was recorded based on VAS. If VAS was ≥4 during the surgery, the patient received 1 µg/kg extra fentanyl intravenously, and the time of tourniquet pain onset and the total amount of extra fentanyl administered during the surgery were recorded. Tourniquet cuff did not deflate under 30 minutes and the deflation was intermittently performed in 10 minutes. The recovery time of sensory and motor function w also recorded in patients after deflation of cuff tourniquet. In addition to vital signs such as blood pressure and pulse rate, pain intensity was also recorded based on VSA at 0.5, 2, 4, and 6 hours after the release of the tourniquet. Patients with VSA ≥4 received 0.5 mg/kg pethidine intravenously in order to reduce the pain. It is noteworthy that the time between releasing the tourniquet and administration of the first pethidine dosage (analgesic time) was recorded in all the patients. All local and systemic side effects such as nausea and vomiting, rashes, tachycardia, bradycardia, low blood pressure, high blood pressure, headache, dizziness, tinnitus, hypoxia, respiratory depression, bradypnea, tachypnea, delusion, and nystagmus were also recorded.

Statistical analysis: data were expressed as frequency and percentage for categorical variables, and mean±standard deviation (SD) for the continuous variables. To compare continuous variables, the analysis of variance (ANOVA), and to compare categorical variables, chi-square tests were used. To analyze data about the level of pain at different intervals, the repeated measures ANOVA was used. Data analysis was performed with SPSS version 22 at P-value <0.05 as the level of significance.

Results

Demographic and clinical features of the participants in the study groups are shown in Table 1. No significant difference was observed among the groups in terms of age, gender and duration of the surgery (p>0.05).

The time to onset of sensory and motor blockade after the injection of anesthetics, amount of extra fentanyl administered during the surgery, recovery time of sensory and motor blockade after deflation of cuff tourniquet, the interval between releasing the tourniquet and need for the first dose of pethidine are shown in Table 2. The amount of extra fentanyl administered in groups O (lidocaine + ondansetron) and M (lidocaine + magnesium) was significantly lower than group C (lidocaine) (p<0.01).

The onset time of sensory block was significantly shorter in the M group than group C (p<0.001). The onset time of sensory block was significantly shorter in the M group than group O (p=0.001). The onset time of motor block was significantly shorter in the M group than groups C (p=0.001) and O (p= 0.012) (Table 2).

The recovery time of sensory blockade was significantly longer in the O group than group C (p=0.001) and C (p=0.025). The recovery time of motor blockade was significantly longer in the O group than group C (p=0.014), although the difference was insignificant compared with that of group M (p>0.05).

Figure 1 shows the mean interval between anesthetics injection and tourniquet pain onset in the study groups at different intervals (5, 10, 15, 20, 25, and 30 minutes). The interaction between time and group significantly affected the mean pain intensity in the study groups (f=7.39; p<0.001); significant differences were observed among the groups (f= 17.36; p<0.001). Pain scores showed no significant differences in minutes 5 to 20 among the study groups.

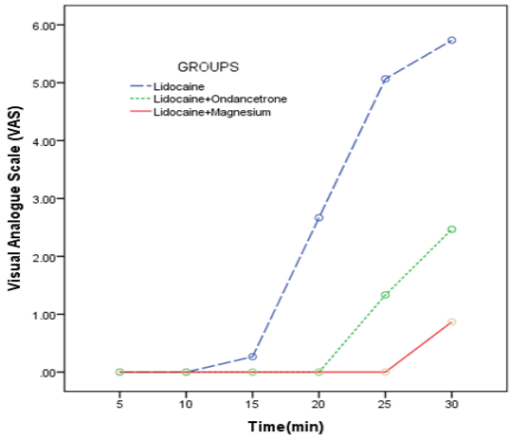

Figure 1. Evaluation of pain intensity after anesthetics injection.

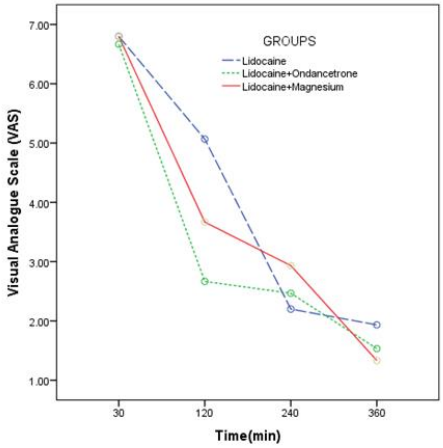

Figure 2. Evaluation of the pain intensity after releasing of cuff tourniquet.

However, the groups O and M showed lower pain scores at minutes 25 and 30 than the group C ($p<0.001$). Intergroup comparisons showed no significant difference between the groups O and M ($p=0.72$).

Figure 2 shows the pain intensity after deflation of cuff tourniquet in the study groups at different intervals (30, 120, 240, and 360 minutes). In terms of time and group interactions, no significant differences were observed among the groups ($p=0.244$; $f=1.39$); there was also no significant difference among the intervals ($p<0.05$). No significant local or systemic side effects were observed in the study participants.

Discussion

Results of the current study indicated that the onset of sensory and motor blockade was significantly faster in the group M (lidocaine + magnesium) than groups C (control) and O (ondansetron + lidocaine). The superiority of magnesium + lidocaine in terms of prolongation of analgesia although was noteworthy

Table 1: Demographic and clinical features of the study participants.

Variable	Lidocaine group(C)	Lidocaine+ ondansetron group(O)	Lidocaine + magnesium group(M)	P value
Age (year)	36.53±14.80	4.33±9.11	36.86±10.19	0.128
Gender male (female)	9(6)	10(5)	9(6)	0.91
Duration of surgery(min)	45±16.58	37.46±9.73	44.46±18.07	0.32

compared with that of the control group, was significantly lower than that of the group ondansetron + lidocaine. Hence, it can be concluded that the administration of magnesium before the stimulation of surgery may play a preventive role in post-operative pain; it is important since the preventive analgesia can be useful for patients by prevention from the formation of central sensitization process or what is happened following the incision or inflammation, or a combination of both of them (21).

Results of the current study indicated that adding ondansetron and magnesium to lidocaine could significantly reduce tourniquet pain in patients at different intervals from the injection of anesthetics, compared with using only lidocaine, however, no significant difference was observed between the ondansetron and magnesium groups; the results were consistent with those of Dabbagh et al. (22) and Hwang et al (23). They showed that the intensity of pain significantly reduced during the surgery following the intravenous administration of 50 mg/kg magnesium sulfate. Results of a similar study by Honarmand et al., showed that adding 8 mg ondansetron to lidocaine for IVRA significantly reduced intraoperative and postoperative pain (9). Badeaux et al., in one study showed ondansetron as an adjunct to lidocaine have anti-inflammatory effects and can be administered to reduce postoperative pain (11). In the current study, although ondansetron and magnesium played a desirable role in the onset and offset of sensory and motor blockade, it could not significantly reduce postoperative pain. The results were in agreement with those of Lu et al., who showed that ondansetron has no significant analgesic effects (24).

In terms of the amount of fentanyl administered during the surgery, the condition was similar, and two groups (O and M groups) had a significant superiority compared to the control group. Mavrommati et al. (25) and Woolf et al. (26) Also showed that with the administration of magnesium sulfate by two methods of bolus and infusion, the need for analgesic and anesthetic drugs decreases during the surgery. In their study, postoperative analgesia also significantly improved; similar results (reduction of the mentioned values) were also reported in Seyhan et al. (27) and Ryo et al. (28) studies.

One of the strengths of the current study was a random allocation of participants and lack of difference regarding demographic characteristics among the study groups; hence, the confounding impacts of such features were eliminated due to the homogeneity of the study groups. One of the limitations of the current study was the lack of comparison among the study groups in terms of different applied doses. It is recommended to compare the effect of different doses of agents administered in the current study in order to compare their effectiveness and side effects in further studies.

Conclusion

Onset time of sensory and motor blocks were significantly shorter in the group M than the other two groups. This superiority was more appropriate than the group C due to the prolonged analgesia, but it significantly less than was the group o. Since no side effects were observed in the study groups, clinically there is no specific risk regarding the co-administration of ondansetron or magnesium with lidocaine. Because

Table 2: Comparison of the administered dose of fentanyl, time to need the first dose of pethidine, and the features of blockades in the study groups.

Variable	Lidocaine group (C)	Lidocaine + Ondansetron group (O)	Lidocaine + Magnesium group (M)	P-value
Time from injection to onset of sensory blockade(min)	3.4±1.8	3.06±1.38	0.93±1.33†+	<0.001
Time from injection to onset of motor blockade(min)	9.60±3.77	8.40±4.03	4.60±2.09†+	0.001
The amount of extra fentanyl administered during the surgery(µg)	56.66±8.61	25±7.31*	28.33±14.61+	0.001
Time from evacuation of cuff tourniquet to recovery from sensory blockade(min)	4.33±2.76	10.20±3.91* †	6.26±4.75	0.001
Time from evacuation of cuff tourniquet to recovery from motor blockade(min)	5.80±3.12	11.93±6.89*	7.66±6.06	0.014
Time from releasing tourniquet to need for receiving the first dose of pethidine(min)	42.13±34.31	36.33±14.81	49.53±43.48	0.554

* Between the groups C and O, + between the groups C and M, †between the groups O and M.

rapid onset and adequate analgesia after releasing the tourniquet very important, in future studies, it is suggested that more studies be done with different doses of each of these two drugs to achieve the best selection.

Conflicts of Interest

The authors declare that they have no conflict of interest.

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