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Research Article

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Comparison of analgesic effect of different doses of granisetron in combination with lidocaine for intravenous regional anesthesia

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ABSTRACT

One of the advantages of intravenous regional anesthesia is rapid return of normal sensation and power of movement at the end of the surgery. The aim of the present study is to compare the effect of different doses of granisetron in combination with lidocaine in intravenous regional anesthesia. In this double blind clinical trial, from May 2014 to July 2015, ninety patients who were candidate for forearm Orthopedic surgeries entered the study. Patients in the first group received 0.5% lidocaine (3 mg/kg), one mg granisetron in the second group, and also 2 mg granisetron in the third group in combination with 0.5% lidocaine (3 mg/kg). Pain during surgery and after it was assessed using visual analog scale. The results showed that mean pain of patients immediately after the inflation of tourniquet and at minutes 15, 30 and 45 in the third group was significantly lower than the other two groups (p=0.0001) and also the difference between granisetron groups(second & third groups) and first group was significant. The average time of onset of tourniquet pain was 33.50±7.56 minutes in the first group, 41.33±4.96 minutes in second, and 44.70±4.39 minutes in the third group and this time in both granisetron groups (second & third groups) was significantly higher than first group (p=0.0001). It seems that using granisetron can significantly reduce the pain during and after forearm surgery.

Keywords: Granisetron, Lidocaine, Pain, Visual Analog Scale

INTRODUCTION

Intravenous regional anesthesia has been recognized as a safe and reliable technique for anesthesia and for preventing bleeding during organ surgery. The advantage of this method includes a quick return of the natural feeling and the power of motion as the surgery ends and this lets the organ to return to its normal state quickly and also it is by using this method that the neurologic symptoms can be reviewed after fracture has been treated (1, 2). The following items can be referred to as the disadvantages of this method: discontinuation of anesthesia, concerns about local anesthetics, beginning of the slow effect of the medicine, less muscle relaxation, pain caused by tourniquet and also less postoperative analgesia (3). Among these, the role of nerve fibers A and non-myelinated fibers C have been considered as effective items on causation of pain caused by tourniquet because the ischemia caused by the closing of tourniquet leads to the increase of compression of peripheral nerve (4) and the serotonin released from the platelets of the ischemic and damaged tissues can play a role in the transmission of the feeling of pain through peripheral receptors of pain including 5-HT3 (5).

5-HT3 receptor antagonists such as Ondansetron can also be linked to μ opioid receptors and play the rοle of an agonist (6). It has also been proven that its subcutaneous injection can create local anesthesia (7). Various studies have shown that this medicine, while use with Lidocaine, causes reduction of pain during and after surgery and the pain caused by tourniquet in intravenous regional anesthesia (8, 9).

Another 5-HT3 receptor specific antagonist is granisetron and its impact lasts longer and has a better function than ondansetron (10) and is often used for preventing nausea and vomiting after chemotherapy (11). However, there are various studies in which this medicine has been successfully used for preventing the pain caused by propofol injection (10, 12). Since granisetron blocks 5-HT3 receptor peripherally and centrally (13) and also other antagonists of this receptor have had a role in reducing the pain in intravenous regional anesthesia; thus, the purpose of this study is to review the impact of various doses of granisetron along with lidocaine in intravenous regional anesthesia.

EXPERIMENTAL SECTION

Research method:

In this double-blind clinical trial study, from May, 2014 to August 2015, a number of 90 patients who had visited Valiasr Hospital of the city Arak for forearm orthopedic operations (ulna and radius fractures) entered the study after getting individual consent and given the criterion of entering and exiting the study. The criteria of entering the study included the age between 20-50 years, ASA I-II class and their consent for participating in the study. In case of any allergies to the medicines in the study, pregnancy, contraindication of intravenous regional anesthesia such as sickle cell anemia, previous consumption of opioids and other analgesic medicines, previous use of apomorphine in the recent time (dopamine agonist) and the operation time of less than 40 minutes and more than 90 minutes, the participants entered and exited the study.

After getting the demographic information and recording the vital signs and percentage of arterial oxygen saturation, 2 intravenous access, one was used in the dorsal vein of hand that is being operated and the other was used in the other hand in order to receive crystalloid fluids. At first, 2 milligrams of midazolam was injected as premedication and a paired-tourniquet was placed around 3-4cm higher than the elbows of the operated hand, then for 2 minutes the hand of the patient was place higher so that the blood in the hand would be discharged and would be tightened with an Esmarch bandage. Then the proximal cuff paired-tourniquet is filled with air to a 250 mmHg pressure and the Esmarch bandage is taken out (14). After reassuring that there is no pulse through the pulse oximetry device, the patients are divided into three groups randomly and based on the table of the random numbers. The first or the control group included patients who had received 3mg/kg lidocaine which was diluted with a 0.9% saline to 40cc and its concentration had become 0.5% , in 90 seconds. In the second group, there were patients who had received 3mg/kg lidocaine and 1mg granisetron which was diluted with a 0.9% saline to 40cc and its concentration had become 0.5% , in 90 seconds. Patients in the third group were those who had received 3mg/kg lidocaine and 2mg granisetron dissolved in 0.9% saline with the total volume of 40cc , in 90 seconds. It is necessary to note that preparation of the medicines was done by the personnel (experts) of anesthesia who had no part in collecting the information and after the medicines were coded, they were injected by the anesthesiology residents who were not informed of the codes and the information was collected.

After making sure of the sensory and motor block, the distal cuff was filled with air up to 250mmHg and the proximal tourniquet was returned. Also the time of beginning of painlessness after the first injection was recorded. The VAS scale (Visual Analogue Ruler) was used for measuring the tourniquet pain which included a 10cm ruler which was longitudinally stretched between zero and 10 centimeters. In this ruler, the number zero shows a painless state and the number 10 shows unbearable pain. The patients were asked to mark the rate of their pain on this ruler and the space between zero and the place marked by the patient expressed the rate of patient's pain.

The rate of patients' VAS was measured and recorded right after the tourniquet was filled and the times 15, 30 and 45 minutes by the anesthesiology resident who did not have information about the classifications and in case of presence of a VAS more than 3, one microgram per kilogram of Fentanyl was injected for the patient and the time of the prescription of the first dose of fentanyl was recorded. Also, the time of beginning of the tourniquet pain is also recorded.

After the end of surgery, tourniquet is discharged with intermittent technique. It is necessary to mention that the tourniquet remains closed for at least 40 minutes and at most 90 minutes after the injection of medicine. Patient's

vital signs and percentage of arterial oxygen saturation during the operation and after discharging the tourniquet is measured. The rate of painlessness of the patient after discharging the tourniquet is expressed each 30 minutes to 2 hours (30, 60, 90 and 120 minutes) based on the VAS scale and the highest measured VAS is expressed as the rate of pain of the patient after surgery.

In the postoperative period, up to 2 hours (30, 60, 90 and 120 minutes), in case of a VAS higher than 3, a 75mg diclofenac suppository was prescribed and the time and amount of the prescribed diclofenac was recorded. The time of return of the feeling after the surgery, which is defined through return of pain in all of the dermatomes of the considered organ after the discharge of tourniquet, has been evaluated by the Pinprick test (stimulation with the tip of the needle) and its time is recorded. Also the time of return of motion after the surgery, which is defined with the time spent for the return of the ability to move the fingers of the hand being operated after discharging the tourniquet, was also evaluated. Then the data was analyzed by the SPSS software version 20. In order to analyze the qualitative data, the Chi-square test was used. The ANOVA test and the Toki posttest were used for the quantitative data and in order to evaluate the qualitative data in the interval of the study, the analysis of variance test with repeated observations and the Wilkes Lambada posttest were used. The P-value that is less than 0.05 will be considered as significant.

RESULTS

In this study, 90 patients were evaluated in three groups of 30 patients. In the first group, there were a number of 19 men (63.3%), there were 15 men (50%) in the second group and there were 16 men in the third group (53.3%) and the rest of the patients were women (p=0.557). The average age of the patients in the first group was 35.96±8.3 years, it was 38.20±9.3 years in the second group and it was 37.07±8.5 years in the third group (P=0.613).

The mean of the time needed for anesthesia to begin in the group 1 was equal to 3.77±0.9 minutes, 2.47±0.6 minutes in the group 2 and 1.63±0.7 minutes in group 3 and the difference between the third group and the other two groups is significant (P=0.0001) and on the other hand, the difference between the groups 1 and 2 is also significant (P=0.0001).

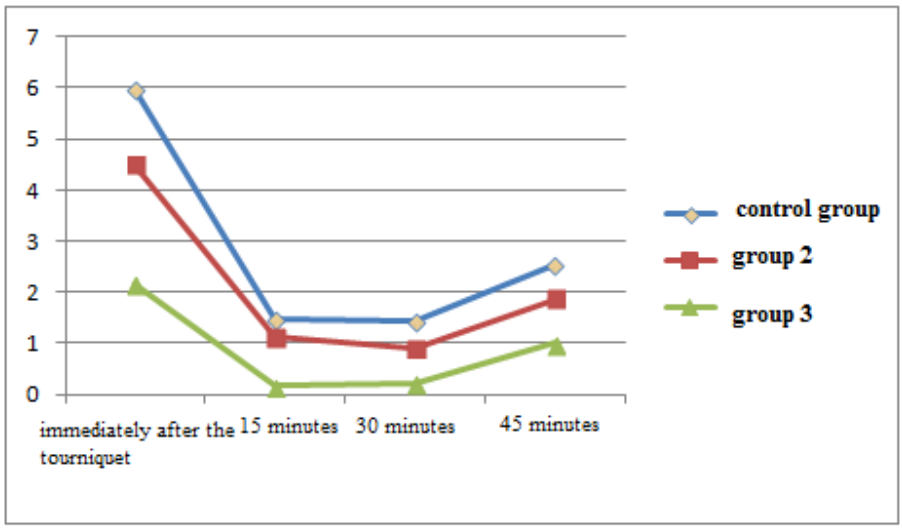
The mean of patients' pain was measured by using VAS scale immediately after the tourniquet is closed and in 15, 30 and 45 minutes after that. As it is seen in table one, except the 15th minute, in the other times, the differences between group 3 and the other two groups and groups 1 and 2 are significant.

Table 1 – mean of rates of VAS after the tourniquet is closed and surgery begins

	Group 1	Group 2	Group 3	P-value		
				2-3	P-3	P-2
Initial VAS	5.97±1.2	4.50±1	2.16±0.95	0.0001*	0.0001*	0.0001*
VAS of the 15th minute	1.46±0.63	1.13±0.63	0.16±0.38	0.0001*	0.0001*	0.059
VAS of the 30th minute	1.43±0.63	0.9±0.66	0.23±0.43	0.0001*	0.0001*	0.002*
VAS of the 45th minute	2.53±0.86	1.87±0.68	1.00±0.052	0.0001*	0.0001*	0.001*

Data has been analyzed by using the statistical test of variance with repeated observations and Wilkes Lambada test and they have shown that the mean of pain at all times in the group 3 has been significantly lower than the other two groups (F=11.59 and P=0.0001) (graph 1).

The mean of the beginning of time of the pain of tourniquet in the control group (group 1) was equal to 33.50±7.56 minutes, 41.33±4.96 minutes in group 2 and 44.70±4.39 minutes in group 3 . This time is significantly lower in both group 2 and group 3 than group 1 (p= 0.0001) but the difference between group 2 and group 3 was not significant(p= 0.069) . based on table 2 after tourniquet is opened, the difference between group 3 and the other two groups in terms of the rate of pain is significant; whereas in the times 90 and 120 minutes the difference between the group 2 and the control group (group 1) was not significant.

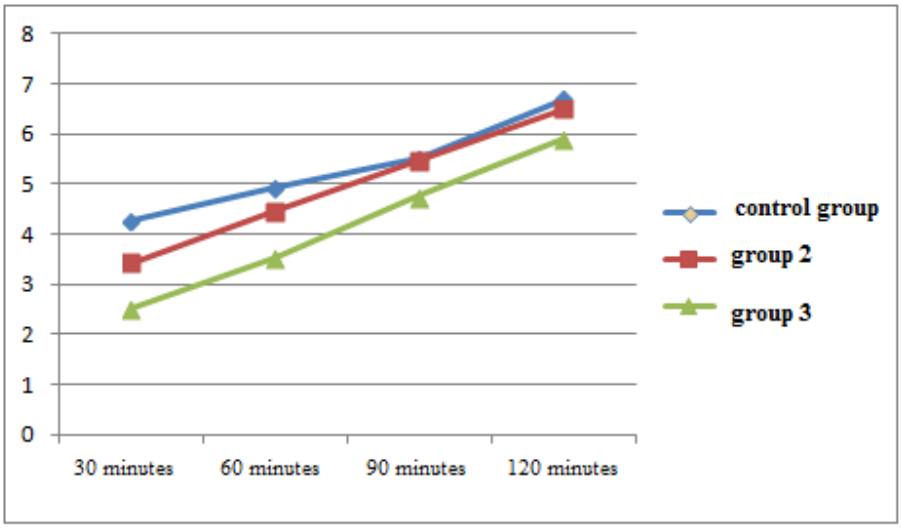


Graph 1 – mean of the rates of pain at various times after the beginning of surgery

Table 2 – mean of the rates of VAS after discharging the torniquet

	Group 1	Group 2	Group 3	P-value		
				2-3	P-3	P-2
30 minutes	4.27±1.2	3.43±0.57	2.53±0.63	0.0001*	0.0001*	0.0001*
60 minutes	4.93±0.74	4.47±0.57	3.53±0.63	0.0001*	0.0001*	0.018*
90 minutes	5.53±0.73	5.47±0.51	4.77±0.68	0.0001*	0.0001*	0.916
120 minutes	6.70±0.70	6.50±0.68	5.90±0.61	0.002*	0.0001*	0.478

The mean of the rates of pain at all intervals after the opening of the tourniquet in the group 3 has been significantly lower than the other two groups (F=4.126and P=0.001) (graph 2).



Graph 2 – mean of the rates of pain in various intervals after opening the tourniquet

Before starting the study, hemodynamic parameters such as blood pressure, heart rate and arterial oxygen saturation were measured and in this regard, there was no significant difference between these groups. After opening the tourniquet, systolic blood pressure (P=0.025) and diastolic blood pressure (P=0.010) in the group 3 were significantly lower than that of the control group (1) and in other subjects, the difference between the groups was not significant.

Table 3 – values of the hemodynamic parameters before and after the operation

		Group 1	Group 2	Group 3
Beginning of the study	**SBP**	120.8±11.5	123.4±6.1	120.8±5.5
	DBP	69.8±8.1	75.3±5.7	74.3±5.9
	HR	73.2±11.4	73.2±7.6	74.1±16.8
The tourniquet being opened	**SBP**	122.9±6.7	119.7±7.8	117.9±6.7
	DBP	78.1±6.2	73.3±6.6	72.6±5.8
	HR	81.1±10.1	81.1±8.5	84±14.5

DISCUSSION

The results obtained from the present research showed that using granisetron injected with 0.5% lidocaine was able to reduce the rate of postoperative pain of the patients who were the candidates for forearm orthopedic operations depending on its dose. This medicine has had long-term effects and after opening the tourniquet, it was able to lead to reduction of the pain of the patients to a considerable extent compared with the control group.

Granisetron, as a routine, is used at the time of anesthesia for preventing postoperative nausea and vomiting. However, many studies have been done which show the palliative effect of the 5HT3 antagonists in the reduction of organ's postoperative pain (9). Studies have shown that this group of medicine can block sodium channels like local anesthetics and has an analgesic effect (7). It has been proven that 5HT3 peripheral receptors take part in the path of pain relief. These peripheral receptors can be linked to opioid receptor and act as their agonist (15). Ma, et al., showed that using the granisetron/lidocaine combination can considerably reduce the pain caused by propofol injection (16). Ambesh, et al. also found out that pain felt at the time of propofol injection can be successfully eliminated by prescribing 4 milligrams of Ondansetron (17).

In the study of Farouk, et al., it was confirmed that adding a 5HT3 antagonist to lidocaine for creating intravenous regional anesthesia will significantly lead to the improvement of quality of anesthesia, reduction of the time of beginning and prolongation of the time of motor and sensory blockade , reduction of the pain of tourniquet and reduction of pain during and after the operation (8). In the study of Honarmand, et al., adding 8 milligrams of Ondansetron to lidocaine led to the significant reduction of the pain during and after the operation for 24 hours (9). The results of the two studies mentioned above comply with the results of the present study. Of course in the two studies mentioned above, only one dose of the medicine has been used; whereas in our study, 2 different doses of granisetron were used and given the obtained results, dose dependent effect of 5HT3 antagonist was confirmed .

It seems that local anesthetic effects of granisetron and the medicines that are in the same class as it, is in communication with their anti-nausea effects (7). It has been specified that receptors similar to the 5HT3 intestinal receptors in the primary afferent fibers exist not only in peripheral nerves but also in central nerves (18). These receptors also exist in the superficial lamina propria of the dorsal horn neurons. Arcrionic, et al., have stated that continuous infusion of ondansetron for preventing postoperative nausea and vomiting can reduce the analgesic effects of tramadol which is probably due to the block of 5HT3 CSF receptors (19). The results of the study of Stratz, et al., showed that 5HT3 receptor antagonists have anti-inflammatory effects and because of this feature of them that they can be effective on reducing postoperative pain (20). They also found out 5HT3 receptor antagonists can be used as an alternative or complementary for local usage of corticosteroids.

These anti-inflammation and analgesic effects of the 5HT3 receptor antagonists have been evaluated in various studies. Farber, et al., showed that tropisetron has an analgesic effect in patients in fibromyalgia pain (21). Also, the analgesic effect of alosetron in women with irritable bowel syndrome has been proven (22). Muller, et al., have also shown that local prescription of 5HT3 antagonists has a quick analgesic effect on various rheumatismal diseases (23).
We propose that in future study in this field, various doses and a larger number of 5HT3 receptor antagonist medicines shall be reviewed so that a medicine with more effectiveness and less side-effects would be introduced.

CONCLUSION

It seems that using granisetron can significantly lead to the reduction of pain during and after the surgery of the patients who were candidates for forearm operations. Given the limited side effects and proper prices of this

medicine, granisetron can be ordinarily used for reducing the pain of patients and also for preventing postoperative nausea and vomiting.

REFERENCES

[1] Brill S, Middleton W, Brill G, Fisher A. *Acta anaesthesiologica Scandinavica*. **2004**;48(1):117-22.
[2] Hutchinson DT, McClinton MA. *The Journal of hand surgery*. **1993**;18(2):206-10.
[3] Choyce A, Peng P. *Journal canadien d'anesthesie*. **2002**;49(1):32-45.
[4] Estebe JP, Le Corre P, Levron JC, Le Moing JP, Le Naoures A, Ecoffey C. *Journal of clinical anesthesia*. **2002**;14(8):578-83.
[5] Zeitz KP, Guy N, MalmbergAB, Dirajlal S, Martin WJ, Sun L, et al. *The Journal of neuroscience : the official journal of the Society for Neuroscience*. **2002**;22(3):1010-9.
[6] Long-term Use of Ondansetron, Dolasetron and Granisetron for the Prevention of Nausea and Vomiting: A Review of the Clinical Effectiveness and Safety. Ottawa (ON) **2014**.
[7] Ye JH, Mui WC, Ren J, Hunt TE, Wu WH, Zbuzek VK. *Anesthesia and analgesia*. **1997**;85(5):1116-21.
[8] Farouk S. *European journal of anaesthesiology*. **2009**;26(12):1032-6.
[9] Honarmand A, Safavi M, Adineh-Mehr L. *Advanced biomedical research*. **2013**;2:52.
[10] Ahmed A, Sengupta S, Das T, Rudra A, Iqbal A. *Indian journal of anaesthesia*. **2012**;56(2):135-8.
[11] Hsu ES. *American journal of therapeutics*. **2010**;17(5):476-86.
[12] Singh DK, Jindal P, Singh G. *Saudi journal of anaesthesia*. **2011**;5(1):50-4.
[13] Yarker YE, McTavish D. Granisetron. *Drugs*. **1994**;48(5):761-93.
[14] Nasr YM, Waly SH. *Egyptian Journal of Anaesthesia*. **2012**;28(1):37-42.
[15] Gregory RE, Ettinger DS. *Drugs*. **1998**;55(2):173-89.
[16] Ma YS, Lin XM, Zhou J. *Journal of Sichuan University Medical science edition*. **2009**;40(3):536-8.
[17] Ambesh SP, Dubey PK, Sinha PK. *Anesthesia and analgesia*. **1999**;89(1):197-9.
[18] Kidd EJ, Laporte AM, Langlois X, Fattaccini CM, Doyen C, Lombard MC, et al. *Brain research*. **1993**;612(1-2):289-98.
[19] Arcioni R, della Rocca M, Romano S, Romano R, Pietropaoli P, Gasparetto A. *Anesthesia and analgesia*. **2002**;94(6):1553-7, table of contents.
[20] Stratz T, Muller W. *Scandinavian journal of rheumatology Supplement*. **2000**;113:66-71.
[21] Farber L, Stratz TH, Bruckle W, Spath M, Pongratz D, Lautenschlager J, et al. *International journal of clinical pharmacology research.* **2001**;21(1):1-13.
[22] Camilleri M, Mayer EA, Drossman DA, Heath A, Dukes GE, McSorley D, et al. *Alimentary pharmacology & therapeutics.* **1999**;13(9):1149-59.
[23] Muller W, Fiebich BL, Stratz T.*Zeitschrift fur Rheumatologie*. **2006**;65(6):546, 8-52.