Original Article

Which one is more efficient on propofol 2% injection pain? Magnesium sulfate or ondansetron: A randomized clinical trial

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Abstract

Background: Painful sensation has been reported after propofol injection in most of the patients but no definite mechanism for this painful sensation has been proposed yet. The present randomized clinical trial compares analgesic effect of ondansetron, magnesium sulphate (MS) and placebo on patients after propofol 2% injection.

Materials and Methods: The present randomized clinical trial with parallel design was performed on 90 patients American Society of Anesthesiologists I-II undergoing general anesthesia within vitrectomy operation with propofol induction. Subjects were randomly allocated into three groups with 30 patients each: (1) MS group (2) ondansetron group and (3) normal saline (NS) group as placebo group. Anesthesia induction and maintenance were the same between groups. Pain intensity of propofol injection in subjects was assessed by a four-point scale (none 0, mild 1, moderate 2 and severe 3) at four time intervals (5, 10, 20 and 25 s) after injection.

Results: MS and ondansetron had significant impacts on pain reduction after propofol 2% injection in comparison with NS as placebo. Comparing two trial groups did not have any significant priority for analgesic impact.

Conclusion: Using ondansetron or MS had no priority on each other on declining propofol injection induced pain.

Key Words: Magnesium sulfate, ondansetron, pain, propofol

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INTRODUCTION

Propofol is a common intravenous anesthetic agent used for induction and maintenance of general anesthesia. However, pain has been reported after propofol injection in almost 70% of patients.[1,2] Patients explained their pain experiences as extremely sharp, aching or burning pain. This has been ranked as the seventh most important problem in current practice of clinical anesthesia by American anesthesiologists.[3] Unfortunately the clinical problem of propofol induced pain remains unresolved.[1,4,5] Although investigators did not find clear and definite pathway or mechanism for pain induce by propofol, they designed different interventions in the trial studies for the assessment of the role of some other drugs to alleviate pain of intravenous propofol injection.[1]

In our practice, ondansetron is routinely administered as premedication to prevent postoperative nausea and vomiting in patients scheduled for laparoscopic

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and some ophthalmic surgeries. Some investigators demonstrated that ondansetron, a specific 5-HT antagonist, blocks Na channels in rat brain neurons. They also found that ondansetron is 15 times more potent than lidocaine in causing numbness when injected under the skin.[6]

There are some hypotheses that intravenous administration of ondansetron might decrease propofol injection induced pain.[7-9] However, there is relatively little published data about the efficacy of ondansetron on the propofol induced pain.[8,9]

Magnesium, as an N-methyl-D-aspartate (NMDA) antagonist, has shown antinociceptive effect in humans. Primarily its effect is based on the regulation of calcium ion influx into the cell, which is a natural physiological analgesic mechanism. This drug has been used as an adjuvants in neuroaxial and peripheral blocks and has been studied to attenuate the pain by propofol injection as well.[9,10] In the present randomized clinical trial in patients having ophthalmologic operation, we used ondansetron to assess their analgesic impact compared with magnesium sulfate (MS).

MATERIALS AND METHODS

The present randomized clinical trial with parallel design was approved by Ethical Committee of Iran University of Medical Sciences and informed consents were obtained from all study population members. Considering alpha = 0.05, beta = 20% and the calculation power 80%; sample size was calculated as 90 patients. The study population was randomly selected from patients undergoing vitrectomy operation using general anesthesia with American Society of Anesthesiologists physical status I and II. Range of age was between 20 and 70 years. The clinical trial was performed in Hazrat Rasul Medical Complex between September 2012 and April 2013.

Patients who had known sensitivity to propofol or ondansetron, were receiving analgesic or sedative medication in the last 24 h; had infection on the dorsum of the left hand, indications for rapid sequence intubation; presence of cardiac conduction defects; epilepsy; and use of antiarrhythmic medications, thin dorsal veins, renal and liver diseases, neuro-muscular diseases, pregnant women and uncooperative patients were excluded.

Entrance chance of all population to each of trial groups was the same and there was not any rewards or penalties for patients participating into any specific trial group. Allocation rate of study population into trial groups was the same and equally 30 patients were allocated to each of three trial groups with a total number of 90 patients. A table of random numbers was used as follows: The MS group received 150 mg MS (via injection of 3 ml of 500 mg MS which was diluted into 10 ml normal saline (NS) 0.9%). The ondansetron group received four milligrams ondansetron (3 ml diluted into NS 0.9%) and in NS group, 3 ml NS 0.9% as injected for control population. All syringes were prepared by another colleague and were similar and the injectionist and evaluator were not aware of the contents. Patients were monitored in the operation room with Electrocardiography, Pulse-oximetry, capnography and non-invasive blood pressure test. A 20-gauge angiocather was inserted into a superficial radial vein of the left hand followed by infusion of 500 ml/h Ringer's solution. After 10 min, Ringer's infusion was stopped and for gravity drainage of venous blood, the arm with the angiocather was elevated for 20 s. Then a pneumatic tourniquet on the upper arm was inflated to 80 mm Hg for occluding the venous drainage. The solutions were prepared by an independent anesthesiologist and the researcher was not aware of the contents of the solutions. Over a period of 10 s one of the pretreatment solutions was injected to the patient. At 1 min later, the occlusion was released and two milliliters Propofol 2% (40 mg) (Lipuro 2%, B Braun, Germany) was injected from angiocatheter over a period of 10 s. Before propofol injection no other analgesics or sedatives were administered. Level of pain was measured in patients of three trial groups at four time intervals (5, 10, 20 and 25 s) after intervention; Because the pain of propofol injection begins immediately after injection and also propofol causes loss of consciousness in <1-2 min, it was necessary to monitor very quickly. Pain was graded from 0 to 3 in accordance to the scale advocated by McCrirrick and Hunter: 0 - no pain or no response to questioning; 1 - mild pain, reported in response to questioning Propofol only without any behavioral signs; 2 - moderate pain, reported in response to questioning and accompanied by a behavioral sign or pain reported spontaneously without questioning; 3 - severe pain, strong vocal response or response accompanied by facial grimacing, arm withdrawal, or tears.[11]

Anesthesia induction was performed in the same way in three groups with propofol (2 mg/kg) and Fentanyl (2-3 μg/kg) and Cisatracurium (0.2 mg/kg). Maintenance of anesthesia was achieved with Propofol infusion (100 μg/kg/min). Blood pressure and heart rate measurements were recorded in arrival time, 3rd min after induction and 5th min after intubation.

Statistical analysis

Study data were entered into SPSS version 16.0 software (SPSS inc., Chicago, IL, USA) and pain levels were presented as qualitative groups. Study data were analyzed with independent Analysis of Variance test for comparing mean of quantitative variables including blood pressure and heart rate between study groups and Chi-square test for comparing qualitative variables such as visual analog scale level between study groups. All statistical tests were performed with 95% confidence interval and $P < 0.05$ were assumed as significantly meaningful.

RESULTS

Finally, 48 males and 42 females participated in the present randomized clinical trial. Mean of age and body mass index (BMI) in study subjects were 43.43 ± 14.05 (18-95) years and 23.77 ± 2.59 (19-30) kg/m^2. Mean of age ($P = 0.73$) and BMI ($P = 0.95$) had no significant differences between trial groups. Gender of subjects had no significant association with trial groups ($P = 0.58$). At the beginning of the study (baseline time) mean of arterial blood pressure ($P = 0.11$) and heart rate ($P = 0.57$) in study subjects had no significant differences between study groups [Table 1].

After anesthesia induction in study subjects, mean of arterial blood pressure 3 min after induction (before intubation) ($P = 0.27$) and 5 min after intubation ($P = 0.13$) had no significant difference between three trial groups. Mean of heart rate 3 min after induction ($P = 0.57$) and 5 min after intubation ($P = 0.24$) had no significant difference between three trial groups [Table 2].

After 5 s from intervention, incidence of pain was 76% for NS group, 26.7% for ondansetron group and 26.6% for MS group. There is a significant difference in analgesic impact between the two drugs with NS ($P < 0.001$), but there is no significant association in terms of analgesic impact between the two drugs ($P = 0.82$). After 10 s, there is a significant association in analgesic impact between the two drugs with NS ($P < 0.001$), but there is no significant association between analgesic impact between the two drugs ($P = 0.70$). After 20 s, [Table 3] there is significant difference in analgesic impact between two drugs with NS ($P < 0.001$), but there is no significant association in terms of analgesic impact between two drugs ($P = 0.58$). After 25 s, there is significant difference in analgesic impact between two drugs with NS ($P < 0.001$), but there is no significant association in terms of analgesic impact between two drugs ($P = 0.58$) [Figures 1-4].

DISCUSSION

The present study showed that using drugs such as MS or ondansetron had significant impact on declining pain after propofol injection in comparison with NS as placebo. Between the two trial drugs, neither of them had a significance priority in analgesic impact.

Propofol is one of the common drugs in anesthesia induction and maintenance, but it induces pain and can cause extreme distress among patients.[12] Mechanism

Table 1: Basal comparison of study variable between trial groups

Basal variable	Study groups			Total	*P* value
	Magnesium sulfate	Ondansetron	Normal saline		
Sex (%)					
Female	12 (28.6)	16 (38.1)	14 (33.3)	42 (100)	0.585
Male	18 (37.5)	14 (29.2)	16 (33.3)	48 (100)	
Age (year)	45.10±15.06	42.57±13.58	42.63±13.88	43.43±14.05	0.733
Body mass index (kg/m^2)	23.85±3.08	23.65±2.49	23.80±2.18	23.77±2.58	0.954
Mean arterial blood pressure (mmHg)	95.83±17.66	97.46±14.54	89.63±3.08	94.31±15.18	0.108
Heart rate (beat/min)	78.53±12.03	77.13±12.52	75.46±8.86	77.04±11.15	0.571

Table 2: Mean of arterial blood pressure and heart rate in different time between trial groups

Study variable	Normal saline	Ondansetron	Magnesium sulfate	*P* value
Mean of arterial blood pressure before anesthesia induction	95.83±17.66	97.44±14.54	89.63±12.21	0.11
Mean of arterial blood pressure 3rd min after anesthesia induction	86.27±15.86	88.0±11.59	82.70±10.87	0.28
Mean of arterial blood pressure after intubation	98.87±14.87	100.3±12.78	93.53±10.94	0.11
Mean of arterial blood pressure 5th min after intubation	94.23±12.35	89.00±11.45	91.67±11.00	0.13
Mean of heart rate before anesthesia induction	78.53±12.03	77.13±12.52	75.47±8.66	0.09
Mean of heart rate 3rd min after anesthesia induction	79.37±14.38	83.93±13.48	79.33±10.33	0.57
Mean of heart rate after intubation	88.47±10.72	92.33±12.12	87.96±9.63	0.29
Mean of heart rate 5th min after intubation	77.56±9.96	77.10±15.27	78.53±7.13	0.24

Table 3: Frequency of pain intensity between study groups

Visual analog scale scores	Study groups (%)			Total	*P* value
	Normal saline	Ondansetron	Magnesium sulphate		
At 5 s					
None	7 (13.7)	22 (43.1)	22 (43.1)	51 (100)	<0.001
Mild	11 (45.8)	6 (25.0)	7 (29.2)	24 (100)	
Moderate	12 (80.0)	2 (13.3)	1 (6.7)	15 (100)	
Sever	-	-	-	-	
At 10 s					
None	4 (9.3)	19 (44.2)	20 (46.5)	43 (100)	<0.001
Mild	2 (16.7)	6 (50)	4 (33.3)	12 (100)	
Moderate	14 (58.3)	5 (20.8)	5 (20.8)	24 (100)	
Sever	10 (90.9)	-	1 (9.1)	11 (100)	
At 20 s					
None	4 (9.8)	19 (46.3)	18 (43.9)	41 (100)	<0.001
Mild	-	-	1 (100)	1 (100)	
Moderate	11 (40.7)	7 (25.9)	9 (33.3)	27 (100)	
Sever	15 (71.4)	4 (19)	2 (9.5)	21 (100)	
At 25 s					
None	4 (9.8)	19 (46.3)	18 (43.9)	41 (100)	<0.001
Mild	-	-	1 (100)	1 (100)	
Moderate	11 (40.7)	7 (25.9)	9 (33.3)	27 (100)	
Sever	15 (71.4)	4 (19)	2 (9.5)	21 (100)	

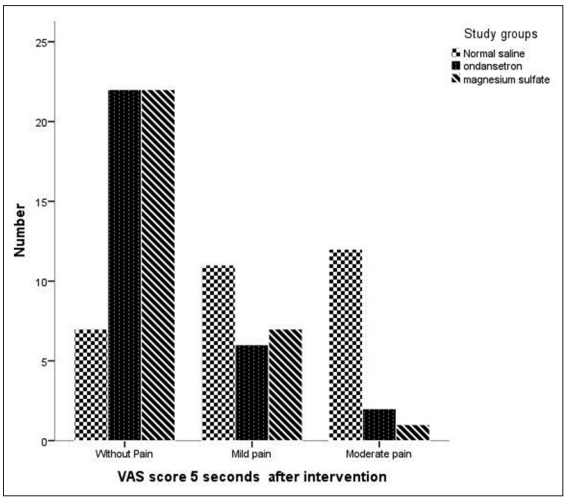

Figure 1: Frequency of pain intensity between patients of two drugs at 5 min after intervention (*P* = 0.00)

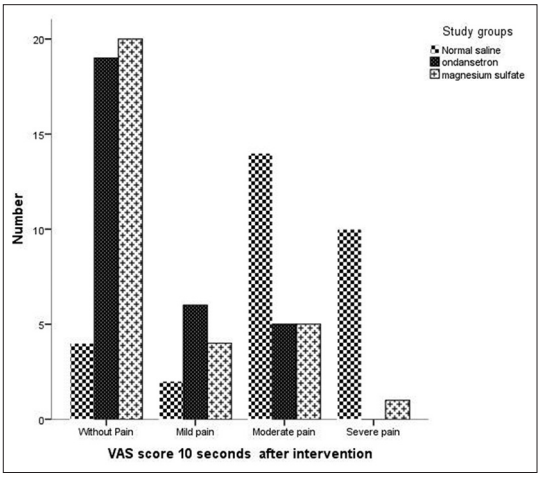

Figure 2: Frequency of pain intensity between patients of two drugs at 10 min after intervention (*P* = 0.00)

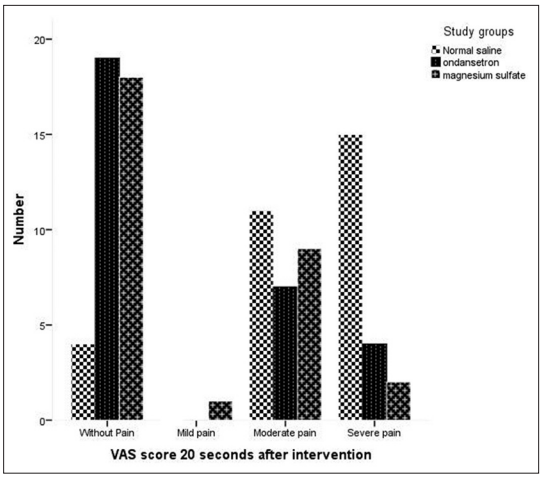

Figure 3: frequency of pain intensity between patients of two drugs at 20 min after intervention (*P* = 0.00)

of pain induction by propofol in patients is not unclear. Some investigators believe that propofol as a member of phenol group can irritate the skin; mucus membrane and venous intima immediately stimulate nociceptors and free nerve endings.[7] Some other investigators found that propofol might increase the contact between aqueous phases of propofol and free nerve endings, resulting in delayed pain within half a minute.[13]

Some studies reported that propofol had no effect on the concentration of bradykinin in plasma compare with placebo.[14,15] Yull *et al*., in their study reported that propofol induced pain might be related to the release of local kininogens and nonstroidal anti-inflammatory drugs may have a role in pain reduction.[16] Although injection pain of propofol has been reported formerly, this could not cause a limitation and physicians try to solve this discomfort. Some interventions such as injecting lidocaine or other drugs prior to propofol injection had been assessed in randomized clinical trials.[1,2,7,17-20]

Ondansetron has blocking ability for sodium channels. Peripheral 5-HT3 receptors involve nociceptive pathways.[6] Ondansetron binds to the opioid μ receptors in humans and exhibits agonist activity.[21] As a result of its multifaceted actions as an Na channel blocker also, ondansetron may potentially be used to alleviate pain induced by a drug such as propofol.[22-24]

Magnesium acts both as an intracellular calcium and a NMDA receptor antagonist. With the second effect it couples to an ion channel permeable to K^+ and Ca^+ in a voltage-dependent manner. Magnesium also

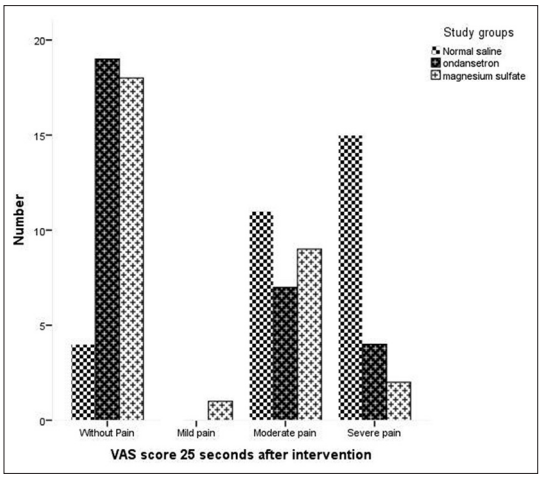

Figure 4: Frequency of pain intensity between patients of two drugs at 25 min after intervention ($P = 0.00$)

has a vasodilatory effect mediated by endothelium-derived nitric oxide. These mechanisms may explain the ability of magnesium to reduce pain on the injection of propofol.[25,26] In our study, Magnesium showed significantly better pain control compared with placebo group which is similar to previous investigations on propofol 1%. In this study we used propofol 2% which is reported to have more rapid loss of consciousness, more prolonged sedation and delivers fewer loads of lipids to the blood stream and few studies have been done on its induced pain on injection.[25] In conclusion, there was no priority between the two drugs for prescribing in declining pain accompanied with propofol injection.

Limitation of study

In the first 5 s the incidence of pain in two drug groups were lower comparing with the other measured intervals; we recommend using higher dosages of ondansetron and magnesium sulphate in future studies to have longer pain control in the 1 min interval.

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