RESEARCH ARTICLE

Comparing Intravenous Lidocaine, Ondansetron and Their Combination on Reducing Pain of Injection of Propofol

Sussan Soltani Mohammadi[1]*, Maliheh Khosravi[1], Gita Shoeibi[1]

Background: Propofol is a widely used intravenous anesthetic drug. One of its side effects is pain during injection. We investigate the effects of intravenous ondansetron, lidocaine, and their combination on pain reduction of intravenous propofol.

Methods: Eighty eight women with ASA class (American Society of Anesthesiologists) classification I-II patients undergoing elective gynecologic surgeries allocated into four equal groups including normal saline, lidocaine, ondansetron, and the combination of two drugs. All drugs were prepared in the same volume of 5 ml. Pain during propofol injection after intravenous injection of study drugs was assessed using Numeric Rating Scale (NRS). Demographic data and pain scores were recorded and compared in all patients.

Results: The overall incidence of pain on propofol injection was lower in lidocaine (4%), ondansetron (9%) and combination group (zero) than in saline group (72%) (P=0.001).

Sixteen patients (72%) in saline group had moderate to severe pain. Two patients (9%) in ondansetron group and one patient (4%) in lidocaine group had mild pain (P= 0.06). No patient in lidocaine, ondansetron and combination group had moderate to severe pain (P>0.05).

Conclusion: Pretreatment with ondansetron with or without lidocaine is effective in preventing pain from propofol injection.

Keywords: lidocaine; Ondansetron; Pain; Propofol

Propofol is one of the most popular intravenous anesthetic drugs. It has been used widely because of its numerous advantages including rapid induction and recovery and reducing postoperative nausea and vomiting. However, the incidence of pain following propofol injection is seen in almost 70% of patients, in the absence of other pretreatments [1-3].

The mechanism by which propofol causes pain on injection is not fully understood. However, the activation of pain mediators, such as the kinin cascade system, has been suggested as a possible cause [3]. A Number of different interventions have been used to alleviate pain incidence and intensity during propofol injection, including administrating lidocaine, heating or cooling, diluting propofol, injecting it into a large vein, and using ondansetron, metoclopramide, clonidine, ketamine, narcotics, and sodium thiopental. It is not clear, which is the most effective [4-11].

In a study by Lee et al on 200 patients undergoing general anesthesia with propofol, they concluded that pretreatment with ramosetron before the injection of microemulsion propofol is more effective than lidocaine or normal saline in preventing pain from a microemulsion propofol injection [12].

In another study by Singh et al on 120 patients to compare lidocaine and ramosetron on propofol injection pain, they concluded that pretreatment with romasetron and lidocaine are equally effective in preventing pain from propofol injection [13].

The aim of our study is to evaluate the efficacy of ondansetron, lidocaine and their combination on reduction of pain induced by propofol injection.

Methods

This randomized double blinded controlled trial was performed in our hospital since April to September of 2013.The study protocol conformed to the ethical guidelines of the 1989 Declaration of Helsinki and ethical approval was provided by the Ethical Committee of Tehran University of Medical Sciences.

Eighty eight women with ASA class (American Society of Anesthesiologists classification) I-II aged 18-70 years, who were scheduled for elective gynecologic surgeries under general anesthesia, were included and written informed consent was obtained separately before surgery. Patients with history of allergy to local anesthetics, neurological disorders, use of analgesic or sedative drugs in the 24 hours prior to surgery and drugs that act on serotonin receptors or

From the [1]Department of Anesthesiology and Critical Care, Dr Shariati Hospital, Tehran University of Medical Sciences, Tehran, Iran.

Received: 2 October 2015, Revised: 20 October 2015, Accepted: 3 November 2015

The authors declare no conflicts of interest.

Funding/Support:

The source of financial support of study was Students' Scientific Research Center of Tehran University of Medical Sciences grant. Role of the Sponsors: The funding organizations were public institutions, and had no role in the design and conduct of the study, collection, management, and analysis of the data; or preparation, review, and approval of the manuscript.

*Corresponding author: Sussan Soltani Mohammadi, MD. Department of Anesthesiology & Critical Care, Dr Shariati Hospital, Tehran University of Medical Sciences, Tehran, Iran. E-mail: soltanmo@sina.tums.ac.ir

affect the level of serotonin were excluded. Patients were randomly allocated into four equal groups including saline control (group S, n=22), ondansetron (4mg, group N n=22), lidocaine (20 mg, group L, n=22) and ondansetron 4mg plus lidocaine 20mg (group C, n=22). Randomization was done by means of computer-generated codes. Study drugs were prepared in the same shape of 5ml syringe, according to the randomization code, by an anesthesia staff that was not involved in the study. Envelopes containing the information of the randomization were sealed and kept in the patient's folder until the end of the study period.

On arrival to the operating room, standard monitoring was applied to all patients including pulse oximeter, electrocardiogram, noninvasive arterial blood pressure (NIBP).A 20-gauge intravenous catheter was placed on the dorsum of non-dominant hand of the patients and 3ml/kg lactate Ringer's solution was infused before anesthesia. Before surgery, patients were educated about the numeric rating scale (NRS) in which; a score of 0 to 3, corresponding to 0=no, 1=mild, 2=moderate, 3=severe pain. Patients received no premedication. While the venous drainage was occluded by placing an air-filled tourniquet (pressure inflated to 70 mm Hg) on the upper arm by an assistant; a blinded anesthetist injected prepared study drugs or saline according to the allocation. The occlusion was released after 30 seconds. First one-fourth of induction dose (2 mg/kg) of propofol was injected slowly over 10 seconds. The pain intensity was measured based on NRS, as follows: 0 (No pain), 1(Mild pain; mild arm and facial movements, verbal expression), 2(Moderate pain; obvious arm movements and grimacing) and 3(severe pain; pulling back the arm, moaning and complaining of pain and describing it as irresistible). The remaining propofol was injected after pain assessment for induction of anesthesia. If the patient lost consciousness before pain assessment she was excluded from the study. In total, of ninety six patients scheduled consecutively for elective gynecologic surgeries, six were excluded due to fulfilling the exclusion criteria and two others for loss of consciousness before pain assessment. Finally 88 patients were allocated for statistical analysis.

Statistical analysis

A sample size of 22 patients by group was calculated to detect a reduction of 50% in incidence of pain with a power of 80% and a significance level of 5%. Statistical analysis was performed using SPSS package (version 19, SPSS, Chicago, IL).Normality of distribution of data was tested by the Kolmogorov-Simirnov test. For comparison of quantitative variables between the four groups, the ANOVA test and for qualitative variables the Chi-squared test or Fisher's exact test were used. The statistically significant level was $P<0.05$.

Results

There were no significant differences in demographic data including age, weight and ASA classes between the study groups (Table1). The overall incidence of pain on propofol injection was lower in lidocaine (4%), ondansetron (9%) and combination group (zero) than in saline group (72%) (P=0.001). There was no significant difference in the incidence of pain between lidocaine, ondansetron and combination group (P=0.06). Sixteen patients (72%) in saline group had moderate to severe pain. Two patients (9%) in ondansetron group and one patient (4%) in lidocaine group had mild pain (P= 0.06).No patient in combination group had pain (Table2). There were no complications related to study drugs in the groups.

Table 1- Comparing demographic data between the study groups

Variables	Group L (n=22)	Group O (n=22)	Group C (n=22)	Group S (n=22)
Age (years)	42.7±13.7	45.3±10.1	41.8±14.3	46.3±10.1
Weight (kg)	65.4±9.0	66.4±9.7	65.7±10.3	69.8±12.9
ASA class I/II (n)	11/11	9/13	10/12	11/11

Group S: Patients who received normal saline, Group L: Patients who received lidocaine 20 mg, Group O: Patients who received ondansetron 4 mg, Group C: Patients who received combined drugs (lidocaine20mg+ondansetron 4mg), Data are presented as mean± SD

Table 2- Incidence and severity of pain following propofol injection

Variables	Group S (%)	Group L (%)	Group O (%)	Group C (%)	P-value
Pain (Overall)	16(72)	1(4)	2(9)	0	0.001
0(No pain)	6(27)	21(95)	20(90)	22(100)	0.01
1(Mild pain)	0	1(4)	2(9)	0	0.06
2(Moderate pain)	4(18)	0	0	0	0.05
3(Severe pain)	12(54)	0	0	0	0.03

Data is presented as number of patients (%). Group N: Patients who received normal saline, Group L: Patients who received lidocaine 20 mg, Group O: Patients who received ondansetron 4 mg, Group C: Patients who received combined drugs(lidocaine20mg+ondansetron 4mg).

Discussion

Propofol-induced pain is a common problem and can be very distressing to the patient. It has been ranked by American anesthesiologists as the seventh most important drawback of current clinical anesthesiology.4In this study, the incidence of injection pain was 72% in the placebo group. The incidence of pain in the groups pretreated with ondansetron 4 mg, lidocaine 20mg or combination of ondansetron 4mg and lidocaine 20 mg were 9%, 4% and

zero respectively. These results prove to be effective in reducing injection pain by ondansetron with or without lidocaine.

Although the reason for pain during propofol injection is not completely clear, many different methods have been used for decreasing its frequency and intensity. The most popular method for reducing injection pain is to mix lidocaine with propofol. This technique is easy, fast, does not affect the physiochemical property of the drug and more importantly is associated with a clinically and statistically significant reduction in the incidence and severity of pain [13].

The mechanism of the analgesic effect of lidocaine remains unclear, but is generally considered to be by the inhibition of the kinnin cascade or the dilutional effect on propofol [11]. Analgesic effects of lidocaine on propofol injection pain are not solely related to its local analgesic properties. Lidocaine decreases propofol solution pH, which leads to migration of propofol to the lipid phase and decline of its concentration in the aqueous phase, which reduces pain, eventually [14-15]. In a study by Singh et al on 120 patients with ASA class I -II that were randomly assigned into three groups (40 in each) there was significant reduction in the pain for propofol injection and both lidocaine and ramosetron were equally effective. Their results correlated with our study [13].

Another study was conducted by Ambesh et al on 80 patients allocated into two equal groups. Group I received 2 mL of intravenous 0.9% saline pretreatment, and Group II received ondansetron (4 mg in 2 mg/mL solution) pretreatment in the dorsum of the hand, followed by propofol 1 min later. Pain was reduced significantly in the ondansetron group. Their results correlated with our study, however we also used lidocaine alone and in combination with ondansetron [5]. Further study may be required on the effect of propofol injection pain according to lidocaine dose change and tourniquet compression time.

In conclusion pretreatment with ondansetron 4 mg with or without lidocaine 20 mg are equally effective in preventing pain from propofol injection.

Acknowledgement

Thanks to the cooperation of physicians, nurses, anesthesia staff and also patients.

References

1. Zahedi, H, Maleki, A. Ondansetron Pretreatment Reduces Pain on Injection of Propofol. Acta Medica Iranica. 2012; 50(4):239-243.
2. Tan CH, Onsiong MK. Pain on injection of propofol. Anaesthesia 1988; 53:468-76.
3. Cheong MA, Kim KS, Choi WJ. Ephedrine reduces the pain from propofol injection. Anesth Analg. 2002; 95(5):1293-6.
4. Macario A, Weinger M, Truong P, Lee M. Which clinical anesthesia outcomes are both common and important to avoid? The perspective of a panel of expert anesthesiologists. Anesth Analg 1999; 88(5):1085-91.
5. Ambesh SP, Dubey PK, Sinha PK. Ondansetron pretreatment to alleviate pain on propofol injection: a randomized, controlled, double-blinded study. Anesth Analg.1999; 89(1):197-9.
6. Ishiyama T, Kashimoto S, Oguchi T, Furuya A, Fukushima H, Kumazawa T. Clonidine-ephedrine combination reduces pain on injection of propofol and blunts hemodynamic stress responses during the induction sequence. J Clin Anesth. 2006; 18(3):211-5.
7. Scott RP, Saunders DA, Norman J. Propofol: clinical strategies for preventing the pain of injection. Anaesthesia. 1988; 43(6):492-4.
8. Saadawy I, Ertok E, Boker A. Painless injection of propofol: pretreatment with ketamine vs thiopental, meperidine, and lidocaine. Middle East J Anesthesiol. 2007; 19(3):631-44.
9. O'Hara JR Jr, Sprung J, Laseter JT, Maurer WG, Carpenter T, Beven M, et al. Effects of topical nitroglycerin and intravenous lidocaine on propofol-induced pain on injection. Anesth Analg. 1997; 84(4):865-9.
10. King SY, Davis FM, Wells JE, Murchison DJ, Pryor PJ. Lidocaine for the prevention of pain due to injection of propofol. Anesth Analg. 1992; 74(2):246-9.
11. Ye JH, Mui WC, Ren J, Hunt TE, Wu WH, Zbuzek VK. Ondansetron exhibits the properties of a local anesthetic. Anesth Analg. 1997; 85(5):1116-21.
12. Lee HY, Kim SH, So KY. Prevention of microemulsion propofol injection pain: a comparison of a combination of lidocaine and ramosetron with lidocaine or ramosetron alone. Korean J Anesthesiol. 2011; 61(1):30-4.
13. Singh D, Jagannath S, Priye S, Shivaprakash, Kadli C, Reddy D. Prevention of propofol injection pain: Comparison between lidocaine and ramosetron. J Anaesthesiol Clin Pharmacol. 2014; 30:213-6.
14. Shao X, Li H, White PF, Klein KW, Kulstad C, Owens A. Bisulfite-containing propofol: is it a cost-effective alternative to Diprivan for induction of anesthesia? Anesth Analg. 2000; 91(4):871-5.
15. Gehan G, Karoubi P, Quinet F, Leroy A, Rathat C, Pourriat JL. Optimal dose of lignocaine for preventing pain on injection of propofol. Br J Anaesth. 1991; 66(3):324-6.