Original Research Article

Indian Journal of Anesthesia and Analgesia
2019; 6(2) (Part - I): 465-469
DOI: http://dx.doi.org/10.21088/ijaa.2349.8471.6219.16

Low Dose Ketamine for Prevention of Propofol Injection Pain

SP Sharma[1], Raghu K[2], Nived Mohanan[3], Damodar P[4]

[1]Assistant Professor, [3,4]Post Graduate, Department of Anaesthesiology, Command Hospital (Air Force) Bangalore, Karnataka 560007, India. [2]Anesthesiologist, Department of Anaesthesiology, 4 Air Force Hospital, Kalaikunda, West Midnapore (D), West Bengal 721303, India.

Abstract

Background and aims: Pain on injection of propofol is a well-known side effect faced by all anesthesiologists in their day to day practice. The aim of the study was to assess the efficacy of low dose ketamine in the prevention of pain on injection of propofol. *Materials and methods:* A prospective, randomized, and double-blind study was conducted on 100 patients, from either gender, aged 20-50 years, of the American Society of Anaesthesiologists Grade I or II, scheduled for various surgeries under general anesthesia. The patients were randomly divided into two groups of 50 each to receive either ketamine 0.5 mg/kg (Group K) or saline (Group S) infusion over 10 min. Venous drainage was occluded manually for one minute. This was followed by an injection of propofol 2 mg/kg IV over 25s. The patients were asked for pain on injection every 5s until the loss of consciousness. The pain scoring was done using McCririck and Hunter scale. The primary outcome of the study was the incidence of pain on propofol injection. Secondary outcomes such as increased secretions, emergence agitation were recorded. *Results:* Nine patients in group K (18%) and 42 patients in group S (84%) developed pain on injection of propofol. The incidence of pain was statistically significant between the two groups ($p = < 0.001$). Three patients in group K (6%) and 23 (46%) patients in group S had severe pain ($p = < 0.001$). Three patients in group K experienced increased secretions, which was not significant in comparison with the other group (6% vs 0%, $p = 0.242$). Four patients in group K had emergence agitation, but this was again not statistically significant when compared to group S (8% vs 0%, $p = 0.117$). *Conclusion:* We conclude that pretreatment of a smaller dose of ketamine was effective in the prevention of pain on injection of propofol without major side effects.

Keywords: Ketamine; propofol; pain; injection.

How to cite this article:

SP Sharma, Raghu K, Nived Mohanan et al. Low Dose Ketamine for Prevention of Propofol Injection Pain. Indian J Anesth Analg. 2019;6(2):465-469.

Introduction

Propofol is the most commonly used intravenous induction agent during general anaesthesia. Main advantages of Propofol are rapid onset, short duration of action and easy titration [1]. Despite these advantages, about three out of five patients experience pain on injection of propofol, with one of these patients reporting severe or excruciating pain. Pain on Propofol injection is considered as a seventh most important problem faced by anesthesiologists [2].

Explanations given for pain on injection include endothelial irritation, osmolality difference, and activation of pain mediators [3]. Many methods have been introduced to reduce the incidence of pain which includes adding lidocaine to propofol, cooling of propofol, diluting the propofol solution, injecting propofol into a larger vein, and pretreatment with IV injection of lidocaine,

Corresponding Author: Raghu K, Anesthesiologist , Department of Anesthesiology, 4 Air Force Hoapital, Kalaikunda, West Midnapore (D), West Bengal 721303, India.

E-mail: raghunandan007@gmail.com

Received on 23.11.2018, **Accepted on** 26.12.2018

metoclopramide, ondansetron or ketamine with or without a tourniquet [4-6].

Ketamine, an NMDA receptor agonist mainly used as an induction agent found to reduce the pain on propofol injection in smaller doses by virtue of its local anaesthetic property [7]. The present study was conducted to evaluate the effect of a small dose of ketamine in the prevention of propofol-induced pain on injection.

Materials and methods

This was a prospective, randomised, double-blind study undertaken after taking approval from our Institutional ethical committee during the period from November 2017 to March 2018. The study involved 100 patients from either gender aged 20-50 years, of the American Society of Anaesthesiologists (ASA) grade I or II, scheduled for various elective surgeries under general anaesthesia. Excluded from the study were patients with known hypersensitivity to propofol, history of drug abuse, psychiatric, cardiovascular, renal, hepatic and thyroid disease. All patients were visited on the day prior to the surgery, explained in detail about the anaesthetic procedure and written informed consent was obtained. Patients were kept nil orally from 12 O'clock midnight prior to the day of surgery.

Inside the operating room monitors like pulse oximetry, non-invasive blood pressure, electrocardiogram were connected and basal values were recorded. An 18 gauge IV cannula was secured in the vein on the non-dominant hand. Patients were randomly allocated to two groups (Group K or Group S) using a computer-generated table with random numbers. Group K received 0.5 mg/kg Ketamine loaded in 10 ml syringe and group S received 10 ml normal saline. The study drugs were given as a slow infusion over 10 min. Immediately after infusion, we occluded venous drainage manually. One minute later occlusion was released. This was followed by injection of propofol 2 mg/kg IV over 25s. Starting from the time of injection the patients were assessed for pain during injection every 5s until the patient became unresponsive, and the degree of pain was scored as advocated by McCririck and Hunter scale [8] (Table 1).

Neither the patients nor the anesthesiologist monitoring the respondents were aware of the group allocation and thus the study was double-blinded. It was followed by a standard anaesthesia technique consisting of Inj. Fentanyl 1.5 µg/kg I.V and Inj. Vecuronium as appropriate for the weight of the patient. Patients were intubated with an appropriate sized oral endotracheal tube and anaesthesia was maintained with nitrous oxide, oxygen, sevoflurane and intermittent positive pressure ventilation.

Heart rate (HR), blood pressure, peripheral oxygen saturation (SpO_2) and end-tidal carbon dioxide (Et CO_2) were monitored intraoperatively. Patients developing Hypotension (SBP <100 or fall > 20% baseline values) was treated with Inj. Ephedrine 6 mg IV and heart rate less than 50 bpm was considered as bradycardia and treated with Inj Atropine 0.6 mg IV.

The sample size was calculated based on previous studies [9]. To detect a 30% difference in severity of pain between the two groups with a power of 85% and at an alpha value of 0.05, we required 38 patients in each group. To increase statistical power, we included 50 patients in each group. Mean and standard deviation were used for age and weight, and the independent t-test was used to compare if the difference between the two groups was significant. Categorical variables are expressed as frequencies and percentages and compared using Fisher's exact test. For all statistical tests, $p < 0.05$ was taken to indicate a significant difference.

Results

One hundred patients aged 20-50 years, of ASA grade I or II, of either gender scheduled for various surgeries under general anaesthesia were enrolled for this study [Table 2]. Patients were divided into two groups [Figure 1]. 50 patients were included

Table 1: McCririck and Hunter pain scale

Score	Response	Interpretation
0	Negative response (no) to question	No pain
1	Pain reported 'yes'only in response to thequestion without anybehavioural change	Mild pain
2	Voluntary complaintof pain or behaviouralchanges	Moderate pain
3	Strong vocal responseor facial grimacingor arm withdrawal ortears on injection	Severe pain

Table 2: Patient Parameters

Age and Weight are presented as mean ± SD. Test done was unpaired t-test. n-number of patients; SD- standard deviation

Parameter	Group K (n = 50)	Group S (n = 50)	p value
Age (years)	34.70 ± 6.24	35.92 ± 4.99	0.2829
Gender (M:F)	46/06	41/09	0.2336
Weight (kg)	64.14 6.50	64.84 6.09	0.5796
ASA (I/II)	34/16	28/22	0.3030

Table 3: Pain scores

Pain score	Group K (n = 50)	Group S (n = 50)	p value
0	41 (82 %)	(16%)	<0.001
1	2 (4%)	5 (10 %)	0.436
2	4 (8%)	14 (28%)	0.0174
3	3 (6%)	23 (46%)	<0.001

Analysis was done by fisher's exact test

Table 4: Hemodynamic data

Parameter	Group K (n = 50)	Group S (n = 50)	p value
Secretions	3	0	0.242
Emergence Agitations	4	0	0.117

Analysis was done by fisher's exact test

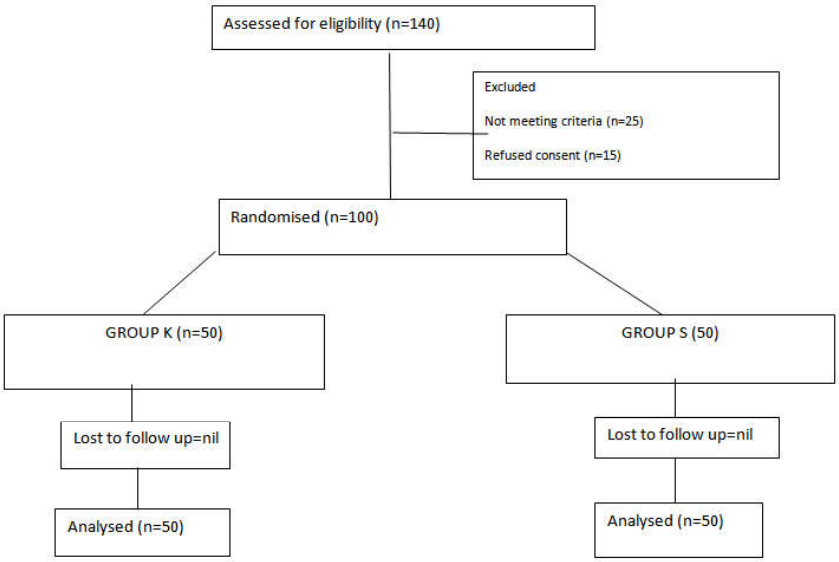

Fig. 1: Consort flow chart

in group K and 50 patients in group S. Group K received 0.5 mg /kg propofol and group S received saline over 10 minutes. There was no statistical difference between the two groups in age, weight, height [Table 2]. An incidence of pain on injection and complications like increased secretions, emergence agitation were noted. Nine patients in group K (18%) and 42 patients in group S (84%) developed pain on propofol injection. The incidence of pain was statistically significant between the two groups (p = < 0.001) [Table 3]. Three patients in group K (6%) and 23 (46%) patients in group S had severe pain (p = < 0.001). Three patients in group K experienced increased secretions, which was not significant in comparison with the other group (6% vs 0%, p = 0.242). Four patients in group K had emergence agitation, but this was again not statistically significant when compared to group S (8% vs 0%, p = 0.117) [Table 4].

Discussion

Propofol is the most widely used intravenous (IV) induction agent. Its properties are almost similar to an ideal IV anesthetic agent, but pain on its injection still remains a problem. The pain on propofol injection may not be a serious complication, but most patients remember it as one of the unpleasant experience during conduction of anaesthesia. The incidence of pain on propofol injection varies between 28-90% [10].

Propofol is an alkylphenol (2,6 diisopropylphenol); oil at room temperature and insoluble in aqueous solution but is highly lipid soluble. Mechanisms behind pain on injection include irritation of endothelium, the difference in osmolality and activation of pain mediators. Pain is immediate as well as delayed after 10–20 s.[11] The immediate pain is due to irritation of vein endothelium whereas delayed pain is due to the release of mediators such a kininogen from kinin cascade [12].

Many methods have been introduced to reduce the incidence of pain on propofol injection with variable results. The most widely used method is pretreatment with preservative-free lignocaine before injection of propofol, other methods include cooling of the propofol which reduces pain possibly by delaying the activation of enzyme cascade of pain mediators and Injecting propofol into a large forearm vein which reduces the pain, probably by reducing contact between drug and endothelium. Recently ketamine an NMDA receptor agonist found effective in reducing pain. Ketamine produces analgesia both by local mechanism due to its structural similarity with local anaesthetic cocaine and also by analgesic modulation via NMDA and μ-opiate receptors at the neuraxial level.

Not many studies are conducted on ketamine usage in the prevention of pain on propofol injection. So we conducted this study to assess its efficacy in preventing pain due to propofol injection. The dose of ketamine was based on a study conducted by Barbi et al.[9]

Our study demonstrated the decreased incidence of pain in ketamine group when compared to control group. Incidences of complications like increased secretions and emergence agitation do occurred in ketamine group but they were not statistically significant.

Ashok Chaudhari [13] et al. conducted a study to assess the efficacy of ketamine pretreatment to alleviate the propofol injection pain. The incidence of pain was 14% in the ketamine group and 96% in the control group. When compared to our study the incidence of pain on injection is almost similar in ketamine group but the incidence was higher in their control group.

Tan and Kua [14] et al. studied the effect of ketamine pretreatment on propofol injection pain and found that the incidence of pain was reduced from 84% to 26%. The incidence of pain is similar to our study.

Elsayed A et al. [15] conducted the study to compare the efficacy of ketamine in the prevention of pain on propofol injection. They found out that the incidence of pain in the ketamine group was 16% and in the saline group was 84%. The incidences of pain in the two groups were similar to our study.

Conclusion

Pretreatment with a smaller dose of ketamine provides a simple and safer method in the prevention of pain on injection of propofol without major side effects.

References

1. Marik PE. Propofol: Therapeutic indications and side-effects. Curr Pharm Des. 2004;10:3639-49.
2. 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. AnesthAnalg. 1999;88: 1085-91.
3. Stokes DN, Robson N, Hutton P. Effect of diluting propofol on the incidence of pain on injection and venous sequelae. Br J Anaesth. 1989;62:202-3.
4. Picard P, Tramèr MR. Prevention of pain on injection with propofol: A quantitative systematic review. AnesthAnalg. 2000;90:963-9.
5. Jalota L, Kalira V, George E, Shi YY, Hornuss C, Radke O, et al. Perioperative Clinical Research Core. Prevention of pain on injection of propofol: Systematic review and meta-analysis. BMJ. 2011;342:d1110.
6. Koo SW, Cho SJ, Kim YK, Ham KD, Hwang JH. Small-dose ketamine reduces the pain of propofol injection. AnesthAnalg. 2006;103:1444-7.
7. Visser E, Schug SA. The role of ketamine in pain management. Biomed Pharmacother. 2006;60:341-8.
8. McCrirrick A, Hunter S. Pain on injection of propofol: The effect of injectate temperature. Anaesthesia. 1990;45:443-4.

9. Barbi E, Marchetti F, Gerarduzzi T et al. Pretreatment with intravenous ketamine reduces propofol injection pain. PaediatrAnaesth. 2003 Nov; 13(9):764-8.
10. Dubey PK, Kumar A. Pain on injection of lipid-free propofol and propofol emulsion containing medium-chain triglyceride: A comparative study. AnesthAnalg. 2005;101:1060-2.
11. Briggs LP, Clarke RS, Dundee JW, Moore J, Bahar M, Wright PJ. Use of di-isopropyl phenol as main agent for short procedures. Br J Anaesth. 1981;53:1197-202.
12. Tan CH, Onsiong MK. Pain on injection of propofol. Anaesthesia. 1998;53:468-76.
13. Ashok Chaudhari and Devavrat Vaishnav. Ketamine in prevention of pain during propofol injection. International Journal of Biomedical Research. 2016;7(3):118-121.
14. Tan CH, Onsiong MK, Kua SW. The effect of ketamine pretreatment and propofol injection pain in 100 women. Anaesthesia. 1998;53:296-307.
15. Elsayed AA, Rayan AA. A comparative study between a small dose of ketamine, lidocaine 1%, and acetominophen infusion to decrease propofol injection pain. Ain-Shams J Anaesthesiol 2015;8:437-42.