http://jmscr.igmpublication.org/home/
ISSN (e)-2347-176x ISSN (p) 2455-0450
crossref DOI: https://dx.doi.org/10.18535/jmscr/v8i6.19

IGM Publication
Journal Of Medical Science And Clinical Research
An Official Publication Of IGM Publication

Original Article

A comparative study of Lignocaine and Ondansetron as pretreatment to prevent pain on injection of Propofol

Authors
Dr Anitha Paul Mampilly MD, DNB[1], Dr Venugopal A, DA, MD, DNB[2], Dr Rachel Cherian Koshy, MD, PDCC[3], Dr Jagathnath Krishna K M[4]
[1]Assistant Professor, Department of Anaesthesiology, Cochin Cancer and Research Centre, Kalamassery, Kochi, Kerala
[2]Additional Professor, Department of Anaesthesiology, Regional Cancer Centre, Thiruvanathapuram, Kerala, India
[3]Professor and Head of the Department, Department of Anaesthesiology, Regional Cancer Centre, Thiruvanathapuram, Kerala, India
[4]Associate Professor, Department of Cancer epidemiology and Biostatistics, Regional Cancer Centre, Thiruvanathapuram, Kerala, India
*Corresponding Author
Dr Venugopal A
Additional Professor in Anaesthesiology, Regional Cancer Centre, Thiruvanathapuram, Kerala, India Pin: 695011

Abstract
Background and Aims: *Propofol is considered as an ideal induction agent for General anaesthesia. However no drug or technique could effectively alleviate the pain on its injection. In the present study we compared the efficacy of pre-treatment with Lignocaine and Ondansetron in reducing the incidence and severity of Propofol induced pain and their safety profile.*
Materials and Methods: *We included 200 patients with American society of Anaesthesiologists (ASA) grade I & II between the age group 18 to 65 years undergoing elective surgery under general anaesthesia. Pain during Propofol injection was compared between Lignocaine 1.5 mg/kg and Ondansetron 0.1mg/kg. Pain was assessed using four point scale (FPS) and numerical rating scale (NRS). The association between categorical variables were done using Chi-square or Fisher's exact test. Continuous variables following normality were assessed using Student's t-test and for non-normal variables Mann Whitney U test was used. A p-value <0.05 was considered as significant.*
Results: *About 80% of patients in either of the groups didn't have pain on Propofol injection. Both the drugs were found to be equally effective in reducing the incidence of pain, and intensity was found comparable. But the pain due to injection of Ondansetron itself was found to be significant compared to Lignocaine (p-value <0.001) along with rash appearing at the site of injection (p-value 0.003).*
Conclusion: *Though both the drugs were found equally effective in reducing the incidence of Propofol induced pain, Lignocaine was found to have a better safety profile than Ondoansetron comparing their side effects.*
Keywords: *General Anaesthesia; Pain; Propofol; Lignocaine; Ondansetron.*

Introduction

Propofol because of its excellent pharmacokinetic properties like easily titrable levels of anaesthesia, absence of cumulation, a rapid and clear headed recovery and minimal side effects is a widely accepted intravenous (IV) anaesthetic agent for induction and maintenance of anaesthesia.[1] However, the most common problem encountered during induction is the pain associated with its injection.[1,2] Propofol is usually injected to a peripheral vein to the dorsum of the hand resulting in limb withdrawal due to pain interfering with its injection and smooth induction of anaesthesia. Pain experienced by the patient at the injection site can range from mild discomfort to severe or even excruciating pain resulting in patient dissatisfaction and even behavioural signs such as withdrawal of the limb, facial grimacing or tears from the eyes.[3] Local anaesthetic agent lignocaine and various analgesics have been studied extensively to reduce the incidence and intensityof pain.[2-5] Ondansetron, a 5-hydroxytryptamine-3(5-HT-3) receptor antagonist is commonly used as an antiemetic for the prophylaxis of nausea and vomiting (PONV) related to anaesthesia.[6] It has been shown to bind to opioid μ receptors and thereby agonistic effect and local anaesthetic property due to sodium channel blockade, both of which can be made use in reducing Propofol induced pain.[7,8] Therefore if given prior to induction of anaesthesia, Ondansetron can reduce both the pain on injection of Propofol and PONV effectively.

Literature on pain management with Ondansetron shows varying results when compared to Lignocaine whereas studies on its side effects and safety profile are sparse.[8-10] We compared the efficacy of pre-treatment with Lignocaine and Ondansetron in reducing the incidence and severity of Propofol induced pain and also to evaluate the safety profile of Ondansetron in patients undergoing oncosurgery.

Methods

After getting approval from the institutional review board with reference number IRB/08-2014/02 dated 26/08/2014 (ethics committee approval was exempted and mentioned in IRB clearance letter) the study was carried out in 100 patients in the Department of Anaesthesiology at a tertiary care hospital during the period from October 2014 to April 2015. Written informed consent was obtained from all the patients prior to surgery. In our Department of Anaesthesiology, as part of a previous study, we had the data of 100 patients with ASA physical status 1 and 2 in the age group 18 to 65 years assessed for pain on Propofol injection pre-treated with IV Lignocaine in a dose of 1.5mg/kg. In the present study we compared this data (retrospective data) with another 100 patients who were assessed for pain on Propofol following pre-treatment with Ondansetron 0.1mg/kg (prospective data). Those who received Lignocaine were included in group 1 and Ondansetron in group 2.

Those with ASA stage 3 and 4,history of hypersensitivity to Propofol and Lignocaine, diabetes, those with chronic and complex pain syndromes, psychiatric illness, those having difficulty to communicate, cardiac instability as evidenced by low ejection fraction, QT prolongation in the ECG were excluded from the study. All patients included in the study were informed regarding the procedure and educated about the pain scale used for the assessment of pain. They were premedicated with Tablet Alprazolam 0.5 mg on the night before surgery and tablet Pantoprazole 40 mg with Alprazolam 0.5 mg given at morning on the day of surgery at least 2 hours before induction. All patients were ensured fasting for a minimum of 6 hrs for solids. A five lead electrocardiogram, non invasive blood pressure and a pulse oximeter were attached and baseline readings were obtained before induction. A 20 gauge cannula was inserted into a larger peripheral vein at the dorsum of the hand after local infiltration of the puncture site and IV fluid was started. In Group 1 patients, following routine

preoxygenation, they were given pre-treatment with IV 2% Lignocaine 1.5mg/kg and the limb was occluded manually for 1 minute at mid forearm for the drug to act. Patients were then given one fourth (0.5 mg/kg of Propofol) of total calculated dose (2 mg/kg) of Propofol (Troypofol, long chain triglycerides from Troika) over 5 seconds. The study drug was freshly prepared and was stored at room temperature. Pain was assessed after 15 seconds of injection by another anaesthesiologist using a standard questionnaire, on the comfort of injection, verbal response and behavioural signs such as facial grimacing, arm withdrawal or tears from the eyes. Pain was graded using FPS and also by NRS. According to the former scale: 0 = no pain, 1= mild pain (pain reported only in response to questioning without any behavioural signs), 2 = moderate pain (pain reported in response to questioning and accompanied by a behavioural sign or pain reported spontaneously without questioning) and 3= severe pain (strong vocal response or response accompanied by facial grimacing/arm withdrawal/tears). In NRS, patients were asked to grade pain in numerical values of 0 to 10 where 0 is no pain and 10 is the worst imaginable pain. Grade 0-3 was taken as mild pain, 4 - 6 as moderate pain and 7- 10 as severe pain. IV midazolam 0.03 mg/kg and fentanyl 1-2 microgm/kg were given and induction completed with Propofol (rest of the dose). Tracheal intubation was facilitated with vecuronium in a dose of 0.1mg/kg and anaesthesia maintained with a mixture of oxygen, nitrous oxide and Sevoflurane to achieve a MAC of 1. End tidal CO2 monitoring was our routine practice to confirm the tracheal placement of the tube as well as to assess the ventilation status of all our patients. Haemodynamic monitoring continued intraoperatively using our multipara monitor for heart rate, electrocardiogram, non invasive blood pressures, pulse oximetry and end tidal CO2 along with temperature monitoring as a routine. Diclofenac Sodium 75mg was given intravenously for pain management. Pain at the injection site was also assessed after extubation using the NRS as above. Any redness, swelling or allergic reactions at the site were noted and recorded.

The same study was carried out on another 100 patients using Ondansetron 0.1mg/kg (Group 2) as pre-treatment drug following the same procedure as described above and pain was assessed using the same parameters. This study data obtained for Ondansetron group (prospective data) was compared with the data obtained from Lignocaine group (retrospective data) and efficacy of Ondansetron to alleviate Propofol pain was compared with that of Lignocaine.

Data was entered in Microsoft Excel and Statistical Packages for the Social Sciences (SPSS; Windows ver. 11.0, SPSS Inc., Chicago, IL) was used for statistical analysis. The association between categorical variables were done using Chi-square test or Fisher's exact test and the significance between the two groups for continuous variables following normality were assessed using Student's t-test. Mann Whitney U test was used to compare pain according to NRS between the groups. A p-value <0.05 was considered as significant.

Results

Both the study groups were comparable with respect to age, gender, and weight. ASA status and co-morbidities of the patient were also found comparable between the groups [Table 1]. Pain scores according to FPS is also summarised in Table 1. 80 % of patients pre-treated with Lignocaine and Ondansetron did not have pain on Propofol injection.. 2% of patients treated with Lignocaine had severe pain but none with Ondansetron had severe pain. Moderate pain was reported in 6% in the Lignocaine group and 4% in the Ondansetron group. But 12% of patients receiving Lignocaine had mild pain which was 15% with Ondansetron. When compared using chi square test and Fisher's exact test, both Lignocaine and Ondansetron were found to be equally efficient in reducing the severity of pain on Propofol injection with a p value of 0.525

[Table 1]. Patients with severe pain were less than 2% and didn't require any treatment as such. When pain was assessed using NRS, 70% patients in Lignocaine group and 75 % in Ondansetron group did not complain of pain. Only 5 % in Lignocaine group and 2 % in Ondansetron group had severe pain. When compared using the Mann Whitney U- test, both Lignocaine and Ondansetron were equally effective in reducing the severity of pain on Propofol injection with a p value of 0.454. The intensity of pain particularly that of severe quality was less in the Ondansetron group compared to Lignocaine. Distribution of pain between the two groups according to the demographic profile were also compared by chi square test and found insignificant [Table 1]. It was also found that prior chemotherapy received by the patients did not have any correlation with the incidence of pain in either of the group.

Regarding adverse effects, when Ondansetron was given as pre-treatment drug, the drug by itself caused pain on injection in 24 % of patients whereas none in the lignocaine group reported pain. Based on Fishers exact test, the p value between the groups was 0.001 which was considered statistically significant [Table 1]. Localised rash was also seen immediately after injection of Ondansetron over forearm in 9% of patients which subsided later whereas no such adverse effects were noticed in the Lignocaine group. This was also found significant statistically as the p value was 0.003 [Table 1]. Pain and rash on injection site of Ondansetron was a unique finding in our study.

Table 1 Patient demographics and clinical characteristics

Variables		**Treatment Groups**		**P-value**
		1	2	
Age	Mean	51.82	49.95	0.226
	SD	10.591	11.184	
Weight	Mean	59.5	59.48	0.988
	SD	8.673	10.125	
Sex	F	67 (67%)	64 (64%)	0.655
	M	33 (33%)	36 (36%)	
ASA	I	41 (41%)	52 (52%)	0.119
	II	59 (59%)	48 (48%)	
Comorbidities	ASTHMA	4 (8.5%)	1 (2.6%)	0.305
	CAD	2 (4.3%)	0 (0%)	
	HTN	31 (65.9%)	31 (79.5%)	
	HYPOTHYROID	10 (21.3%)	7 (17.9%)	
Pain (4 Point scale)	0	80 (80%)	81 (81%)	0.525
	1	12 (12%)	15 (15%)	
	2	6 (6%)	4 (4%)	
	4	2 (2%)	0 (0%)	
Adverse Effects: Pain	N	100 (100%)	76 (76%)	0.001
	Y	0 (0%)	24 (24%)	
Adverse effects: Rash	N	100 (100%)	91 (91%)	0.003
	Y	0 (0%)	9 (9%)	

SD – Standard Deviation, ASA – American Society of Anaesthesiologists
CAD – Coronary artery disease, HTN - Hypertension

Discussion

Pain on injection of Propofol has been reported in majorityof patients who received it.[2,4] It still remains a concern for the anaesthesiologist in day to day practice with incidence varying between 28 to 90% in adults.[9, 11] Factors like site of injection, size of vein, speed of injection, temperature of Propofol, buffering effect of blood, and concomitant use of drugs such as local anaesthetics, analgesic, 5HT-3 antagonists and opiates appear to affect the incidence and intensity of pain.[1-5, 12] Cooling of Propofol to 4 degree is found to reduce pain.[8] IV anaesthetic agents like Ketamine, selective alpha 2 agonists like clonidine and dexmeditomidine, steroid methyl prednisolone were also found to be effective.[13-16] Two mechanisms have been suggested for pain on Propofol injection. Propofol may cause a direct irritant effect on venous nociceptive receptors or free nerve endings involving myelinated A delta fibres leading to immediate pain.[17] The delayed pain which is reported to have a latency of 10-20 s where the drug acts on the vascular endothelium, thereby activating the kallikrein-kinin system resulting in release of bradykinin leading to vasodilatation and increase vessel wall permeability. This allows increased diffusion of Propofol across the blood vessel, thereby increasing the contact between aqueous phase of Propofol and free nerve endings.[18]

Several techniques and drugs have been tried since decades with varying degree of success for reducing Propofol injection pain since its introduction into clinical practice. In a systematic review and Meta analysis to determine the most efficacious approach for pain management concluded that use of antecubital vein or pre-treatment with Lignocaine in conjunction with venous occlusion of the forearm as the two most effective techniques.[1] In a landmark quantitative systematic review which included 56 randomized controlled trials from 6264 patients, Picard and Tramer showed that about 70% of patients were reported to have pain on Propofol injection.[2] They found that when pre-treated with Lignocaine 0.5 mg/kg with application of tourniquet to forearm for 30-160 sec, about 60 % patients had no pain on Propofol injection which was very significant. Widely used techniques to reduce Propofol induced pain in current day practice are injection to a larger vein like antecubital and adding Lignocaine to it.[4, 12, 19-21] Various 5-HT 3 antagonists have been tried to alleviate Propofol induced pain with varying results.[3,22,23] Lignocaine in varying doses was also found to reduce pain significantly.[24, 25]

Our study population did not have any significant difference among both the study groups (i.e. Lignocaine pre-treated and Ondansetron pre-treated) with respect to age, gender, weight, ASA status, history of co morbidities and prior chemotherapy which could have been some possible confounding factors in the study. For the administration of drugs, the same formula based on body weight has been applied to all patients. Standard pain assessment scales like FPS and NRS were used for assessment of the severity of pain. Incidence of pain on Propofol injection following pre-treatment with Lignocaine and Ondansetron were almost similar in both the groups studied but a difference was seen when assessed by the two different pain scales. Around 20 % patients had pain with FPS and 25-30 % with NRS, the difference was found statistically insignificant. Our results were comparable with a study done by Preetha and Archana where 74% of those injected with lignocaine or Ondansetron did not experience pain.[26] In another study by Ambesh et al both the incidence and severity of pain who received Ondansetron were comparable with our study.[22] Prashant et al in their study comparing Lignocaine and Ondansetron found that 67% in the lignocaine group and 72% in Ondansetron group were pain free following Propofol.[27] Regarding the intensity of pain, those received Ondansetron had less intense pain compared to lignocaine which was again a similar observation with our study.[26,27] However it contradicted the observations made by Reddy et al where Ondansetron was found significantly more

effective in relieving Propofol injection pain compared to Lignocaine.[28] In another significant observation by Ye et al, Ondansetron was found 15 times more effective than lignocaine in relieving Propofol injection pain which was again contradictory.[8]

Most significant observation made during our study was regarding the adverse effects that occurred while injecting the study drug. When Ondansetron was given as pre-treatment drug, the drug by itself caused pain on injection in about 24 % of patients whereas none had pain with lignocaine. Localised rash was also seen immediately after injection of Ondansetron over forearm in about 9 % of the patients. No such adverse effects were noted in Lignocaine group during the study and hence were found statistically highly significant. Unfortunately the incidence of pain on injection of Ondansetron was not available in the literature and hence the reason remains unknown to us. Data analysis of our study also reveals that the perception of pain on Propofol injection has no relation with factors like age, weight, gender, prior chemotherapy or other co-morbidities like asthma, coronary artery disease, hypertension and hypothyroidism since the differences were statistically insignificant.

Limitations

The study was limited by the fact that manual occlusion was done for occluding the vein which varied from person to person. The absence of a placebo group in the study limited an accurate calculation of the quantitative assessment of incidence of pain on injection of Propofol as it was found unethical.

Conclusion

Pre-treatment with Ondansetron a 5- HT-3 receptor antagonist commonly used as an antiemetic in anaesthetic practice is as effective as Lignocaine in attenuating Propofol induced pain. The incidence of pain was significantly reduced by both Lignocaine and Ondansetron with an edge to the later as it reduces the severity of pain better. It also controls PONV effectively leaving behind the pain and rash due to the drug itself which requires further studies to validate as an adverse effect.

No support obtained.
Acknowledgements - Nil
Conflicts of interest- Nil.
Institutional Review Board clearance obtained bearing sanction number: -IRB/08-2014/02 dated 26/08/2014. Ethics clearance excempted. Chairman – Dr. Paul Sebastian, Director, RCC, Thiruvanathapuram, Kerala, India

References

1. Jalota L, Kalira V, George E, Shi YY, Hornuss C, Radke O, Pace NL, Apfel CC. Prevention of pain on injection of propofol: systematic review and meta-analysis. BMJ 2011;342:d1110.
2. Picard P, Tramèr MR. Prevention of pain on injection with propofol: a quantitative systematic review. Anesth Analg 2000; 90(4):963-9.
3. 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(2):213-6.
4. Nathanson MH, Gajraj NM, Russell JA. Prevention of pain on injection of propofol: A comparison of lidocaine with alfentanil. Anesth Analg 1996;82(3):469-71.
5. Vijayant GA, Tej KK, Avtar S, Anju G, Rupinder MS, Daljit KK. Analgesic effect of Lignocaine, tramadol, ketorolac and ketoprofen in ameliorating Propofol injection pain. J Anaesthesiol Clin Pharmacol 2005;21(4): 89-93.
6. Swaika S, Pal A, Chatterjee S, Saha D, Dawar N. Ondansetron, ramosetron, or palonosetron: Which is a better choice of antiemetic to prevent postoperative nausea

and vomiting in patients undergoing laparoscopic cholecystectomy? Anesth Essays Res. 2011;5(2):182-6. doi: 10.4103/0259-1162.94761.

7. Gregory RE, Ettinger DS. 5-HT3 receptor antagonists for the prevention of chemotherapy-induced nausea and vomiting. A comparison of their pharmacology and clinical efficacy. Drugs 1998;55(2):173-89.
8. 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.
9. Rahimzadeh P, Faiz SH, Nikoobakht N, Ghodrati MR. Which one is more efficient on propofol 2% injection pain? Magnesium sulfate or ondansetron: A randomized clinical trial. Adv Biomed Res 2015;4:56. doi: 10.4103/2277-9175.151593. eCollection 2015.
10. Ansari MU, Garg G, Lodha LR, Qureshi SU, Porwal S. Pretreatment with intravenous Ondansetron to alleviate pain on Propofol injection. A randomized controlled and double blind study. J of pharm Biomed Sci 2013;32:1274-78.
11. Tan CH, Onsiong MK. Pain on injection of propofol. Anaesthesia 1998; 53(5):468-76.
12. Tariq MA, Kamran M. Incidence of pain on Propofol injection and efficacy of addition of Lignocaine selecting big vein or both combined in reducing it. J of post graduate medical institute 2006;20:8-11.
13. Hwang J, Park HP, Lim YJ, Do SH, Lee SC, Jeon YT. Preventing pain on injection of propofol: a comparison between peripheral ketamine pre-treatment and ketamine added to propofol. Anaesth Intensive Care 2009; 37(4):584-7.
14. 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.
15. He L, Xu JM, He T, Liu L, Zhu R. Dexmeditomidine pre-treatment alleviates propofol injection pain. Ups J Med Sci 2014;119(4):338-42. doi: 10.3109/03009734.2014.941049. Epub 2014 Oct 24.
16. Shivanna S, Priye S, Singh D, Jagannath S, Mudassar S, Reddy DP .Efficacy of methylprednisolone and lignocaine on propofol injection pain: A randomised double-blind prospective study in adult cardiac surgical patients. Indian J Anaesth 2016;60(11):848-851.
17. Eriksson M, Englesson S, Niklasson F, Hartvig P. Effect of lignocaine and pH on Propofol induced pain. Br J Anaesth 1997;78(5):502-6.
18. Nishiyama T. How to decrease pain at rapid injection of propofol: effectiveness of flurbiprofen. J Anesth 2005;19(4):273-6.
19. Scott RP, Saunders DA, Norman J. Propofol: clinical strategies for preventing the pain of injection. Anaesthesia 1988 Jun;43(6):492-4.
20. Gehan G, Karoubi P, QuinetF, 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.
21. 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.
22. 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.
23. Dubey PK, Prasad SS. Pain on injection of propofol: the effect of granisetron

pretreatment. Clin J Pain 2003;19(2):121-4.
24. El-Radaideh KM. Effect of pre-treatment with lidocaine, intravenous paracetamol and lidocaine-fentanyl on propofol injection pain. Comparative study. Rev Bras Anestesiol 2007;57(1):32-8.
25. Sunny A, Veerabhadraiah T, TrivikramS. Comparison of pretreatment with lignocaine and Ondansetron for pain on injection of propofol during induction of anaesthesia. Internet J Anesthesiol 2013;32:1373–6.
26. Preetha R, Archana BN. To compare the efficacy of intravenous pre treatment with Injection Ondansetron 4mg and Injection Lignocaine 40 mg preceded by venous occlusion for reducing pain on injection of Propofol in adult surgical patients. Asian J Biochem and pharmac Research 2014;4:(3) 161-8.
27. Prashant J, Pachore, Sonal A, Chaudhari, Abhimanyu S, Tarkase, Ganesh K, Nikam. Comparative Study of Ondansetron with Lignocaine to alleviate pain during injection of propofol. J evolution of medical and dental sciences. 2014;31:10828-35.
28. Reddy MS1, Chen FG, Ng HP. Effect of Ondansetron pretreatment on pain after rocuronium and propofol injection: a randomised, double-blind controlled comparison with lidocaine. Anaesthesia. 2001;56(9):902-5.

List of Abbreviations Used

FPS – Four Point Scale
NRS – Numerical Rating Scale
IV – Intravenous
5-HT-3 – 5 Hydroxy Tryptamine Receptor 3
PONV – Post Operative Nausea and Vomiting
ASA – American Society of Anaesthesiologist
MAC – Minimum Alveolar Concentration
ECG - Electrocardiogram