European Journal of Cardiovascular Medicine
Print ISSN: 2042-4884 | E-**ISSN:** 2042-4892
Language: Multilingual
Origin: United Kingdom
Website: https://www.healthcare-bulletin.co.uk/ **Volume 14 Issue: 2 - 2024**
Original Article **Open Access**

Intravenous Granisetron to reducePropofol induced pain: A Randomised Controlled Trial

Nimmy Raju, Neethu Thankam Thomas, Leno Ninan JacobJithin Mathew Abraham,

Abstradct: **Introduction**: Propofol a routinely used intravenous induction agent for general anaesthesia is known to cause pain on injection due to its lipid emulsion property.Various methods have been tried to address propofol induced pain but have produced variable results. Pretreatment with Ondansetron a 5- HT3 antagonist has been shown to alleviate pain on propofol injection.
Aim: To compare the efficacy of intravenous granisetron versus a placebo(normal saline) to reduce pain on propofol injection.
Materials and Method: This randomised double blinded trial included18-60 year old American Society of Anaesthesiologists Physical Status(ASA PS) I and II patients for elective surgery under general anaesthesia.110 patients were randomly allocated into two groups of 55 each.They received either 2ml granisetron(1mg/ml) or 2ml 0.9 %saline. After receiving the test or control drug, patients were asked to score the pain on a four point categorical scale.
Results: Pain in the control group was 92.7% when compared to 10.9% in the intervention group($p < 0.0001$). The severityof pain was also less in the intervention group pre-treated by 2ml of granisetron.
Conclusion: We found that intravenous Granisetron was effective in reducing pain on propofol injection

Keywords:

AFFILIATIONS
[1] *Department of Anaesthesiology, Believers Church Medical College Hospital, Thiruvalla, Kerala, India*
.

CORRESPONDING AUTHOR
Dr. Somula Mounika reddy

INTRODUCTION

Propofol is the most commonly used intravenous induction agent in current anaesthesia practice.Its rapid onset and short duration of action makes it an ideal agent for day care procedures although propofol induced pain remains a cause for concern.(1)

Evidence reveals that among low morbidity outcomes of current clinical anaesthesiology pain during injection of propofol ranks as the 7th most important problem. (2)

The incidence of pain on propofol injection varies between 28-90% in adults and 28-85% in children. (3) Granisetron, a 5HT3 receptor antagonist is given as premedication to prevent post operative nausea and vomiting after general anaesthesia. It has been shown that Ondanisetron can relieve pain after propofol injection without significant adverse effects.(4)Use of Granisetron in reducing pain on propofol administration has also been demonstrated in a study done in North India.(5)This study would help in assessing the effectiveness of Granisetron in a different population.

The degree of patient satisfaction with perioperative care is assuming importance as a determinant of anaesthetic outcome. Since patients presenting for surgery are already anxious and stressed it is important to give them a pain free anaesthesia.

The aforementioned facts highlights the importance of addressing propofol induced pain to ensure better clinical outcome. The use of granisetron will help reduce pain associated with propofol injection with added advantage of preventing post operative nausea and vomiting.

METHODS:

This double-blinded randomised controlled study was conducted at a tertiary care institute in South India. Ethics committee approval was obtained. Written and informed consent was obtained from eligible patients. *Inclusion criteria:* included ASA-PS(American Society of Anaesthesiologists- Physical Status) I and II,age between 18-60 years, elective surgeries under general anaesthesia. *Exclusion criteria*: patients with difficulty in communication, those who refused to give their consent, patients allergicto propofol or granisetron and patients who have taken sedatives or analgesics within 24 hours prior to surgery.

The computer-generated variable block size randomisation numbers were concealed in serially numbered sealed envelopes for allocation concealment.

110 patients were randomly allocated into two groups of 55 each. They received either 2ml granisetron (1mg/ml) or 2ml 0.9 %saline.

All patients included in the study underwent a detailed preanaesthetic checkup. Basic laboratory investigations were done in all patients. The patients were on fasting for 6 hours and no sedative premedication was given on the night prior to surgery. The study drugs were prepared at operating room temperature by an anaesthesiologist not involved in the induction of anaesthesia. The patient and investigator were blinded regarding contents of the solution. Drugs and equipment necessary for resuscitation and general anaesthesia were kept ready. On arrival to the operation theatre, a 20G cannula was inserted on dorsum of patient's hand and an intravenous fluid drip was started. Standard monitors (heart rate, non invasive blood pressure, ECG, pulse oximetry) were attached and baseline haemodynamic parameters were noted. None of the patients were given any premedication before pretreatment injection.

Each patient received 2 ml of pre-treatment agent,5 minutes after intravenous cannulation while venous drainage was occluded manually at mid arm by an assistant. After 1 minute, occlusion was released and 2 ml bolus propofol(20 mg) was given.15 seconds later patient was asked to score the pain on a 4 point categorical pain scale-

0- No pain(negative response to questioning)
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 behavioural sign or pain reported spontaneously without questioning)
3- Severe pain(strong vocal response or response accompanied by facial grimacing, arm withdrawal or tears)

Adverse effects like dizziness, weakness, allergic reaction if any were noted. Intravenous premedication was given after pain assessment. Anaesthesia induction was achieved with intravenous propofol in a dose of 2.5 mg/kg, subsequent muscle relaxation and intubation was accomplished with Suxamethonium 2 mg/kg intravenously and anaesthesia was maintained with N2O ,O2 and Isoflurane. Injection Vecuronium was used as muscle relaxant intraoperatively.
Sample size was calculated based on the reference study using the formula

$$n=\frac{(Z\alpha+Z\beta)^2*2*p*q}{d2}$$

$Z\alpha = 1.96$ for α at 5% error

$Z\beta = 2.33$ for β at 90% error

p = average proportion of the 2 groups

q = 1-p

d = expected difference between p and q

Statistical analysis was done using SPSS Version 21. Categorical variables were expressed as counts or percentages. Continuous variables were expressed as mean $\pm$ standard deviation. The difference in proportion between intervention and control arms were tested using t-test for proportions

RESULTS:

The socio-demographic parameters in the intervention and control groups were normally distributed with respect to gender and PSA category. There is no statistical difference between the intervention and control arm as determined by t-test, p value>0.05.
Hence the distribution of demographic variables is comparable for gender and PSA category.

(Table 1) Comparison of sociodemographic details

Variable	Intervention arm	Control group	p-value
Gender	Number(%)	Number(%)	
Male	29(52.7)	24(43.6)	4
Female	26(47.3)	31(56.4)	
ASA PS			
I	34(61.8)	32(58.2)	4
II	21(38.2)	23(41.8)	

(Table 2) Comparison of relevant variables and haemodynamic parameters

Variable	**Intervention group**	**Control group**	**p value**
Mean weight	61.18	62.07	0.71
Mean age	41.64	41.6	0.84
Mean SBP	129.91	132.58	0.38
Mean PR	78.11	78.76	0.82
Mean spO2	99.15	99.25	0.581

Both the intervention and control groups are comparable in terms of age, weight and hemodynamic variables such as systolic BP, diastolic BP, Oxygen saturation and respiratory rate considering baseline values and values at 1 and 3 minutes after propofol injection, using the t-test for difference in means.

(Table 3) Comparison of incidence of pain in the two groups

Pain	Number (%)	Number (%)	P value
	Intervention arm	Control arm	0.0001
Yes	6(10.9)	51(92.7)	

(Table 3)Comparison of severity of pain in both groups

Pain category	Intervention group (n=55) **Number (%)**	Control group (n=55) **Number (%)**
Nil	49(89.1)	4(7.3)
Mild	6(10.9)	8914.5)
Moderate	0(0)	28(50.9)
Severe	0(0)	15(27.3)
Total		

A large majority of patients (92.7%) experienced pain in the control arm where a placebo was given, while only 10.9% of patients experienced mild pain in the intervention group where 2ml granisetron was given. The result was statistically significant on t-test for proportions with a p-value- 0.0001.
The severity of pain was also lesser in the granisetron group compared to the placebo group. While 78.2% experienced moderate- severe pain in the control arm, none of the patients pre-treated with granisetron(intervention arm) experienced moderate-severe pain. Only 10.9% of the patients experienced a mild pain. There was a significant difference in the intensity of pain experienced by the study subjects in both the arms. (p-0.0001)

No patient in either group experienced pain or discomfort during injection withthe pre-treatment solution.
No adverse reactions or major haemodynamic changes were observed after injection of pretreatment solution or propofol.
Thus, it was observed that pretreatment with granisetron along with venous occlusion for 1 minute was greatly useful for the prevention of propofol-induced pain.

DISCUSSION:

The possible reasons for propofol induced pain include high concentration of free Propofol in the aqueous phase of an emulsion and the lipid carrier,endothelialirritation,osmolalitydifferences,unphysiologicalPh and activation of pain mediators.(6,7,8)Other factors include site of injection,size of the vein,speed of injection and concomitant use of drugs like opiates and local anaesthetics.(9,10)

Many methods have been used to reduce pain on propofol injection with variable results.

Ondansetron is a selective serotonin 5HT-3 receptor antagonist. Ye et al demonstrated that ondansetron blocks sodium channels in rat brain neurons. It was 15 times more potent than lignocaine in causing numbness when injected under the skin(11).Ondansetron has shown binding atμopoid receptors and exhibited agonist activity.(12) Granisetron is a more refined 5HT-3 antagonist with super efficacy and longer duration of action than ondansetron and relieved pain by a similar mechanism.(13)

Hence granisetron provides a relatively safe and simple way of reducing incidence of pain on propofol injection.

CONCLUSION:

This study was done to evaluate the efficacy of intravenous granisetron to reduce propofol induced pain. Considering the extensive use of propofol in anaesthetic practice, the pain reported on propofol injection needs to be addressed. Many techniques used to reduce propofol induced pain have produced variable and unsatisfactory results. Lignocaine added or given before injection of propofol is the most widely employed method although with a failure rate of 13-44%.(14)Cooling propofol to 4 degree reduced pain only to 23%.(15) Alfentanil has shown to reduce the incidence of pain from 85 to 36% only.(16) Although the different methods reduced the severity of pain, the overall incidence of pain was only mildy reduced.

Granisetron relieves pain by its multifacted actions asa sodium channel blocker,5HT-3 receptor antagonist and μopoidagonist. Results demonstrated an unacceptably high incidence of pain 92.7% of placebo cases which was decreased to as much as 10.9% by granisetron pretreatment with venous occlusion at mid arm. Based on the results obtained in this study, it can be concluded that pretreatment with granisetron along with venous occlusion for 1 minute is an effective method in alleviating propofol induced pain. Granisetron also has the added advantage of reducing post operative nausea and vomiting and so this method will be very useful especially in day care surgeries.

Financial support and sponsorship- Nil
Conflict of interest- Nil

REFERENCES:

1. Smith I,WhitePF, NathansonM, Gouldson R:Propofol:An update on its clinical use. *Anaesthesiology*. 1994;81:1005-43
2. MarcarioA,WeingerM,T ruongP,LeeM.Which clinical anaesthesia outcomes are both common and important to avoid?The perspective of a panel of expert anaesthesiologists?*AnaesthAnalg*.1999;88:1085-91
3. Hynyen M, Korttila K, TammistoT.Pain on IV injection of propofol(ICI 35868) in emulsion formulation:Shortcommunication.*ActaAnaesthesiolScand*.1985;29:651-2
4. AmbeshSP,DubeyPK,SinhaPK.Ondansetronpretreatment to alleviate pain on Propofol injection-A randomised double blinded study.*AnaesthAnalg*. 1999;July 89(1):197-9.
5. Ahmed A,SenguptaS,DasT,RudraA,IqbalA.Pretreatment with intravenous granisetron to alleviate pain on Propofolinjection:A double blind randomised controlled trial.*Indian J Anaesth*. 2012;56:135-8.
6. Clarke RSJ,DundeeJW,GarrettRT,McArdleGK,SuttonJA.Adverse reactions to intravenous anaesthetics- A survery of 100 reports.*British Journal ofAnaesthesia*.1975;47:575-85.
7. KlementW,ArndtJO.Pain on intravenous injection of some anaesthetic agents is evoked by the unphysiological osmolality or pH of their formulations.*Br J Anaesth*. 1991;66:189-95.
8. KlementW,ArndtJO.Pain on injection of propofol: effects of concentration and diluent.*Br J Anaesth*. 1991;67:281-4.
9. Cameron E,JohnstonG,CroftsS, MortonNS. The minimum effective dose of lignocaine to prevent injection pain due to propofol in children.*Anaesthesia*.1992;47:604-6.
10. Scott RPF,SaundersDA,Norman J et al.Propofol : clinical strategies for preventing pain on injection.*Anaesthesia*.1988;43:492-4.
11. Ye JH, MuiWC, RenJ, HuntTE,WuWH,ZbuzekVkK et al. Ondansetron exhibits the properties of a local anaesthetic.*AnaesthAnalg*. 1997;November 85(5):1116-21.
12. NorouziA,FakhfouriG,RahimianR.How can 5HT-3 receptor antagonist exert analgesic properties.*ActaMed Iran*.2012;50(4):225.
13. Gregory RE,Ettinger DS.5HT-3 receptor antagonists for chemotherapy induced nausea and vomiting.A comparison of their pharmacology and clinical efficacy.*Drugs*.1998;55:173-89.
14. King SY, Davis FM, WellsJE, Murchinson DJ, PryorPJ. Lidocaine for the prevention of pain due to injection of propofol.*AnaesthAnalg*.1992;74:246-9.
15. McCrirrickA, HunterS. Pain on injection of propofol:The effect of injectatetemperature.*Anaesthesia*. 1990;45:443-4.
16. Fletcher JE,SeavellCR,BowenDJ.Pretreatment with alfentanil reduces pain caused by propofol.*Br JAnaesth*. 1994;72:342-4.