ORIGINAL ARTICLE

Effect of paracetamol pre-treatment on Propofol injection pain among surgical patients

Henry Y Embu, Audu M Ngeh, Erdoo S Isamade, Samuel I Nuhu

Abstract

Background: Propofol injection pain is often a cause of distress for patients. This study was conducted to find the incidence of Propofol induced pain and the efficacy of Paracetamol (Acetaminophen) in the prevention of Propofol injection pain among surgical patients at a tertiary hospital.

Methods: The study was a prospective, double blind randomized clinical trial carried out at the Jos University Teaching Hospital main theatre. Consenting American Society of Anesthesiologists (ASA) physical status I or II patients scheduled to undergo general anaesthesia for elective surgery were allocated into one of two study groups of 35 each. Group I was the Paracetamol (drugamol®) group, who received 2mg/kg of intravenous Paracetamol while the control group (group II) received 5ml of 0.9% saline with venous occlusion. The venous occlusion was released 2 minutes after injecting the study drug and one-fourth of the total calculated dose (2.5mg/kg) of Propofol (Pofol 1%® Dongkook Pharmaceutical) was delivered through the iv line over a period of five seconds and the patients assessed for pain on a 4-point scale.

Results: The two groups were comparable in demographic characteristics and ASA classification. Twenty-one (60.0%) patients in the control group and 1 (2.9%) patient in the Paracetamol group experienced pain on injection of Propofol, p = 0.000. There were no significant haemodynamic variations between the two groups during the study period.

Conclusion: Paracetamol when applied with tourniquet significantly attenuated Propofol injection pain in our adult patients with no significant haemodynamic variations.

Key words: Paracetamol, Propofol, Injection pain

Highland Med Res J 2020;20(1):35-39

Introduction

Propofol is currently the favored intravenous induction agent. It produces smooth induction of anaesthesia with more rapid awakening and better conditions for intubation when compared with thiopentone and ketamine and is therefore often the preferred anaesthetic for induction of anaesthesia, day case surgeries or when laryngeal mask airway is to be used.[1] Propofol has an added advantage of reducing postoperative nausea and vomiting and is a preferred choice for total intravenous general anaesthesia. However, Propofol also has its challenges. The most significant of these is pain on injection. This pain usually causes discomfort and occasional fear and anxiety to the patient. The incidence of pain on injection of Propofol as reported by some authors can be as high as 90% or as low as 28% in adults.[2,3] Among 33 clinical anaesthesia problems with low morbidity which included incisional pain, nausea, vomiting, perioperative anxiety, and discomfort from intravenous line insertion, Propofol induced pain ranked 7th.[4,5] Although the definite mechanism of Propofol induced pain is unknown, activation of some mediators such as the release of kininogens from the wall of the vein triggering a local kinin cascade system during intravenous injection has been blamed.[6,7]

Several methods as seen from the literature have been proposed to decrease pain on injection of Propofol. These include: the use of lidocaine pre-treatment, addition of lidocaine to Propofol, the use of ketamine, metoclopramide, tramadol or ondansetron,magnesium sulfate, thiopentone and ketarolac.[7-10] Physical measures have also been used such as the cooling or warming of Propofol.[7]

Paracetamol (acetaminophen) is a para-aminophenol that possesses analgesic and antipyretic activity similar to aspirin. The intravenous formulation was introduced in Nigeria following the ban on importation and manufacture of all drugs containing Dipyrone (Metamizole) by the National Agency for Food Drug Administration and Control (NAFDAC) in 2005. The intravenous formulation in the operating room comes as 10mg/ml in a 100ml vial of 1g. Paracetamol is thought to have a strong central action and there are speculations of peripheral effects as well. In our study, we attempted to find out the incidence of Propofol injection pain and the efficacy of Paracetamol in the prevention of Propofol injection pain among patients presenting for general anaesthesia at the Jos University Teaching Hospital. We also sought to find out if pretreatment with Paracetamol had any effects on their haemodynamic profiles following Propofol induction.

Department of Anaesthesia, Jos University Teaching Hospital, Jos, Nigeria

All correspondences to:
Dr. Henry Y. Embu
Email: embuy@yahoo.com

Patients and Methods

The study was a prospective, double blind randomized clinical trial carried out at the Jos University Teaching Hospital main theatre complex from 1st February, 2012 to 31st April, 2012.

Inclusion and exclusion criteria

All consenting ASA physical status I or II patients aged 20-60 years, scheduled to undergo general anaesthesia for elective surgery during the study period were included in the study. Exclusion criteria were patients with vascular disease, hemodynamic instability, habituation to analgesics, and sedatives, and patients on anti-anxiety drugs, or having allergy or sensitivity to Propofol or Paracetamol.

The sample size was determined with the formula for interventional studies[11]and it came up to 35 participants per group.

Ethical consideration/informed consent

Ethical clearance was obtained from the Jos University Teaching Hospital ethical committee. The essence of the study was explained to the patients. They were given the option to choose either to participate in the study or to decline. The study subjects were assured of anonymity and confidentiality.

Study design

Consenting American Society of Anesthesiologists (ASA) physical status I or II patients scheduled to undergo general anaesthesia for elective surgery were allocated by balloting into one of two study groups. The patients picked their group allocation from a sealed envelope. Group I was the Paracetamol (Drugamol®) group, who received 2mg/kg of iv Paracetamol diluted and made up to 5mls. The control group i.e. group II were given 5ml of 0.9% saline. The dosage of Paracetamol was chosen based on previous studies.[12,17]

A preoperative anaesthetic assessment was done for eligible patients during which the nature of the study was explained to them and they were allowed to make an informed decision on whether to take part in the study or not. Those that consented were recruited for the study.

Routine anaesthetic machine check was done and the necessary resuscitation drugs were made available. In the pre-anaesthetic room, consenting patients were allocated to their study group after picking from the sealed envelope. Their demographic data (age, weight, tribe, religion, occupation, and educational status) were documented. Baseline vital signs – pulse rate, non invasive blood pressure and oxygen saturation were obtained using a multi parameter monitor GE Healthcare model Dash 4000 and documented. A size 20G cannula was inserted into the superficial radial vein of the patient's hand.

Pre-hydration with 0.9% saline at 100ml/hour for 5 minutes was done. After the infusion was stopped, the arm with the intravenous line was elevated for 15 seconds to allow for gravity drainage of venous blood. The venous drainage was occluded using a rubber tourniquet on the upper arm. The patient was pre-treated over a period of 10s with one of the pretreatment solutions; $2mgkg^{-1}$ Paracetamol (Drugamol®) made up to 5ml (Group I) or 5ml of 0.9% saline (Group II). The patients were asked if they felt any pain during administration of the pretreatment solution. The pain during injection was assessed based on a four-point scale: [12]

None – 0, Mild – 1, Moderate – 2 and Severe – 3

The venous occlusion was released 2 minutes after injecting the study drug and one-fourth of the total calculated dose (2.5mg/kg) of Propofol (pofol 1%®Dongkook Pharmaceuticals) was delivered through the iv line over a period of five seconds. No other analgesic or sedative was administered before the Propofol injection. During the injection, the patients were asked standard questions regarding any pain. The patients were evaluated forPropofol induced pain using a verbal rating scale.[12]

None	- 0 (Negative response to questioning)
Mild pain	- 1 (Pain reported only in response to questioning)
Moderate pain	- 2 (Pain reported in response to questioning and Accompanied by behavioral signs or pain reported spontaneously without questioning)
Severe pain	- 3 (Strong vocal response or response accompanied by facial grimacing, arm withdrawal, or tears)

The remaining calculated dose of Propofol, was then injected to induce anaesthesia. Tracheal intubation was facilitated with 1mg/kg suxamethonium. Pulse rate, systolic, diastolic, mean arterial blood pressures and oxygen saturation were recorded before administration of pre-treatment solution (as baseline), at laryngoscopy, one and five minutes after intubation. Anaesthesia was maintained with isoflurane in oxygen and intra operative analgesics were administered. Patients were extubated at the end of surgery and transferred to the recovery room. Within 24hrs after the operation, the injection site was checked for pain, edema or allergic reaction by the primary investigator who was blinded to the group assignment. This was done postoperatively in the recovery room and in the ward the following day after surgery.

Data analysis

Numerical data were expressed as mean ± SD while categorical data were expressed as frequencies or percentages. The groups were compared using the t-test for numerical variables. The chi-squared test was used to assess differences between categorical variables. SPSS version 16.0 was used to analyze the data and $P < 0.05$ was considered statistically significant.

Results

The patients' demographic characteristics were similar in the two groups (Table I). The ASA status of the patients in both the Paracetamol and control (saline) groups were also similar. The Paracetamol group had 29(82.9%) ASA I and 6(17.1%) ASA II patients. The control group had 20(57.1%) and 15(42.9%) patients classified as ASA I and ASA II respectively and this was not statistically significant, $p = 0.053$.

Table 1. Demographic Characteristics and American Society of Anesthesiologists (ASA) classifications of patients administered either Paracetamol or Saline (Placebo)

PARAMETERS	Paracetamol Group N=35	Saline (Control) Group N=35	P value
Age (Years) Mean(±SD)	31.2(±7.9)	36.5(±11.5)	0.091
Weight (Kg) Mean(±SD)	63.7(±13.5)	63.3(±23.6)	0.701
Sex (%)			
Male	14(40.0%)	15(42.9%)	0.606
Female	21(60.0%)	20(57.1%)	
ASA			
I	29(82.9%)	20(57.1%)	0.053
II	6(17.1%)	15(42.9%)	

Table 2: Pain score during injection of Propofol in patients administered either Paracetamol or saline.

PAIN SCORE	Paracetamol group N =35(%)	Control Group N =35(%)
None =0	34(97.1)	14(40.0)
Mild pain =1	1(2.9)	7(20.0)
Moderatepain =2	0	8(22.9)
Severe pain =3	0	6(17.1)
Pain =(1+2+3)	1(2.9)	21(60.0)
Total	35(100)	35(100)

$X^2 = 33.457$, df = 6, P value = 0.000

None of the patients reported having pain during the injection of the pre-treatment drugs in both the Paracetamol and the control groups.

The incidence and severity of pain during the injection of Propofol in the two groups was compared (Table 2). Twenty-one (60.0%) patients in the control group and 1 (2.9%) patient in the paracetamol group experienced pain on injection of Propofol which was statistically significant($p = 0.000$).

Table 3: Hemodynamic variations between the Paracetamol and saline groups

	PULSE RATE (Mean ± SD)			MeeanArterial Pressure (Mean ± SD)		
	Control	Paracetamol	P	Control	Paracetamol	P
Baseline	89±4	92±5	0.378	95±3	98±3	0.216
At Laryngoscopy	108±4	112±3	0.107	108±4	110±3	0.412
1-minute post laryngoscopy	104±5	110±3	0.09	96±4	98±5	0.606
5 minutes post laryngoscopy	100±4	106±4	0.146	86±3	90±4	0.057

Table 3 shows the haemodynamic variations of the two groups. The mean pulse rate (PR) in the two groups were not significantly different i.e. control vs Propofol groups at different intervals from baseline (89±4 vs 92±5, p=0.378), at laryngoscopy (108±4 vs 112±3, p=0.107), at one minute (104±5 vs 110±3, p =0.091) and at five minutes (100±4 vs 106±4, p =0.146) post laryngoscopy. The table also shows the trend of mean arterial blood pressure (control vs Propofol group) at baseline (95±3 vs 98±3, p=0.216), at laryngoscopy (108±4 vs 110±3, p=0.142), one minute (96±4 vs 98±5, p =0.606) post laryngoscopy and five minutes (86±3 vs 90±4, p=0.057) post laryngoscopy which were also not significantly different.

Table 4: Variations in saturation between the Paracetamol and saline groups

	SATURATION (Mean±SD)		p
	Control	Paracetamol	value
Baseline	97±1.5	96±2.0	0.420
At Laryngoscopy	99±1.0	98±1.5	0.351
1-minute post Laryngoscopy	98±1.0	99±1.0	0.185
5-minutes post Laryngoscopy	98±1.5	99±1.0	0.130

The mean SpO_2 (Oxygen saturation) in the two groups were also comparable at baseline, at laryngoscopy, one minute post laryngoscopy and five minutes post laryngoscopy (Table 4).

No complications were observed at the injection site within 24 hours after surgery in the two groups.

Discussion

The incidence of Propofol injection pain was quite high among our patients. Pain associated with Propofol injection is a common problem.[12]This pain can be very discomforting and distressing to the patient and can lead to patient dissatisfaction with the technique of anaesthesia. The incidence of pain on injection of Propofol varies between 28% - 90% in adults during induction of anaesthesia and may be severe.[2,3]In children, the incidence varies between 28% -88%, the younger the child the higher the incidence and severity probably due to smaller veins in the younger children.[2] There appears to be no gender difference in the incidence of Propofol injection pain.[2]

Canbey et al[12] and Dubey and Prasad[13] reported similar incidences of Propofol pain to our study of 64% and 62% respectively in the control group while Ozkan et al[14], Dedic et al[15] and Agarwal et al[16] reported much higher incidences than we found in our study. There were a few differences in methodology between our study and theirs which may have accounted for the differences in the incidences of Propofol injection pain. Argarwal and colleagues used tourniquet like in our study but there was no prior venous drainage before application of the tourniquet. The use of a tourniquet isolates the arm veins from the rest of the circulatory system, presenting a useful model for studying the peripheral actions of a drug in the absence of central effects.[17]Though Paracetamol is thought to act centrally through the cyclo-oxygenase system, there is evidence to suggest that Paracetamol selectively suppresses peripheral PG E2 release and increases COX-2 gene expression in a clinical model of acute inflammation, indicating a possible relationship between PG E2, which is selectively suppressed by Paracetamol and bradykinin which determines the intensity of propofol injection pain.[18]

A number of factors appear to affect the incidence of pain on injection of Propofol. These include Propofol concentration in aqueous phase and buffer effect of blood, injection site, and speed of injection and the size of the vein[2]. Other factors include speed of intravenous fluid used, and the temperature of Propofol.[2] Propofol injection pain may be immediate or delayed. Immediate pain probably results from direct irritant effect of kinin cascade while delayed pain has a latency of between 10seconds and 20seconds.

Sun and others,[6] pointed out certain factors in the causation of Propofol injection pain. The size of the vein used was noted by them, no pain was experienced when the large antecubital fossa vein was used. This may be because of less contact of the drug with the walls of the blood vessels. In our study we used the radial vein which is not as large as the antecubital vein. Duration of exposure of vein wall to Propofol injection is another important factor. They noticed that slow injection of Propofol caused more pain than rapid bolus injection. Perhaps, the rapid bolus is quickly cleared from the vein and replaced by blood.

We found that Paracetamol significantly reduced the incidence and severity of propofol induced pain in our patients. The study by Canbay et al[12] reported a Propofol pain incidence of 22.0% in the Paracetamol group. In their study a tourniquet was also applied but while they pre-treated all their patients with 50mg of Paracetamol we pre-treated our patients with 2mg/kg of Paracetamol making the mean dose of Paracetamol in our study 127.5±27mg which is much higher than 50mg used in the Canbay study. This may account for the lower incidence of Propofol injection pain in the Paracetamol group in our study compared to the Canbay study. Borazan et al[17] in their double-blind randomized study also pre-treated their patients with 2mg/kg Paracetamol but reported a incidence of Propofol injection of 8% which was higher than observed by us. In their study they also applied tourniquet but only for 1 minute compared to 2 minutes in our study. This suggests that the attenuation of Propofol injection pain by Paracetamol may also depend on the duration of tourniquet application during pre-treatment as well as the dose of Paracetamol.

The haemodynamic variables were comparable. There were no significant changes in the mean pulse rate, mean arterial pressure, and mean SpO_2 in the two groups at different intervals of baseline, laryngoscopy, at one minute and at five minutes post laryngoscopy. The study by Canbay et al[12] and Borazan and colleagues[17] also showed similar results. Hypotension and bradycardia often followed Propofol administration.[19]Propofol may lead to a reduction in the systemic vascular resistance and cardiac output is often thought to decreased.[20] Some studies though did not demonstrate a decrease in cardiac output with varying doses of Propofol.[21] Similarly Propofol is also considered to have a direct relaxant effect on venous smooth muscles and in this way an increase in venous capacitance may contribute to hypotension in patients.[22] Some studies that reported reduction in blood pressure following Propofol administration include those of Edomwonyi et al[23] and Abdul and Nauman.[19]Our patients did not experience hypotension probably because Propofol was administered slowly and the increase in pulse rate and mean arterial pressure seen in both groups at laryngoscopy can be attributed to the vasopressor response to laryngoscopy.

None of our patients in the two groups experienced local reactions to Propofol injection

Conclusion

The incidence of Propofol injection pain among our

patients was high. We also found that Paracetamol when applied with tourniquet significantly attenuated Propofol injection pain in our adult patients. There were also no significant difference in the haemodynamic variables of our patients following Propofol injection in those pretreated with Paracetamol and the placebo group. It would be interesting to find out if significant attenuation would occur if Paracetamol and Propofol were administered simultaneously without tourniquet and how Paracetamol will compare to more common methods like lignocaine.

Limitations: Our study did not measure plasma levels of Paracetamol and so could not determine the magnitude if any of central influence of Paracetamol in the attenuation of Propofol injection pain. We also did not assess the sedation levels of our patients while administering Propofol as some patients may become more rapidly sedated than others.

Conflict of interest

We declare that there are no conflicts of interest.

Reference

1. Gupta M, Mishara S, Gupta D, Gujjar M, Bhalnagar S. Prevention of pain on Propofol injection : A Comparative Randomized, double blind study between Lignocaine, Pethidine, Dexamethasone and placebo. The Internet J Anaesthesiol. 2007; 11(2): cited at www.ispub.com. Accessed 12/10/2018
2. Jalota C, Kalira V, George E, Shi YY, Hornuss C, Radke O et al. Prevention of pain on injection of Propofol: systemic review and meta-analysis. BMJ. 2011; 342.doi: https://doi.org/10.1136/bmj.d1110 Accessed 17/06/2019
3. Hamid Z, Mahshid N, Mohamadali S. Prevention of Propofol injection pain with small – dose ketamine. Middle East J Anesthesiol. 2009;20(3):401-403.
4. Wang W, Wu L, Zheng C, Sun L. Is Propofol injection pain really important to patients? BMC Anesthesiology. 2017; 17(24). https://doi.org/10.1186/s12871-017-0321-7 Accessed. Accessed 25/10/2019
5. 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; 88:1085-1091.
6. Sun NC, Wong AY, Irwing MG. A comparison of pain on intravenous injection between two preparatiions of Propofol. Anesth Analg 2005; 101(3): 675-678.
7. Lee P, Russel W J. Preventing pain on injection of Propofol: A comparison between Lignocaine pretreatment and Lignocaine added to Propofol. Anaesth Intensive Care. 2004; 32: 481-484.
8. Hamid Z, Mahshid N, and Mohamadali S. Prevention of Propofol injection pain with small-dose ketamine. Mid East J Anaesth. 2009; 20(3):401-401.
9. Memi D, Turan A, Karamanlio B, Kaya G, Sutt N, Pamukcu Z. The use of Magnesium Sulfate to prevent Propofol injection pain. Anesth Analg. 2002; 95: 606-608.
10. Agarwal A, Ansari MF, Gupta D, Pandey R. Raza M, Singh PK et al. Pre-treatment with Thiopental for prevention of pain associated with Propofol injection. Anesth Analg. 2004; 98:683-686.
11. Taafeek I. Sample size determination. In: Taafeek I ,ed. Research methodology and dissertation writing. Nigeria Lagos: Olocouger prints Lagos. 2009;74-75.
12. Canbay O, Celebi N, Arun O, Karagoz A H, Saricaoglu F, Ozgen S. Efficiency of Intravenous acetaminophen and lidocaine on Propofol injection pain. Br J Anaesth. 2008; 100(1): 95-98.
13. Dubey PK, Prasad SS. Pain on injection of Propofol: The effect of Granisertron pre-treatment. Clin J Pain. 2003;19:121-124.
14. Ozkan S, Sen H, Sizlan A, Yanerates O, Mutlu M, Dagli G. Comparison of Acetaminophen (with or without Tourniquet) and Lidocaine in Propofol injection pain. Bull Clin Psych Pharm. 2011; 21(2): 100-104.
15. Dedic A, Adam S, Gommers D, Van Bommel J,. Propofol injection pain: is it still an issue? The effect of premedication. Minn Anestesiol. 2010; 76(9): 720-724.
16. Agarwal A, Dhiraj S, Raza M,Ravinder P, Chandra KP,Prabhat K. et al. Vein Pre-treatment with Magnesium Sulfate to prevent pain on injection of Propofol is not justified. Can J Anaesth. 2004; 51:130-133.
17. Borazan H, Erdem TB, Kececioglu M, Otelcioslu S. Prevention of pain on injection of Propofol: A comparison of lidocaine with different doses of paracetamol. Eur J Anesthesiol. 2010; 27(3): 253-257.
18. Lee YS, Kim H, Brahim JS. Acetaminophen selectively suppresses peripheral prostaglandin E2 release and increases COX-2 gene expression in a clinical model of acute inflammation. Pain. 2007; 129:279–286
19. Abdul Z and Nauman A. The effects of duration of Propofol injection on haemodynamics. Mid East J Anaesth. 2010; 20(6):845-850.
20. Vuyk J, Sitsen E, Reckers M. Intravenous Anaesthetics. In: Miller BD. Eriksson IJ, Fleisher LA, Wiener-Kronish JP, Cohen NH, Young WL, eds. Miller's Anesthesia. Philadelphia, PS, USA: Elsevier. 2014; 821-863.
21. de Wit F, van Vliet AL, de Wilde RB, Jansen JR, Vuyk J, Aarts LP, et al. The effect of Propofol on haemodynamics: cardiac output, venous return, mean systemic filling pressure and vascular resistances. Br J Anaesth. 2016; 116 (6): 784-789
22. Rathmell JP, Roson CE. Intravenous sedatives and hypnotics. In: Flood P, Rathmell JP, Shafar S, eds. Stoelting's Pharmacology and Physiology in Anaesthesia Practice. Riverwoods, IL, USA: Wolters Kluwer Health. 2015; 160-203
23. Edomwonyi NP, Okonofua BA, Weerasinghe SA, Dangnan F. A comparative study of induction and recovery characteristics of Propofol and midazolam. Niger Postgrad Med J. 2001; 8(2): 81-85.