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Effect of Dilution of Propofol on Pain at Site of Injection: Comparison Between 1% vs. 0.33% Formulation

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Author`s Contribution

[1]Conception or design of the work, data collection
[2]Final approval of the version to be published
[3,4]Critical revision, analysis and
[5]Active Participation in active methodology

Funding Source: None
Conflict of Interest: None

Received: July 28, 2021
Accepted: Oct 21, 2021

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ABSTRACT

Objective: To study the effect of propofol dilution on pain at injection site with formulations of 1% and 0.33%.

Methodology: A randomized controlled trial was conducted for 24 months at the Department of Anaesthesia and Critical Care, Pakistan Institute of Medical Sciences Islamabad. A total of 100 patients were included in the study. Patients were divided into two equal groups: group C received 1% propofol while patients of group D received 0.33% formulation diluted with distilled water. Patients received propofol at the start of anesthesia before any premedication. A 5ml volume was injected over a period of 5s in an 18G cannula over dorsum of hands. Behaviourial pain scale was used and descriptive data analysis was done.

Results: Then mean age of patients was 37.36±14.77 with 46 males and 56 females. Pain at the injection site was experienced in 20 (40%) patients of group C whereas 16 (32%) patients experienced pain in group D. There was no association of pain with a strength of propofol solution (p value 0.405).

Conclusion: Strength of propofol solution has no association of pain at the injection site and dilution has no better effect in terms of pain score

Keywords: Intravenous anaesthesia, Pain at the site of injection, Propofol.

Cite this article as: *Nasir KK, Hussain R, Waqar SH. Shahani AS, Tahir Z. Effect of Dilution of Propofol on Pain at Site of Injection: Comparison Between 1% vs. 0.33% Formulation. Ann Pak Inst Med Sci. 2021; 17(3):227-231.doi. 10.48036/apims.v17i3.554*

Introduction

Propofol is an intravenous anesthetic agent famous for its rapid onset of action. It is a drug used for the maintenance of total intravenous anesthesia and for sedation of ICU patients.[1] It is given as 1 % solution that is available commercially. It has achieved great popularity because of its favorable recovery characteristics and antiemetic effect.[2]

The mechanism by which propofol induces a state of general anesthesia may involve the facilitation of inhibitory transmission by GABA. It is an ideal anesthetic agent for outpatient anesthesia. The formulation of propofol consists of white aqueous emulsion in soybean oil and purified egg lecithin. One of the major drawbacks with its use is pain at the injection site.[3]

Pain on injection with propofol injections is still a major issue. Several components involved in this occurrence have been investigated for their pain-relieving properties.[4] Since its discovery, various attempts have been made for reducing this pain.[5] Various methods have been devised. These include mixing propofol with lignocaine, using a large intravenous cannula, using a large vein in the antecubital fossa instead of the dorsum of hand to give the drug. Ondansetron pre-treatment has also been hypothesized to reduce the incidence of pain on injection of propofol.[6]

All phenols irritate skin and mucous membrane. Thus, propofol being an alkylphenol is expected to cause pain in spite of the fact that it is almost isotonic.[7] Various factors that affect pain at the site of injection include size and site of the cannula, concentration of propofol, speed of injection, size of the vein in which propofol is injected and pre-treatment with different drugs.[8,9]

The quest to solve this problem continues. Sourabh Aggarwal et al studied the effect of dilution of propofol on pain at the injection site.[10] Double and triple dilution of 1% propofol was used to study the effect on pain at the injection site. Stokes DN et al concluded that dilution of propofol significantly reduced the incidence of severe pain during injection.[11]

The purpose of this study was to see the effect of dilution of propofol on pain at the injection site. Hypothesis was that dilution of propofol reduces pain at the injection site. The effect of propofol dilution on pain at the injection site with formulations of 1% and 0.33% was studied, so that to find out a better dilution for the patients.

Methodology

A randomized controlled trial was conducted for 24 months at the Department of Anaesthesia and Critical Care, Pakistan Institute of Medical Sciences Islamabad. A total of 100 patients were included in the study, who have ASA status of I, II, and III and planned for elective surgery under general anesthesia. After getting approval from the hospital ethical committee of Pakistan Institute of Medical Sciences, ~~a~~ written informed consent was taken from all the patients. A pre-anesthetic assessment of the patient was done. The patients were divided into two groups by the lottery method. One group received propofol 1% and the other group received 0.33%. In total 100 patients were allocated into two groups C and D representing strength of propofol solution being administered or in simple terms C representing concentrated and D representing diluted. Patients in group C received 5ml of 1% propofol before induction of anesthesia whereas patients in group D received 5ml of 0.33% propofol. Both groups were observed for pain at the site of injection according to behavioral pain score.

Inside the operation room, once the patient was prepared for general anesthesia, standard monitoring with Electrocardiogram (ECG), Pulse Oximetry (SPO2) and Non-invasive blood pressure measurements (NIBP) was started. Intravenous access with one 18 gauge cannulas was established on the dorsum of the hand. The patient was injected with 5 ml of propofol in 5 seconds and pain assessed according to behavioral pain scale by another doctor who was unaware of that, which formulation was being used. Data was recorded on the questionnaire and presence or absence of pain was assessed according to the behavioural Pain scale, it was observed and recorded by two personals at a time.

Data was collected, recorded, arranged and analyzed on SPSS version 25. The mean and standard deviation were calculated for quantitative variables like patient age, weight, pain at site of injection. Frequency and percentages were calculated for gender, ASA I, II and III graded patients and no pain. Chi-square test was applied to compare no pain between two groups. P value<0.05 was considered to be significant. Effect modifiers like age, gender, weight, ASA, were controlled by stratification. Post stratification chi-square test was applied.

Results

The main characteristics of the patients of both groups are shown in Table I.

Overall 36 patients experienced pain at injection site. Pain was experienced by 20 (40%) patients in group C whereas 16 (32%) patients in group D. Fig: 1. 16 (32%) patients experienced pain in group D whereas 34 (68%) did not (p value=0.305). In group C out of 50 patients, 20 (40%) experienced pain whereas 30(60%) did not (p value=0.403). (Table 2)

Association of no pain with the strength of propofol solution was calculated and the p value came out to be 0.405, which was not significant. Stratification of effect modifier age (years) was compared with pain at site of injection. Three strata, consisting 18-27.33 years, 27.34 – 45 years and 45.01-60 years namely A, B and C respectively were formulated. The p values for groups A, B and C came out to be 0 .604, 0.639 and 0.804 respectively which were not significant.

Stratification of effect modifier gender was compared with no pain at site of injection with two groups M and F. There were 12 and 18 patients with no pain in group M i.e. male population with p value of 0.146 which was not significant. Whereas there were 18 and 16 in group F with no pain and a p value of 0.835 which was not significant. (Table III)

Stratification of effect modifier weight (kg) was compared with no pain at site of injection. There were three strata, with weights 45-65, 65.01-70 and 70.01-160 named E, F and G. The p values for groups E, F and G were found to be 0.642, 0.568 and 0.542 respectively which were not significant.

Stratification of effect modifier ASA status of the patient pain was compared with pain at site of injection. The p value for ASA I was found to be 0.227 and for ASA II it was 0.708. Both of these were insignificant.

Discussion

Propofol is the commonest agent used for induction of anesthesia because of its favourable pharmacokinetics and pharmacodynamics. But the pain caused by it at injection site can become a concern for the patients and cause distress. Many studies have been conducted since its inclusion in the formulary of induction agents.[12-14] These studies have tried to highlight the ways by which pain can be reduced at the injection site, but none have come up with an absolute way to reduce pain. This study is one of these efforts and used different concentrations of propofol to study the effect of pain at the injection site.

Table I: Characteristics of the patients.

	Group C (Concentrated) (n=50)	Group D (Diluted) (n=50)	Total
Mean age (years)	33.68±14.94	41.04+13.78	37.36±14.77
Gender			
Male	22 (44%)	24(48%)	46
Female	28 (56%)	26(52%)	54
Mean weight (kg)	67.24+15.34	73.02 +7.86	70.13±11.60
ASA			
I	37 (74%)	40 (80%)	77 (77%)
II	13 (26%)	10 (20%)	23 (23%)
III	0	0	0

Table II: Comparison of Pain among both groups.

	Group C (Concentrated) (n=50)	Group D (Diluted) (n=50)	P value	Total
Pain score	1.54 ± 0.76	1.36 ± 0.56	0.405	1.45 ± 0.67
Pain at site of injection				
No pain	30 (60%)	34 (68%)	0.403	64 (64%)
Pain	20 (40%)	16 (32%)	0.305	36 (36%)

Table III: Age with no pain at site of injection.

PATIENT AGE (years) STRATAS			Propofol solution strength		Total	P value
			1% propofol	0.33% propofol		
18-27.33	pain at site of injection	no pain	12	3	15	0.604
		pain	13	5	18	
	Total		25	8	33	
27.34-45.00	pain at site of injection	no pain	10	18	28	0.639
		pain	4	5	9	
	Total		14	23	37	
45.01-60	pain at site of injection	no pain	8	13	21	0.804
		pain	3	6	9	
	Total		11	19	30	

Soltesz S et al studied the effect of dilution of propofol on pain at the injection site in 60 pediatric patients of aged 2-6 years.[15] They divided the patients into two groups of 30 each, with one group receiving 1%% formulation and the other group receiving 0.5% formulation. All children were pre-medicated with midazolam and remifentanil in appropriate dosages. Their findings were that the incidence of pain in the group receiving 0.5% formulation was lesser than the other group receiving 1% formulation i.e. 23% compared to 70%[8]. They concluded that dilution has an effect on reducing the pain at the injection site.[15]

One of the most pioneer studies in this perspective is by Stokes DN.[11] In this study the patients were divided into two groups receiving 1% and 0.5% propofol. Propofol was diluted by adding 5% dextrose. The incidence of pain was lesser in the population receiving 0.5% propofol. Stokes DN concluded that pain can be reduced by dilution of propofol but, use of a different dilutant could have been a reason for results in comparison to our study.

The pain induced by propofol was studied by comparing serial dilutions of propofol in Intralipid and 5% glucose and injecting these through intravenous and intracutaneous routes by Klement W and Arndt JO.[16] They found out that propofol caused pain in a concentration-related manner in six out of eight patients after IV injection and in all eight subjects after intracutaneous injections. The pain was maximal with the concentrated formulation of propofol. Dilution with 10% Intralipid reduced pain more than that with 5% glucose. They concluded that the intensity of pain after IV injection of propofol was related to its free aqueous concentration. The intracutaneous route was a different factor in comparison to our study along with the use of a different solution for dilution.

Doenicke AW et al theorised that the attentiveness of propofol in the aqueous phase of the solution may be the most important variable which is responsible for deciding the pain experienced during the intravenous injection of the drug.[17] They assumed that concentration of propofol in the aqueous phase of the solution or preparation which is 18.57 micrograms/mL can be lessened by increasing the fat content of the solvent i.e. the lipoid phase. Their results recommended that a smaller concentration of propofol component in the aqueous phase of the emulsion solution moderates pain on injection. The mechanism of action is quite distinguishable as with the addition of more lipid (10 mL), a higher percentage of propofol is captivated by fat particles. As a result, they determined that if solvents that permit a smaller concentration of the drug in the aqueous phase of oil-in-water emulsions were used for propofol and other drugs that cause pain on injection, pain would be reduced and patient satisfaction may be increased.

Sourabh Aggarwal in his study divided the patients in three groups receiving 1%, 0.5% and 0.33% formulation of propofol. No pain was knowledgeable by 20% of patients getting threefold diluted (0.33%) propofol and harshness of pain was expressively reduced as likened to 1% and 0.5% propofol. The patient populace size in each group was 20. The diluent used was normal saline. There was no statistically substantial alteration in the pain score in group II as compared to patients in group I. However, there was a statistically noteworthy lessening in the pain score in group III as compared to patients in group I (P value 0.02) and group II (P value 0.03). The patients of group I, II, and III conventional 1% propofol 2 ml, 0.5% propofol 4 ml, and 0.33% propofol 6 ml, correspondingly, over a period of 4 s and pain felt was evaluated. They concluded a substantial diminution in both incidence and severity of pain during injection of propofol with 0.33% propofol without momentous adverse hemodynamic properties during induction.[10]

The various differences in our study compared to the studies conducted previously, on the effect of concentration of propofol on incidence of pain may be due differences in variables such as, population size, diluent used, infusion time, and site of injection, cannula size, pain assessment tools and age.[18]

Conclusion

There was no difference in the incidence of pain in patients who received 0.33% diluted formulation of propofol as compared to the patients receiving 1% formulation. It is further stated that more studies will have to be done that may prove purposeful.

References

1. Desai SP, Desai MS, Pandav CS. The discovery of modern anaesthesia-contributions of Davy, Clarke, Long, Wells and Morton. Indian Journal of Anaesthesia. 2007; 51 (6): 472–8.
2. Abou-Chebl A, Yeatts SD, Yan B, Cockroft K, Goyal M, Jovin T, et al. Impact of General Anesthesia on Safety and Outcomes in the Endovascular Arm of

Interventional Management of Stroke (IMS) III Trial. Stroke. 2015; 46 (8):2142-8. https://doi.org/10.1161/STROKEAHA.115.008761
3. Liljeroth, E. Pain induced by propofol - clinical studies on drug composition and administration. Department of Anaesthesia and Intensive Care, Lund. 2007: 17-28.
4. Zaman B, Noorizad S, Seyed Siamdoust S, Alimian M, Parak S. The Effect of Propofol Infusion Before Administration of Its Bolus Dose on Propofol Injection Pain and Serum Complement C3 Levels; A Randomized Clinical Trial. Anesth Pain Med. 2019; 9(6):e84067. https://doi.org/10.5812/aapm.84067
5. Hirmanpour A, Talakoub R, Safavi M, Honarmand A, Shafa A, Emamdoost K. Comparing the injection pain of propofol emulsion 1% (MCT/LCT) and propofol emulsion 2% (Propofol Lipuro) in combination with lidocaine in patients undergoing gynecologic surgery with general anesthesia. Arch Anesth Crit Care. 2017; 3(3):342-7.
6. Vretsakis G, et al. Management of intraoperative fluid balance and blood conservation techniques in adult cardiac surgery. The Heart Surgery Forum. 2011; 14: 28. https://doi.org/10.1532/HSF98.2010111
7. Brown EN, Lydic R, Schiff ND. General Anesthesia, Sleep and Coma. New England Journal of Medicine. 2010; 363(27):2638–50. https://doi.org/10.1056/NEJMra0808281
8. Desousa KA. Pain on propofol injection: Causes and remedies. Indian J Pharmacol. 2016; 48(6):617-623. doi:10.4103/0253-7613.194845. https://doi.org/10.4103/0253-7613.194845
9. Mohanchandra Mandal: Opioids as co-induction agents - the pros and cons. Int J Crit Illn Inj Sci. 2017; 7(2): 77–78. https://doi.org/10.4103/IJCIIS.IJCIIS_25_17
10. Sourabh Aggarwal, Mahendra Kumar, and Vishal Sharma: A single-center randomized-controlled trial to study effect of dilution on propofol-induced injection pain at injection site. Saudi J Anaesth. 2011; 5(3):282-85.https://doi.org/10.4103/1658-354X.84102
11. 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(2): 202-03. https://doi.org/10.1093/bja/62.2.202
12. Jalota L, Kalira V, George E, Shi Y, Hornuss C, Radke O et al. Prevention of pain on injection of propofol: systematic review and meta-analysis BMJ. 2011; 342 :d1110. https://doi.org/10.1136/bmj.d1110
13. Rajasekhar D, Rao DVK. The Effect of Dilution of Propofol on Propofol Induced Injection Pain A Randomized Controlled Study. IOSR Journal of Dental and Medical Sciences (IOSR-JDMS). 2019; 18(6): 23-26.
14. Guen ML, Grassin-Dalyle S, Cornet C, Genty A, Chazot T, Dardelle D et al. Comparison of the Potency of Different Propofol Formulations-A Randomized, Double-blind Trial Using Closed-loop Administration. Anesthesiology. 2014; 120:355-64. https://doi.org/10.1097/01.anes.0000435741.97234.04
15. Soltész S, Silomon M, Gräf G, Mencke T, Boulaadass S. Effect of a 0.5% Dilution of Propofol on Pain on Injection during Induction of Anesthesia in Children. Jour et Anesthesio. 2007; 106: 80-84. https://doi.org/10.1097/00000542-200701000-00015
16. Klement W, Arndt JO. Pain on injection of propofol: effects of concentration and diluent. Br J Anaesth. 1991; 67(3):281-4. https://doi.org/10.1093/bja/67.3.281
17. Doenicke AW, Roizen MF, Rau J, Kellermann W, Babl J. Reducing pain during propofol injection: the role of the solvent. Anesth Analg. 1996; 82(3):472-4. https://doi.org/10.1213/00000539-199603000-00007
18. Kim J, Kim D, Lee HG. Effect-site concentration of remifentanil for preventing propofol injection pain during induction of balanced anesthesia. Anesthesia and Pain Medicine 2020; 15(2):152-156. https://doi.org/10.17085/apm.2020.15.2.152