The Professional Medical Journal
www.theprofesional.com

**DOI:** 10.29309/TPMJ/2020.27.1.4403

**ORIGINAL PROF-0-4403**

# PAIN DURING INTRAVENOUS PROPOFOL INJECTION AND ITS PREVENTION IN THE PEDIATRIC POPULATION. A RANDOMIZED CONTROLLED TRIAL.

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**Article received on:**
24/07/2018
**Accepted for publication:**
06/05/2019

**ABSTRACT… Objectives:** The aim of our study is to observe the pain difference as experienced by the pediatric patient when administered different preparations of propofol utilizing the verbal rating scale. **Study Design:** Prospective double-blind randomized control trial. **Setting:** A large tertiary care hospital in Karachi, Pakistan. **Period:** 6 months from June 2016 to November 2016. **Material & Methods:** The final patient population included in the study was n= 180 and were divided into six groups. These patients received general anesthesia and underwent surgery. Patients in Group A received 2ml of normal saline and a mixture of propofol and normal saline after waiting for half a minute. Group B patients received 0.5mg/kg Lidocaine followed by normal saline after waiting for half a minute. Group C received 2ml of normal saline followed by a mixture of propofol and Lidocaine after half a minute. Group D received 0.2mg/kg of Ketamine followed by a mixture of normal saline and propofol. Group E patients received 2ml of normal saline followed by a mixture of propofol and Ketamine half a minute later. And finally, patients belonging to group F received 2ml of normal saline followed by a mixture of propofol M/LCT and normal saline half a minute later respectively. **Results:** The gender, age, body weight and ASA grade of all the pediatric patients were similar having a P value of >0.05. The incidence rate of propofol injection pain in the groups were found to be Group A= 76.66%, Group B= 66.66%, Group C= 50%, Group D= 60%, Group E= 63.33%, Group F= 60% respectively. The incidence rate for adverse events was significantly lower in all the groups as compared to Group A that is the normal saline and propofol group having a p-value of less than 0.01. And the incidence rate of adverse events was lower in Groups C, D, E, and F were significantly lower than Group B having a p-value of less than 0.05. All the experimental groups had significantly lower scores of the VRS scale as compared to the control group (Group A) and the intergroup differences were found to be statistically significant having a p-value of less than 0.01. **Conclusion:** In our study, we found that the injection pain of propofol administration in the pediatric population was significantly reduced when using M/LCT pre-injection, 0.5mg/kg lidocaine or 0.2mg/kg of Ketamine. Another good combination is mixing 180mg propofol with 40mg of lidocaine or mixing propofol with 16mg of Ketamine.

**Key words:** Injection Pain, Ketamine, Lidocaine, Propofol, Pediatric.

**Article Citation:** Raza H, Siddiqui MA, Soomro A, Kamlaish. Pain during intravenous propofol injection and its prevention in the pediatric population. A randomized controlled trial. Professional Med J 2020; 27(1):191-196.
**DOI:** 10.29309/TPMJ/2020.27.1.4403

## INTRODUCTION

Propofol which is an anesthetic agent with ultrashort action when delivered intravenously and a very rapid onset of effect.[1] The main adverse reaction experienced by patients upon administration is the sensation of pain which is more pronounced in intravenous injection and ranks seventh among thirty-three major clinical concerns, with an incidence rate between 28% and 90% respectively.[2,3] In the pediatric population the problem of pain has been mitigated to some extent by using a local anesthesia or mixing the drug with lidocaine or by cooling the drug prior to administration.[4] In about 60% of the patients IV injection of 0.5mg/kg lidocaine upon tying a rubber tourniquet on the forearm between 30 seconds to 120 seconds prior to the administration of propofol decreased the pain in 60% of the patients.[5] The incidence rate of propofol injection pain is between 32% and 48% and despite efforts by anesthesiologists, it cannot be completely prevented.[6] The available form of

propofol is made by mixing it with soybean oil emulsion (1% of propofol in 10% of soybean oil emulsion). The instability of this emulsion might be a cause of pain.[7] Pharmacists improved this formulation by introducing Medium/long chain propofol which has increased lipid solubility due to using medium/long chain fatty acids as solvents, which decreased the pain experienced by the patient.[7] This medium/long chain fatty acid solvent decreased the aqueous phase concentration of propofol to 14.0 +/- 0.5 mg/liter and reduced the injection pain by about 25% as compared to its long chain alternative with an aqueous phase concentration of 18.6 +/- 0.6 mg/liter and a significant amount of pain experienced by the patient regardless of administration of pre-injection lidocaine 10mg, there aren't many large-scale studies done to study and compare the pain difference of medium/long chain preparation with long chain propofol.[8,9,10] Hence we conducted a double-blind prospective randomized controlled trial to observe the pain difference as experienced by the patient when administered these two different preparations of propofol in the pediatric population utilizing the verbal rating scale.

## METHODS

The type of study was a prospective double-blind randomized control trial, conducted for a period of 6 months duration from June 2016 to November 2016, at a large tertiary care hospital in Karachi, Pakistan. The patient population was divided into six groups. Randomization was done using a random number generator software. Group A receiving a pre-injection of 0.5mg/kg lidocaine or 0.2 mg/kg Ketamine prior to injection of long-chain propofol, while group B received 40mg, the study was approved by the hospitals ethics committee and the patients (for older patients only) and their parents/guardians signed a fully informed consent to participate in the study. The age range of the patients included in the study was 7 years with a minimum age of 5 years and a maximum age of 12 years. Patients were classified using the American Society of Anesthesiologist (ASA) classification as grades I and II. The exclusion criteria were patients with allergy to local anesthetics, the drugs used in the study, asthma, mental disorders, neurological dysfunction, liver or kidney dysfunction, emergency cases, phlebitis and patients in whom the venipuncture was exceptionally difficult. The final patient population included in the study was n= 180 and were divided into six groups. These patients received general anesthesia and underwent surgery. Patients in Group A received 2ml of normal saline and a mixture of propofol and normal saline after waiting for half a minute. Group B patients received 0.5mg/kg Lidocaine followed by normal saline after waiting for half a minute. Group C received 2ml of normal saline followed by a mixture of propofol and Lidocaine after half a minute. Group D received 0.2mg/kg of Ketamine followed by a mixture of normal saline and propofol. Group E patients received 2ml of normal saline followed by a mixture of propofol and Ketamine half a minute later. And finally, patients belonging to Group F received 2ml of normal saline followed by a mixture of propofol M/LCT (medium-/light chain triglyceride) and normal saline half a minute later respectively. Double blinding of was done as the anesthetist involved in preparing the medication was not involved in the administration of it, and the patients were unaware of the medication used as well. Our protocol was inclusive to any adverse events where we had designed to break the double blinding and the anesthetist involved in preparing the medication was also available in the room at all time in case of adverse events. All the patients did overnight fasting preoperatively and did not receive any premedication. A 24G IV catheter was inserted and rinsed with Ringers Lactate. Routine measurements were taken during the procedure such as electrocardiography, pulse oximetry, blood pressure monitoring and end-tidal carbon dioxide monitoring. A t-tube was utilized with a 2ml syringe on one end, the drug was injected at a rate of 1ml/6 seconds, half a minute later induction was done by TV propofol of 2.5mg/kg at a speed of 1ml/6 seconds with a speed pump. The children were then put on 100% oxygen assisted ventilation after they lost consciousness and stopped breathing. Afterward, the patients were given 2ug/kg fentanyl and 0.2mg/kg cus-atracurium besylate. The patients were shifted on inhalation anesthesia following tracheal intubation and utilizing a laryngeal mask. Spontaneous

breathing was maintained throughout the surgical procedure. The pain scale was between 0 and 4, with 0 being no pain and 4 being the most painful condition with intermittent numbers reflecting degrees of pain. The verbal rating scale (VRS) was used to get a baseline reading prior to injection and then during and after 10 seconds injection and if possible every minute until anesthesia was achieved. Other variables such as heart rate and adverse reactions were noted in a predefined proforma which also included patients other demographic variables. Data were analyzed using IBM SPSS version 21 for windows. The mean and standard deviation was utilized for categorical data, one-way analysis of variance or ANOVA was used to make intra-group comparisons. Chi-square test was used for numerical data and rank sum test was used for ordinal data. A p value of less than 0.05 was considered to be statistically significant.

## RESULTS

The total number of patients in the study was n=180, divided into six groups of n=30 patients each. The gender, age, body weight and ASA grade of all the pediatric patients were similar having a P value of >0.05. For other patient characteristics refer to Table-I. The incidence rate of propofol injection pain in the groups were found to be Group A= 76.66%, Group B= 66.66%, Group C= 50%, Group D= 60%, Group E= 63.33%, Group F= 60% respectively. The incidence rate for adverse events was significantly lower in all the groups as compared to Group A.

That is the normal saline and propofol group having a p-value of less than 0.01. And the incidence rate of adverse events was lower in Groups C, D, E, and F were significantly lower than Group B having a p-value of less than 0.05. The differences among the other groups were not found to be statistically significant, having a p-value of greater than 0.05. The Verbal Rating Scale (VRS) score was used to determine the intensity of pain as experienced by the patients. All the experimental groups had significantly lower scores of the VRS scale as compared to the control group (Group A) and the intergroup differences were found to be statistically significant having a p-value of less than 0.01. The heart rates of patients in all the groups were similar prior to the injection of propofol (p-value of >.0.5), and after the injection of propofol, their heart rates were significantly elevated (p-value of <0.05). The other details pertaining to heart rate as described in Table-I. There were no significant differences when it comes to adverse reactions among all the groups having a p-value of >0.05.

## DISCUSSION

Propofol is widely being used to its rapid action and short half-life. However, its administration is linked with the sensation of significant amount of pain.[11,12,13] This pain is caused due to the interaction of the aqueous phase of the emulsion and the free nerve endings. It might also be caused due to bradykinin production and the activated kinin cascade system.[14,15] Bradykinin has its effect on the vascular wall, making it more permeable to propofol hence more activation of the nerve endings.[16] The incidence rates of pain during propofol injection in adults is reported to be between 28 to 90% and in children to be between 30 and 90%. Making a mixture of propofol and lidocaine is shown to decrease the intensity of pain in children (59% with propofol alone and 22.5% with propofol and lidocaine mixture).[17] Lidocaine might stabilize the kinin cascade system it might also produce lipid droplets which may cause a fat embolism.[18]

In our study patients belonging to the propofol with normal saline (Group A) and lidocaine with normal saline (Group B) were more likely to experience pain. 10% M/LCT (medium-/light chain triglyceride) prepared with propofol can decrease the pain experienced by the patients. In our study the pain intensity in the M/LCT group was significantly lower than that of after normal saline treatment, however, it was slightly higher than that of lidocaine treatment. Ketamine works on the NMDA receptors and helps in establishing local anesthesia hence lowering the pain felt.[19,20] Pre-injection with Ketamine reduces pain from 84% to 26% and also reduced the blood pressure reducing effects as caused by the administration of propofol.[21]

| Variable | Group A | Group B | Group C | Group D | Group E | Group F | P-Value |
|---|---|---|---|---|---|---|---|
| Age in years | 6.42 +/- 1.69 | 6.36 +/- 1.76 | 7.71 +/- 1.34 | 6.69 +/- 1.58 | 7.12 +/- 1.68 | 7.12 +/- 1.98 | 0.298 |
| Body weigh in kg | 21.39 +/- 4.16 | 23.36 +/- 5.78 | 21.69 +/- 6.62 | 21.35 +/- 7.40 | 23.55 +/- 6.30 | 24.16 +/- 5.01 | 0.398 |
| ASA grade I | 20 | 20 | 22 | 17 | 16 | 16 | 10.993 |
| ASA grade II | 10 | 10 | 8 | 13 | 14 | 14 | |
| **Gender** | | | | | | | 0.756 |
| Male | 19 | 20 | 18 | 20 | 19 | 18 | |
| Female | 11 | 10 | 12 | 10 | 11 | 12 | |
| **Degree of pain** | | | | | | | |
| Mild pain | 7 | 9 | 9 | 10 | 10 | 8 | |
| Moderate pain | 12 | 10 | 5 | 8 | 8 | 9 | |
| Severe pain | 4 | 1 | 1 | 0 | 1 | 1 | |
| Painless | 7 | 10 | 15 | 12 | 11 | 12 | |
| **Heart Rate** | | | | | | | |
| Before Injection | 92.62 +/- 10.23* | 94.76 +/- 12.31*#◊ | 95.75 +/- 10.55* | 97.34 +/- 11.29* | 93.55 +/- 13.45*# | 95.00 +/- 10.38*#◊ | <0.05 |
| After Injection | 116.42 +/- 12.45* | 116.46 +/- 12.50*#◊ | 105.34 +/- 9.48* | 109.39 +/- 12.77* | 105.32 +/- 13.48*# | 106.49 +/- 10.48*#◊ | <0.05 |
| **Complications** | | | | | | | |
| Nausea/Vomiting | 1 | 2 | 2 | 3 | 3 | 1 | |
| Diplopia | 3 | 1 | 1 | 0 | 0 | 0 | |
| Cardiac disorder | 0 | 0 | 0 | 0 | 0 | 0 | |
| Phlebitis | 0 | 0 | 1 | 0 | 0 | 0 | |
| Mental disorder | 0 | 0 | 0 | 1 | 1 | 0 | |
| Allergy | 0 | 0 | 0 | 0 | 0 | 0 | |

**Table-I. Patient demographics and baseline characteristics.**
*Compared with Group A #Compared with Group B ◊P value less than 0.05

The pain felt by the patient after injection of propofol can be immediate or delayed by 10 to 20 seconds.[22] Pre-injection with Ketamine lowered the injection pain, even lower than the lidocaine pre-injection, without significantly affecting the hemodynamics. However, Ketamine is associated with adverse events such as mental excitability, nausea and vomiting and delayed recovery among others.[23] In our study, the differences in the observed adverse events were not statistically significant, which could be due to the administration of a lower dose of Ketamine or the small sample size of our study. In the pediatric population, it is tantamount to appease the psychological state of the patient thus reducing anxiety which reduces the subjective sensation of pain.[24] In our study we tried to appease the patient as much as possible however there were no fixed criteria. Anesthesiologists have adopted administration of a combination of drugs to reduce the pain of propofol injection.[25] Zhang et al looked at various preparations of propofol with fentanyl, sufentanil and remifentanil in gastrointestinal endoscopy.[26] They found the combination of propofol with sufentanil to be the best combination for reducing pain. West et al compared various methods as well and concluded that M/LCT is effective in decreasing pain.[9] In our study the experimental groups were more effective in reducing the sensation of pain after propofol injection, however, it is important to study the different doses and combination of drugs further to refine the combination and elicit the most effective pain reducing the combination

of drugs.

## CONCLUSION

In our study, we found that the injection pain of propofol administration in the pediatric population was significantly reduced when using M/LCT pre-injection, 0.5mg/kg lidocaine or 0.2mg/kg of Ketamine. Another good combination is mixing 180mg propofol with 40mg of lidocaine or mixing propofol with 16mg of Ketamine.



## REFERENCES


1. Chidambaran V, Costandi A, D'Mello A. **Propofol: A review of its role in pediatric anesthesia and sedation.** CNS Drugs. 2015; 29:543- 563. doi: 10.1007/ s40263-015-0259-6.

2. Habre C, Tramèr MR, Pöpping DM, Elia N. **Ability of a meta-analysis to prevent redundant research: A systematic review of studies on pain from propofol injection.** BMJ. 2014; 348:g5219. doi: 10.1136/ bmj. g5219.

3. Goktug A, Gulec H, Takmaz SA, Turkyilmaz E, Basar H. **Lidocaine alleviates propofol-related pain much better than metoprolol and nitroglycerin.** Braz J Anesthesiol. 2015; 65:338-342. doi: 10.1016/j. bjane.2014.01.006.

4. Walther-Larsen S, A0agaard GB, Friis SM, Petersen T, Møller- Sonnergaard J, Rømsing J. **Structured intervention for management of pain following day surgery in children.** Paediatr Anaesth. 2016; 26:151-157. doi: 10.1111/pan.12811.

5. Oh JE, Lee HJ, Lee YH. **Propofol versus Midazolam for Sedation during Esophagogastroduodenoscopy in Children.** Clin Endosc. 2013; 46:368-372. doi: 10.5946/ce.2013.46.4.368.

6. Pei S, Zhou C, Zhu Y, Huang B. **Efficacy of ondansetron for the prevention of propofol injection pain: a meta-analysis.** J Pain Res. 2017; 10:445-450. doi: 10.2147/ JPR.S128992.

7. Damitz R, Chauhan A. **Rapid dissolution of propofol emulsions under sink conditions.** Int J Pharm. 2015; 481:47-55. doi: 10.1016/j. ijpharm.2015.01.045.

8. Feng AY, Kaye AD, Kaye RJ, Belani K, Urman RD. **Novel propofol derivatives and implications for anesthesia practice.** J Anaesthesiol Clin Pharmacol. 2017; 33:9-15. doi: 10.4103/0970-9185.202205.

9. West N, Dumont GA, van Heusden K, Petersen CL, Khosravi S, Soltesz K, et al. **Robust closed-loop control of induction and maintenance of propofol anesthesia in children.** Paediatr Anaesth. 2013; 23:712-719. doi: 10.1111/pan.12183.

10. Brouse CJ, Karlen W, Dumont GA, Myers D, Cooke E, Stinson J, et al. **Monitoring nociception during general anesthesia with cardiorespiratory coherence.** J Clin Monit Comput. 2013; 27:551-560. doi: 10.1007/s10877-013-9463-4.

11. Kim JM, Lee JH, Lee HJ, Koo BN. **Comparison of emergence time in children undergoing minor surgery according to anesthetic: Desflurane and sevoflurane.** Yonsei Med J. 2013; 54:732-738. doi: 10.3349/ymj.2013.54.3.732.

12. Singh HS, Singh LD, Singh NR, Singh TH, Thokchom RS, Monohar PS. **Effects of dexmedetomidine and lidocaine in alleviating propofol injection pain: A randomized controlled trial.** J Med Soc. 2015; 29:31-34. doi: 10.4103/0972-4958.158929.

13. Euasobhon P, Dej-Arkom S, Siriussawakul A, Muangman S, Sriraj W, Pattanittum P, et al. **Lidocaine for reducing propofol-induced pain on induction of anesthesia in adults.** Cochrane Database Syst Rev. 2016; 2: CD007874. doi: 10.1002/14651858.CD007874.pub2.

14. Lee M, Kwon T, Kim S, Kim S, Park K, Jeon Y. **Comparative evaluation of the effect of remifentanil and 2 different doses of esmolol on pain during propofol injection: A double-blind, randomized clinical consort study.** Medicine (Baltimore). 2017; 96:e6288. doi: 10.1097/ MD.0000000000006288.

15. Nishimoto R, Kashio M, Tominaga M. **Propofol-induced pain sensation involves multiple mechanisms in sensory neurons.** Pflugers Arch. 2015; 467:2011-2020. doi: 10.1007/s00424-014-1620-1.

16. Wang D, Chen C, Chen J, Xu Y, Wang L, Zhu Z, et al. **The use of propofol as a sedative agent in gastrointestinal endoscopy: A meta-analysis.** PLoS One. 2013; 8:e53311. doi: 10.1371/journal. pone.0053311.

17. Martin DP, Bhalla T, Thung A, Rice J, Beebe A, Samora W, et al. **A preliminary study of volatile agents or total intravenous anesthesia for neurophysiological monitoring during posterior spinal fusion in adolescents with idiopathic scoliosis.** Spine (Phila Pa 1976). 2014; 39:E1318-1324. doi10.1097/ BRS.0000000000000550.

18. Costi D, Cyna AM, Ahmed S, Stephens K, Strickland P, Ellwood J, et al. **Effects of sevoflurane versus other general anesthesia on emergence agitation in children.** Cochrane Database Syst Rev. 2014; CD007084. doi: 10.1002/14651858.CD007084.pub2.

19. Kim J, Kim SY, Lee JH, Kang YR, Koo BN. **Low-dose dexmedetomidine reduces emergence agitation after desflurane anesthesia in children undergoing strabismus surgery.** Yonsei Med J. 2014; 55:508-516. doi: 10.3349/ymj.2014.55.2.508.

20. Chiaretti A, Benini F, Pierri F, Vecchiato K, Ronfani L, Agosto C, et al. **Safety and efficacy of propofol administered by paediatricians during procedural sedation in children.** Acta Paediatr. 2014; 103:182-187. doi: 10.1111/apa.12472.

21. Fallah R, Ferdosian F, Shajari A. **Non-Parenteral Medications for Procedural Sedation in Children- A Narrative: Review Article.** Iran J Child Neurol. 2015; 9:1-8.

22. Chandar R, Jagadisan B, Vasudevan A. **Propofol-ketamine and propofol-fentanyl combinations for nonanesthetist-administered sedation.** J Pediatr Gastroenterol Nutr. 2015; 60:762-768. doi: 10.1097/MPG.0000000000000722.

23. Tian X, Yang YH, Wei HY, Lao JQ, Wang HP, Tian YY. **Rapid sedation induced by fentanyl combined with propofol via an intrathecal chemotherapy injection for leukemia in children.** Genet Mol Res. 2015; 14:3687-3693. doi: 10.4238/2015.April.17.18.

24. Ni J, Wei J, Yao Y, Jiang X, Luo L, Luo D. **Effect of dexmedetomidine on preventing postoperative agitation in children: A meta-analysis.** PLoS One. 2015; 10:e128450. doi: 10.1371/journal.pone.0128450.

25. Aronson JK. **Management of pain during injection of propofol.** Adverse Drug React Bull. 2014; 287:1107-1110. doi: 10.1097/ FAD.0000000000000005.

26. Zhang L, Bao Y, Shi D. **Comparing the pain of propofol via different combinations of fentanyl, sufentanil or remifentanil in gastrointestinal endoscopy.** Acta Cir Bras. 2014; 29:675-680. doi: 10.1590/S0102-8650201400160008.

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