

## Pre-Treatment with Ketorolac Alongside Venous Occlusion Can Reduce the Pain of Propofol Injection; A Quasi-Experimental Study

Syed Zulfiqar Haider, Mujahid Ali Khoso, Saeed Bin Ayaz, Muhammad Ali Abbas, Habib Ur Rehman, Hina Iftikhar

Combined Military Hospital, Multan/National University of Medical Sciences (NUMS), Pakistan.

### ABSTRACT

**Objective:** To investigate the efficacy of Ketorolac with and without venous occlusion to relieve pain associated with Propofol injection.

**Study Design:** Quasi-experimental study.

**Place and Duration of Study:** Anesthesiology Department, Combined Military Hospital Multan, from Jan 2020 to Mar 2021.

**Methodology:** One hundred and twenty patients of age more than 16 years with ASA physical status 1 and 2, undergoing elective surgery at Combined Military Hospital Multan were selected. Patients were allocated into the groups to receive Saline with sham occlusion (group-A), 10 mg Ketorolac with sham occlusion (Group-B), or 10 mg Ketorolac with full venous occlusion for 120 seconds (Group-C). Before surgery, the patients were asked to rate any local discomfort on a scale of 0-3 ten seconds after receiving a Propofol injection. On the seventh post-operative day, all the patients were handed a questionnaire to describe any untoward symptoms.

**Results:** The mean age of the patients was  $48.3 \pm 2.8$  years (range: 16 to 80 years). Mild discomfort was experienced by 4 (10%) patients, while 12 (30%) patients had moderate pain and 5 (12.5%) patients experienced severe pain in Group-A. In group- B, 16 (40%) patients had mild discomfort, 7 (17.5%) had moderate pain, and 5 (12.5%) had severe pain. In Group-C, 10 (25%) individuals experienced mild discomfort, 5 (12.5%) patients experienced moderate pain, whereas none of the patients experienced severe pain ( $p < 0.001$ ). Patients among the three groups reported no significant difference in post-injection venous sequelae.

**Conclusion:** Pre-treatment with 10 mg Ketorolac and venous occlusion for 120 seconds can reduce the discomfort of Propofol injection.

**Keywords:** Analgesia, Ketorolac, Pain, Propofol.

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## INTRODUCTION

Propofol is a commonly used intravenous sedative induction drug, especially for brief operations, day-care surgery, or a laryngeal mask airway. Because of its fast onset and recovery and its amnestic properties, it is often used for sedation and anaesthesia.<sup>1</sup> Apart from hypotension (due to vasodilation) and temporary apnea after induction dosages, the most common adverse effects of Propofol is injection discomfort, particularly in tiny veins. In adults, this discomfort is observed in 28-90% of cases, and in children, it is observed in 28-85% cases.<sup>2,3</sup>

The location of injection, the size of the vein, the speed of injection, the buffering effect of blood, the temperature of Propofol, and the use of additional drugs such as local anaesthetics and opioids all appear to have an impact on the occurrence of pain with Prop-

ofol.<sup>4,5</sup> The pain from a Propofol injection might be immediate or delayed. The sensation is typically characterized as tingling, chilly, numbing, or, in the worst-case scenario, acute burning proximal to the injection site. This sensation usually occurs within 10-20 seconds of injection and lasts only as long as the injection.<sup>6,7</sup>

Various ways have been explored to alleviate the pain associated with Propofol injections. Non-pharmacological methods such as chilling or warming Propofol, diluting the Propofol solution, decreasing injection speed, or injecting Propofol into a large vein have shown mixed outcomes.<sup>8</sup> Pharmacological options include adding Lignocaine with/without Meto-clopramide, pre-treatment with opioids, 5 HT3 antagonists, Dexamethasone, Ketamine, Paracetamol, cold Saline, and Nalbu-phine, application of Nitroglycerine ointment to the venipuncture site, and dilution of Propofol with 5% Dextrose or intralipid.<sup>9,10</sup> It has also been observed that, at times, the previously ineffective pharmacological agent proved effective after occluding the injected venous system, probably through retaining the

**Correspondence:** Dr Syed Zulfiqar Haider, Department of Anaesthesia, Combined Military Hospital, Multan Pakistan  
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injected agent and allowing it to block the local kinin cascade linked to pain following Propofol injection.

Ketorolac is a nonsteroidal anti-inflammatory drug (NSAID) that can be used to relieve pain after surgery. It is also a cyclooxygenase inhibitor that prevents prostaglandin synthesis. Using this drug prior to Propofol injection is an expected viable option to reduce pain associated with Propofol. So far, this option has not been tried extensively, especially in Pakistan. The goal of this study was to see how effective Propofol is, as an analgesic, with and without complete venous occlusion, in comparison with placebo. If proved effective, it would add a readily available cheap additive to the armamentarium of analgesics for pain control following Propofol injection.

### METHODOLOGY

This quasi-experimental study was conducted from January 2020 to March 2021, at the Department of Anesthesiology, Combined Military Hospital Multan. After receiving permission from the Hospital Ethical Committee, the study was started. Through non-probability consecutive sampling, data was collected. A sample size was calculated through an online sample size calculator (ClinCalc LLC)<sup>11</sup> while taking the anticipated mean of group-1 as  $1.28 \pm 2$ .<sup>13,12</sup> anticipated mean of group-2 as,<sup>7,12</sup> with  $\alpha$ - error as 0.1 and power of the test as 90%.

**Inclusion Criteria:** Patients of either gender over 16 years of age with ASA physical status 1 and 2 were included in the study.

The patients who were undergoing elective surgeries in different departments like Gynaecology, General Surgery, Urology, Orthopaedics, and Otorhinolaryngology.

**Exclusion Criteria:** Patients with bleeding diathesis, asthma, NSAID allergy, and regular NSAID medication were excluded from the study.

After obtaining informed written consent from all inductees, 120 patients undergoing elective surgeries at Combined Military Hospital Multan were studied. Hospital registration numbers of all patients were recorded. The patients were randomly allocated into three groups, 'A, B & C' based on simple randomization techniques using computer-generated numbers. As part of regular pre-anaesthetic treatment, all the patients were given Pantoprazole 40mg and Metoclopramide 10 mg orally.<sup>12</sup>

After placing a 20 G intravenous cannula on the dorsum of the non-dominant hand, routine monitoring commenced in the anaesthesia room. Two ml of 0.9% Saline with sham occlusion was given to individuals in group 'A.' Patients of group 'B' were given 10 mg Ketorolac plus 1 ml 0.9% Saline (total volume 2 ml) with sham occlusion. Group 'C' received 10 mg Ketorolac plus 1 ml 0.9% Saline with full venous occlusion.

Complete venous occlusion required manual forearm compression with both hands for 2 minutes. The 'sham' occlusion involved wrapping both hands around the forearm for two minutes while exerting no pressure.

The test solution was administered over 10 seconds two minutes later, followed by 4 ml Propofol over 10 seconds. Ten seconds after receiving the test solution and Propofol injection, the patients were asked to score any local pain on a scale of 0-3. Grade-0 was taken as comfortable, "1" as mildly uncomfortable, "2" as painful and "3" as very painful.

The patients were subsequently given standard anaesthetics and taken to surgery. All the patients were given a questionnaire to complete on the seventh post-operative day, asking them to report any symptoms (redness, soreness, hardness, or bruising) on the back of the hand used for induction of anaesthesia.

Statistical Package for Social Sciences (SPSS) version 23 was used for the data analysis. For normally distributed variables, means and standard deviations were computed. The qualitative data was presented as numbers and percentages. The chi-square test was applied to test the significance of pain control in three groups. All the categories, i.e. comfortable, mild discomfort, moderate pain, and severe pain, were compared in three groups. The *p*-value of  $\leq 0.05$  was considered statistically significant.

### RESULTS

There were 120 participants included in the study. The mean age of the participants was  $48.3 \pm 2.8$  years (range: 16-80 years). Group-A comprised 24 males and 16 females, while Group-B had 23 males and 17 females. In Group-C, there were 25 males and 15 females. Mild discomfort was experienced by 4 (10%) patients, while 12 (30%) patients had moderate pain, and 5 (12.5%) patients experienced severe pain in group-A (Table-I).

**Table-I: Pain score following injection of propofol.**

Characteristics	Study Groups			p-value
	Group A (n=40)	Group B (n=40)	Group C (n=40)	
<b>Gender, n (%)</b>				
Male	24 (60)	23 (57.5)	25 (62.5)	0.901
Female	16 (40)	17 (42.5)	15 (37.5)	
<b>Pain Score Following Propofol Injection, n (%)</b>				
Comfortable	19 (47.5)	16 (40)	25 (62.5)	<0.001
Mildly Uncomfortable	4 (10)	12 (30)	10 (25)	
Painful	12 (30)	7 (17.5)	5 (12.5)	
Very Painful	5 (12.5)	5 (12.5)	0	

In group-B, 16(40%) patients had mild discomfort, 7 (17.5%) had moderate pain, and 5 (12.5%) had severe pain. In Group-C, 10 (25%) individuals experienced mild discomfort, 5 (12.5%) patients experienced moderate pain, whereas none of the patients experienced severe pain ( $p<0.001$ ).

Patients in each group received anaesthesia under the set protocol, underwent a planned surgical procedure, and recovered from anaesthesia without any anaesthesia related complications. The different post-injection venous sequelae reported by patients among the three groups were given in the Table-II.

**Table-II: Table showing comparison of adverse sequelae among three groups.**

Complications	Study Groups			p-value
	Group A (n=40)	Group B (n=40)	Group C (n=40)	
Redness	4 (10%)	5 (12.5%)	5 (12.5%)	0.98
Soreness	2 (5%)	3 (7.5%)	4 (10%)	
Hardness	1 (2.5%)	2 (5%)	4 (10%)	
Bruising	1 (2.5%)	1 (2.5%)	2 (5%)	

## DISCUSSION

Our study showed that the intravenous Ketorolac pretreatment reduced discomfort induced by intravenous Propofol injection, which was greater when coupled with venous occlusion. The study by Huang *et al.*,<sup>13</sup> also endorses our results. They observed a dose-related response to Ketorolac and found that Ketorolac in the dosage of 15mg and 30mg produced significant pain reduction after 60 seconds, but the same was not observed for 10mg. However, the dosage of 10mg produced significant analgesia when combined with venous blockage for 120 seconds. Yull *et al.*,<sup>14</sup> also reported similar results and found venous occlusion necessary to achieve pain control after Propofol injection.

The time between the injection of Ketorolac and the Propofol infusion might be the essential element

since it is apparent that 15mg and 30mg of Ketorolac are efficacious when given after waiting for 60 seconds or more. Similarly, Yull *et al.*,<sup>14</sup> found that 10mg Ketorolac with 120 seconds of venous occlusion ( $p=0.019$ ) decreased severe pain following Propofol compared to Saline or Ketorolac without venous occlusion ( $p=0.019$ ). As a result, we can conclude that the duration of venous occlusion is important in determining therapeutic response. Smith *et al.*,<sup>15</sup> could not register the analgesic effect of 10mg of Ketorolac without venous blockage. Nevertheless, some researchers, were able to produce effective analgesia with Ketorolac even without venous occlusion compared with normal saline.<sup>12</sup>

We could not find a significant difference in post-injection venous sequelae among the three groups. Similar findings were observed in previous studies.<sup>12,14,15</sup>

Some authors have compared Ketorolac with other drugs, especially lignocaine and tramadol, in terms of efficacy and side effects following intravenous administration of the drug. Smith *et al.*,<sup>15</sup> reported no significant difference between the treatments in terms of pain during injection ( $p=0.129$ ) or venous sequelae at seven days postoperatively. Madan *et al.*,<sup>12</sup> compared Lignocaine, Ketorolac, Tramadol and commented that Lignocaine was preferred over Tramadol and Ketorolac because it caused less pain and had fewer adverse effects. Picard *et al.*,<sup>16</sup> conducted a meta-analysis on pain prevention after Propofol administration and found that Lignocaine was the most effective medication for decreasing discomfort based on Number-Needed to Treat (NNT), which was 2.4-6.3. Contrarily, Huang *et al.*,<sup>13</sup> found that NNT for Ketorolac pre-treatment was 2.7, indicating that Ketorolac may be superior to Lignocaine in decreasing pain after Propofol injection. Pain on Propofol injection is thought to be either immediate or delayed by 10-20 seconds.

The pathophysiology of Propofol injection pain is unknown, while it has been proposed that immediate pain is caused by venous endothelial irritation, whereas delayed pain is caused by the release of mediators such as kininogen from the kinin cascade. Pre-treatment with nafamostat mesilate, a kallikrein inhibitor, before Propofol injection decreased injection discomfort, according to Iwama *et al.*, who backed up this theory.<sup>17</sup> As Ketorolac is an NSAID, it must likely inhibit the prostaglandin pathway, which takes time. Our findings imply that venous occlusion is required for Ketorolac to remain in the vein and block the kinin

cascade. The most valuable time is 120 seconds, as it is also recognized by Yull *et al*,<sup>14</sup> Massad *et al*,<sup>18</sup> and Madan *et al*,<sup>12</sup> used 60 seconds of occlusion time in their reports. Liaw *et al*,<sup>19</sup> used 60 seconds of venous occlusion followed by tourniquet release and Propofol injection and suggested that increasing tourniquet time may result in more significant discomfort for the patient.

### CONCLUSION

Pre-treatment with 10mg Ketorolac and 120 seconds of venous occlusion can help with Propofol injection discomfort. To improve patient tolerability of this perfect anaesthetic drug, we recommend using Ketorolac as a pre-treatment.

**Conflict of Interest:** None.

**Author's Contribution:** SZH: Conception, data collection, manuscript writing, review, MAK:, SBA: manuscript writing, review analysis, MAA: data collection, HUR: data entry and compilation, HI: review.

### REFERENCES

- Ommid M, Ahad S, Gani S, Dar FR, Rather M, Manzoor H. A prospective evaluative study between low dose ketamine and fentanyl as pre medication for alleviation of propofol injection pain. *J Med Sci Clin Res* 2019; 7(6): 506-512.
- Cheng D, Liu L, Hu Z. Prevention of anesthesia-induced injection pain of propofol in pediatric anesthesia. *Pak J Med Sci* 2017; 33(3): 752-756.
- Shivanna S, Priye S, Singh D, Jagannath S, Mudassar S, Reddy D. Efficacy of methylprednisolone and lignocaine on propofol injection pain: A randomised, double-blind, prospective study in adult cardiac surgical patients. *Indian J Anesth* 2016; 60(11): 848-851.
- Desousa KA. Pain on propofol injection: Causes and remedies. *Indian J Pharmacol* 2016; 48(6): 617-623.
- Hossain MS, Rahman MA, Rashid M, Islam M, Babu AR, Hasan MI, et al. Effect of intravenous dexamethasone on propofol injection pain: a randomized placebo controlled study. *Bangladesh J Otorhinolaryngol* 2019; 25(1): 28-33.
- Hayat M, Afshan G, Nasir M. Efficacy of intravenous paracetamol in combination with lidocaine pretreatment for reducing pain during injection of propofol. *Cureus* 2020; 12(2): e6926.
- Aziz MA, Ahmed Z, Shakoor A, Waheed R, Ahmed YI. Comparison of propofol injection pain pretreatment with nalbuphine and lidocaine. *Pak J Med Health Sci* 2019; 13(2): 237-239.
- Shah SARA, Naqvi SS, Abbas MA. Frequency of pain due to injection of propofol with IV administration of lignocaine with and without metoclopramide. *Pak Armed Forces Med J* 2016; 66(3): S208-212.
- Bakhtiari E, Mousavi SH. Pharmacological control of pain during propofol injection: a systematic review and meta-analysis. *Expert Rev Clin Pharmacol* 2021; 4(7): 889-899.
- Hossain MS, Rahman MA, Islam SA, Munira S, Hasan MI, Mandal MA. Effect of low dose ketamine on propofol injection pain: a double-blind clinical trial. *Khwaja Yunus Ali Med Coll J* 2020; 11(2): 96-99.
- Kane SP. *Clin Calc.com* [Internet Available at]: <https://clincalc.com/stats/samplesize.aspx>. [Accessed 2019 July 9].
- Madan HK, Singh R, Sodhi GS. Comparison of Intravenous Lignocaine, Tramadol and Ketorolac for Attenuation of Propofol Injection Pain. *J Clin Diagn Res* 2016; 10(7): UC05-UC08.
- Huang YW, Buerkle H, Lee TH, Lu CY, Lin CR, Lin SH, et al. Effect of pretreatment with ketorolac on Propofol injection pain. *Acta Anaesthesiol Scand* 2002; 46(8): 1021-1024.
- Yull DN, Barkshire KF, Dexter T. Pretreatment with ketorolac and venous occlusion to reduce pain on injection of Propofol. *Anaesth* 2000; 55(3): 284-287.
- Smith AJ, Power I. The effect of pretreatment with ketorolac on pain during intravenous injection of propofol. *Anaesthesia* 1996; 51(9): 883-885.
- Picard P. Prevention of pain on injection with propofol: a quantitative systematic review. *Anesth Analg* 2000; 90(4): 963-969.
- Iwama H, Nakane M, Ohmori S, Kaneko T, Kato M, Watanabe K, et al. Nafamostat mesilate, a kallikrein inhibitor, prevents pain on injection with propofol. *Br J Anaesth* 1998; 81(6): 963-964.
- Massad IM, Abu-Ali HM, Al-Ghanem SA, Badran IZ, Ammari BA. Duration of venous occlusion with lidocaine for preventing propofol induced pain. *Saudi Med J* 2008; 29(7): 971-974.
- Liaw WJ, Pang WW, Chang DP, Hwang MH. Pain on injection of propofol: the mitigating influence of metoclopramide using different techniques. *Acta Anaesthesiol Scand* 1999; 43(1): 24-27.