

## A randomized controlled trial to compare effects of different volume and concentration of lidocaine for preventing propofol injection pain in adults

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### ABSTRACT

**Background:** Pain on propofol injection is an unwanted effect which can lead to decreased patient satisfaction. Although many studies have shown that pretreatment with lidocaine injection is effective in this pain, nevertheless, very few studies have been done on different concentration and volume of lidocaine, effective of reducing pain significantly. Objective of the current study was to assess and compare the efficacy of intravenous lidocaine with 0.4% and 2% concentration in reducing the incidence and severity of propofol injection pain.

**Methods:** A total of 126 American Society of Anesthesiologist grade I and II patients with age  $\geq 18$  years, scheduled for an elective surgery, were enrolled in the study. Patients were randomized into two equal groups of 63 each. Group A (n = 63) received pretreatment with 0.4% lidocaine and group B (n = 63) received 2% lidocaine. Propofol injection pain was measured by using Numeric Rating Scale (NRS) and Withdrawl Response Scale (WRS). Unpaired t test, ANOVA and Chi square test were used for statistical analysis.

**Results:** A statistically significant decrease in the pain was recorded in group A (0.4% lidocaine) as compared to group B (2% lidocaine). Using NRS scale, 12% of patients in group A as compared to 33% patients of group B, experienced pain (p = 0.02); while using WRS, 8% patients of group A as compared to 27% group B patients experienced pain (p = 0.04).

**Conclusions:** The pain on injection of propofol is significantly decreased by the use of 0.4% lidocaine in comparison with 2% Lidocaine.

**Keywords:** Adults, Injection pain, India, Lidocaine, Propofol, Randomized controlled trial

### INTRODUCTION

Propofol is the most widely used anaesthetic agent, however injection pain is still the most common undesired effect associated with it.<sup>1</sup> Although the pain may not be a serious complication, but most of the patients remember it as one of the unpleasant encounters with anesthetists. In one survey, it was found that pain on propofol injection is seventh most important problem in the current practice of clinical anesthesia.<sup>2</sup> Pain is immediate as well as delayed

after 10-20 s.<sup>3</sup> The immediate pain is due to irritation of venous endothelium whereas delayed pain is due to the release of mediators such a kininogen from kinin cascade.<sup>4</sup> Many pharmacological and non-pharmacological interventions have been studied in the past, to decrease this injection pain.<sup>5-9</sup> Non pharmacological interventions have been developed based on factors known to reduce pain such as, site of injection, size of vein, infusion rate, temperature, microfiltration, venous occlusion and bacteriostatic saline. The pharmacological methods

include pre-treatment with lidocaine propofol admixture, pre-treatment with nonsteroidal anti inflammatory agents, opioids, ketamine, use of lipid free emulsions and the use of different preparations of propofol.<sup>9-14</sup> A meta- analysis concluded that the use of propofol lidocaine admixture was the best pharmacological method to decrease the incidence of pain on injection.<sup>9</sup> The use of lidocaine to prevent propofol injection pain is the most extensively studied technique and is the most common method used in clinical practice. However, almost all the studies published till date have compared lidocaine (in various regimens and dosages) versus placebo or control group, which were those without lidocaine, as shown in meta analysis by Eusabhon P et al.<sup>15</sup> The published studies have also investigated the effects of adding some active adjunct for example remifentanyl, ketamine, etc. in both lidocaine and control groups as shown in quantitative systematic review done by Picard et al, and Jalota L et al.<sup>16,17</sup> However there are only few studies in which all study groups have received lidocaine but in different concentration and volume. Gharavi M et al, studied the effect of lidocaine volume and concentration on preventing incidence and severity of propofol injection pain in 4 to 8 years old children and our research aims to compare this effect in adults.<sup>18</sup> The aim of this study was to investigate the efficacy of lidocaine at two different doses (0.4% and 2%) in mitigating the pain caused by injection of propofol. This was measured using two pain scores, Numeric Rating Scale (NRS), a subjective score in which patient rate his/her pain experience and an objective score, Withdrawl Response Score (WRS), in which investigator assesses response according to withdrawl movements of limbs.

**METHODS**

After obtaining approval from “Institutional Ethics Committee”, the study was carried out as a double-blinded randomized study on 126 American Society of Anesthesiologists (ASA) grade I and II patients of age 18 years and above.

**Inclusion criteria**

The patients, which were included in the study were scheduled to undergo an elective surgical procedure under general anaesthesia in different operation theatres (OTs) of general surgery (laproscopic cholecystectomy, laproscopic appendicectomy, Whipple’s colectomy etc.), plastic surgery (Flap surgery, skin grafting, liposuction etc), urology OT- Percutaneous Nephro lithotomy, Nephrectomy etc.), gastroenterology OT (Pancreas surgery, stomach surgery), gynecology OT (Lap hysterectomy, hysteroscopy etc.) were included.

**Exclusion criteria**

Patients with history of any contraindication to propofol or lidocaine; thrombophlebitis; severe mental or neurological disease and pregnancy were excluded from the study.

This study was conducted in a tertiary care hospital in Mumbai over a period of two years. Patients were divided into two equal groups of 63 each, by sealed envelope technique.

Group A (n= 63) received 0.4% lidocaine and group B (n= 63) received 2% lidocaine, intravenously with a dose of 1mg/kg. 0.4% solution was prepared by diluting 3ml of 2% lidocaine (preservative free) solution 5 times with normal saline. Therefore 15ml (0.4%) was given to group A, while 3ml (2%) was given to group B. During preanaesthetic check-up, written informed consent was obtained and Numeric Rating Scale (NRS) was explained to the patients. NRS is an 11-point pain intensity numerical rating scale in which patients are asked to rate the pain in form of numbers, where 0 = no pain and 10 = worst pain possible.<sup>19,20</sup> Pain was also assessed by Withdrawl Response Scale (WRS), which is based on assessment of withdrawl movements of the arm in response to pain. Table 1 shows the grading of withdrawl movements, with 0 as no response, 1 for movement at the wrist only, 2 for movement involving the arm only (elbow or shoulder), and 3 for generalized response or movement in more than one extremity and reactions such as discomfort or pain.<sup>21</sup>

**Table 1: Withdrawal response Score.**

Withdrawal score	Response
0	No response
1	Movement at wrist
2	Movement involving arm (elbow and shoulder)
3	Generalized response or movement in more than one extremity

In the operation theatre, standard anesthesia monitoring was established and a 20 G cannula was inserted into a vein on the dorsum of non- dominant hand. Then a tourniquet was applied 10cm proximal to intravenous cannulation at the mid forearm for 1 min till the venous drainage was occluded. Then the intravenous lidocaine injection (preservative free) with dose of 1mg/kg was given to the patient and after 30 sec of injection, tourniquet was removed. The total dose of propofol used for induction was 2mg/kg. Out of this only ¼<sup>th</sup> of the propofol was administered first over 5 sec. Patients’ vitals i.e., heart rate (HR), systolic blood pressure (SBP) and diastolic blood pressure (DBP) were recorded from the monitor, which included pre-injection values, after giving ¼<sup>th</sup> dose and full dose of propofol. Another researcher, who was unaware of the group assigned, evaluated the NRS (Numeric Rating Scale) and WRS (Withdrawl Response Score) after 1/4th dose of propofol. After evaluation, rest of the propofol dose was given.

**Sample size**

Taking 80% power and a 5% level of significance, a sample size of total 126 patients, 63 in each group, was

found to be sufficient to detect a clinically important difference of 20% between groups in using a two-tailed z-test of proportions. The 20% assumption was made on the basis of findings of a study done by Gharavi et al.<sup>18</sup>

**Statistical analysis**

The data were analyzed using Statistical Package for the Social Sciences software (SPSS) version 21. Quantitative data was described using mean±standard deviation; comparison between the quantitative variables was done by using t test and ANOVA. Qualitative variables were analyzed using chi square test or Fischer’s exact test. A p value of <0.05 was considered significant.

**RESULTS**

Table 2 shows the demographic data of study participants. Most of the study participants were male in both groups (57% in group A and 55.6% in group B).

**Table 2: Demographic data.**

Variable	Group A n = 63 (0.4% lidocaine)	Group B n= 63 (2% lidocaine)	p value
Age (Mean±SD*)	35.6±12.7	39.37±9.7	0.525
Weight (Mean±SD*)	53.5±6.04	55.8±6.5	0.712
ASA			
I	29	28	0.86
II	34	35	
Gender			
Male	36	35	0.85
Female	27	28	
Height	164±9.7	163±10.2	0.69

\* SD, Standard Deviation

The median age in group A was 35.6±12.7 years and 39.37±9.7 years in group B. The majority of patients belonged to ASA II in group A (54%) and group B (55.6%).

The weight and height of patients in two groups was comparable as shown in Table 2. There was no significant

difference in the patients’ demographic characteristics in two groups.

The comparison of the groups on the basis of their pain experience and response is shown in table 3 and 4. NRS pain scale was classified as “no pain” (0 score); “mild pain” (1 to 3); “ moderate pain” (4 to 6) and “severe pain” (>6). Table 3 shows that in group A, 7 patients (11.1%) experienced mild pain as compared to 17 patients (27%) of group B.

Only 1 patient in group A had moderate pain, while 4 patients (6.3%) in group had moderate pain experience. This data shows that patients of group A, receiving 0.4% lidocaine had lower pain scores as compared to group B and the difference was found to be statistically significant (0.02).

**Table 3: Comparison of NRS pain scale between two groups.**

NRS*	Group A n =63 (0.4% lidocaine)	Group B n = 63 (2% lidocaine)	p value
No pain	55 (87.3%)	42 (66.7%)	0.02
Mild pain	7 (11.1%)	17 (27%)	
Moderate pain	1 (1.6%)	4 (6.3%)	

\*NRS, Numeric rating scale

**Table 4: Comparison of WRS pain scale between two groups.**

WRS*	Group A n =63 (0.4% lidocaine)	Group B n = 63 (2% lidocaine)	p value
0	58 (92%)	48 (76%)	0.04
1	5 (8%)	14 (27%)	

\*WRS, Withdrawl response scale

Table 4 shows that the WRS pain scores were also significantly lower among group A patients as compared to group B (0.04). Only 5 patients (8%) of group A as compared to 14 patients (27%) of group B had WRS score of 1 (as response to pain experienced).

**Table 5: Comparison of hemodynamic parameters.**

Variable	HR (beats/ min)*			SBP (mm Hg) †			DBP (mm Hg) ‡		
	Group A	Group B	p value	Group A	Group B	p value	Group A	Group B	p value
Time									
Pre-injection	78.76 ±10.45	79.62 ±13.67	0.10	128 ±13.5	131 ±13.5	0.45	80.76 ±6.8	80.32 ±9.3	0.76
After ¼ <sup>th</sup> of propofol dose	79.52 ±10.8	81.89 ±12.8	0.22	123.7 ±13.5	121 ±14	0.4	77 ±8.9	80.22 ±9.3	0.12
After full propofol dose	80.29 ±11	82.71 ±12.2	0.29	123 ±10.7	116.8 ±12.8	0.19	78.73 ±9.4	80.10 ±9.5	0.41

\*HR, Heart rate; †SBP, Systolic blood pressure; ‡DBP, Diastolic blood pressure

The hemodynamic parameters i.e., heart rate, systolic BP and diastolic BP of both the groups were comparable before administering the lidocaine injection ( $p > 0.05$ ) as shown in Table 5. There was no significant change in these hemodynamic parameters, in group A and B, when measured after giving one fourth dose and then full dose of propofol ( $p > 0.05$ ).

## DISCUSSION

According to published literature, the incidence of propofol injection pain without the use of any analgesic intervention is approximately 80%.<sup>16</sup> There are different factors that may augment this type of pain including site of injection, the temperature of the propofol solution, size of the vein, and speed of injection. In this study, we matched both groups for these factors. Our study used both subjective (NRS) and objective (WRS) methods to assess and compare pain among patients of both the groups. Only 8 patients (12%) in group A receiving 0.4% lidocaine experienced pain (mild pain = 7, moderate pain = 1) compared to 21 patients (33%) of group B (mild pain = 17, moderate pain = 4) who were given 2% solutions. This difference in the pain perception was statistically significant with  $p$  value of 0.046. This was in accordance with the study by Gharavi M et al, in which there was significant difference in pain perception using NRS pain score between the group B (0.4%) and group A (2%).<sup>18</sup> This study also showed a highly significant reduction in the withdrawal movements in the group A compared to the group B with a  $p$  value of 0.041. The incidence of pain in the group A was 8% (6 patients) and the highest score recorded was 1, according to the WRS score, while in the group B, the incidence of pain with propofol injection was 27% (14 patients) and the highest score recorded was one according to the WRS score. This was in accordance with the study by Shabana AM et al, where they showed a highly significant reduction in the withdrawal movements in the study group (median score 0.22) compared to the control group (median score 1.5) with  $p$  value 0.001.<sup>22</sup> The incidence of pain in the study group was 4% (2 patients) and the number of patients who recorded highest score was 1, while in the control group, the incidence of pain with propofol injection was 24% (12 patients) and the number of patients who recorded highest score were three. Propofol injection pain can stimulate sympathetic nervous system leading to increase in heart rate and blood pressure which can add to the exaggerated sympathetic response during intubation, which can be detrimental to patients having coronary artery disease, patients with head trauma, having raised intracranial pressure, patients with mitral stenosis, aortic stenosis etc. The hemodynamic parameters (HR, SBP and DBP) showed no significant difference between the two study groups in this study and was consistent with the study done by Shabana AM et al, The results in our study showed that lidocaine with the same dose but lower concentration and higher volume is more effective in preventing propofol injection pain.<sup>22</sup> This can be attributed to the fact that larger volume drug can anaesthetize more pain receptors as compared to lesser volume. Similar

findings have been demonstrated by Shabana AM et al.<sup>22</sup> In fact, what needs to be the focus of future studies is the optimum concentration and volume of lidocaine, to decrease pain on propofol injection.

## CONCLUSION

The pain on injection of propofol is significantly decreased by the use of 0.4% Lidocaine in comparison with 2% Lidocaine. Pre-treatment with 0.4% Lidocaine or with 2% Lidocaine have no significant difference in the heart rate, systolic and diastolic blood pressure. The results of this study provide a simple and safe method of reducing the incidence of pain on injection of propofol with the added advantage of using decreased concentration of lidocaine as well as avoiding the administration of other drugs that may be undesirable in certain circumstances.

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