

Original Research Article

A comparison of pain on intravenous injection to two formulations of Propofol, one containing medium chain and long chain triglycerides and the other without medium chain and long chain triglycerides

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ABSTRACT

Background: To assess and compare the Visual Analog Scale (VAS) for pain on intravenous injection in patients receiving the two different formulations of Propofol.

Methods: Total 170 eligible patients were randomized into Group A receiving Propofol MCT/LCT and Group B receiving Propofol LCT. After standard pre-anaesthetic preparation and baseline values recording, the blinded investigator recorded pain intensity after injection of 1mL study drug propofol, using Visual Analog Scale (0-10). Haemodynamic parameters were recorded every minute for 5 minutes. Calculated Propofol dose was injected in 20 seconds, and signs of pain (hand withdrawal, grimacing) were noted. After patient regained full consciousness, recall of injection pain was asked for.

Results: The proportion of patients who experienced pain was similar in both groups (group A: 76/85 =89.41%, group B: 81/85 = 95.29%; statistically not significant (p value=0.247). Patients in group A had longer time for pain onset (11.3 seconds-group A Vs 9.8 seconds-group B; statistically significant, p value =0.008). Pain on injection was higher in Propofol LCT group as compared to Propofol MCT/LCT (VAS scores of group A=3.94±2.0 vs group B = 5.49±1.96; statistically significant; p value = 0.0018). Full dose of Propofol MCT/LCT produced significantly less pain when compared to Propofol LCT (p value = 0.0424). Recall of pain was comparable between the groups. Haemodynamic parameters (Heart rate and Mean Arterial Pressure) remained comparable in both groups.

Conclusions: Pain on injection was higher and statistically significant in Propofol LCT group as compared to Propofol MCT/LCT.

Keywords: Injection pain, Medium chain and long chain triglycerides, Propofol, Visual Analog Scale

INTRODUCTION

Propofol is indispensable in modern day anesthesia. Its introduction pioneered the possibility of day care surgery. Its rapid onset, short duration of action, and minimal side effects are obvious advantages. However, emulsion instability, hyperlipidaemia, pain upon injection,

microbial contamination, Propofol infusion syndrome and difficulty in formulating a stable aqueous delivery vehicle are persistent problems. It has been formulated in a fat emulsion consisting of 10% soybean oil, causing obvious pain and discomfort on injection. Pain on Propofol injection is a common problem, sometimes severe and can be very distressing to the patient. The incidence of

this pain is variable. Mitigating the pain on injection of Propofol has involved three general approaches including modifying the vehicle in which the Propofol is contained, adding a drug to the Propofol emulsion, or administering a drug prior to Propofol injection.

In one such formulation of Propofol [with MCT/LCT], the oil phase consists of medium chain triglycerides (MCT) and long chain triglycerides (LCT). Such a composition, results in smaller concentrations of free Propofol in aqueous phase, thus causing less pain. An improved tolerability with the newer formulation on injection compared to the older formulation [without MCT/LCT] has been claimed and there are studies to show reduced pain intensity with the newer lipid formulations.¹

Based on varying mechanisms and factors associated with Propofol injection and pain, several methods for the prevention of this pain has been tried with varying degrees of success. The methods that have been investigated so far include manipulation of size of vein, and site of injection.^{2,3}

The speed of injection and use of tourniquet have also been looked into by few authors.^{4,5} Change in dilution and change in temperature have also been investigated.^{6,7} However, combination of propofol with other drugs is quite recent.⁸ The suggestion of MCT/LCT Propofol finds place in a recent review.⁹

This study is therefore undertaken to assess if this formulation of Propofol (MCT/LCT) causes pain on intravenous injection in patients undergoing elective surgeries under general anaesthesia with a focus on quantification of this pain using pain scores.

In this context, the primary objective was to assess the intensity of pain during injection of Propofol with the Visual Analog Scale for the test dose of 1cc of propofol and compare the two groups (with and without MCT/LCT).

The secondary objectives were to assess the presence of pain on injection, at the induction dose of Propofol, to assess recall of pain to injection of Propofol in the post-operative period in the recovery room and to correlate the hemodynamic parameters to the response to pain during injection of Propofol, and compare the two groups (with and without MCT/LCT).

METHODS

Institutional review board approval was obtained. The study was conducted in the department of Anaesthesia on patients admitted in a tertiary care postgraduate teaching hospital based in Urban India which cares for large volume of patients. Patients scheduled for elective surgical procedure under general anaesthesia and those who consented to participate in the study, were included.

Inclusion criteria

- Patients with age between 18 years to 55 years.
- American Society of Anaesthesiologist (ASA) Grade I and II.
- Undergoing elective urological, Gynaecological or general surgical procedures.
- Patients undergoing procedure under General anaesthesia.

Exclusion criteria

- Patients with history of known hypersensitivity to Propofol injectable emulsion or any of its components.
- Pregnant women.
- Nursing mothers.
- Morbid obesity (BMI>35).
- Chronic steroid use .
- Patients on antidepressants or opioid dependence.
- Patients with chronic pain (arthritis, malignancies).

The study design was prospective, randomized, and single blinded study. The study was conducted over a one-year duration (July 2016 to June 2017).

The study protocol was explained to each patient and consents were obtained. Routine workup that had been done for surgery in the form of complete blood counts, serum electrolytes, serum creatinine, coagulation profile, blood sugar, electrocardiogram and a chest radiograph were noted. All interventions were done by consultants of the department, when they underwent their surgical procedure. Computer generated random numbers were used to decide which group each patient would belong to.

Patients in group A were to receive Propofol containing MCT/LCT(Fresofol) and in group B are to receive Propofol with LCT(Troypofol). In the operation theatre, a peripheral intravenous line was secured with a 22-gauge cannula on the dorsum of the non-dominant hand and appropriate crystalloids were started. Standard pre-anaesthetic preparation (attachment of monitors, non-invasive blood pressure, electrocardiography, pulse oximeter, EtCO₂ (End tidal carbon dioxide, after induction of anaesthesia) were done.

Baseline values of the above parameters and weight of the patient was recorded. One milliliter of either formulation of Propofol were prepared in a 2mL syringe and labeled A or B by an independent person other than the investigator. The investigator recorded the data after injection of study drug of 1mL Propofol, by asking the patient to quantify pain according to Visual Analog Scale (VAS) scores of 0-10 and haemodynamic parameters recorded every minute for 5 minutes.

Routine anaesthetic induction was carried on as deemed necessary by the Consultant Anaesthesiologist.

Calculated dose of Propofol for induction was injected in 20 seconds, thereafter, the patient was observed for any signs like withdrawal of hand, grimacing or verbalization and presence of any of the signs were considered as 'Pain' and absence as 'No Pain'. Post extubation, after patient regained full consciousness, recall of injection pain was asked for. Post-operative recall of injection pain was asked after patient regained full consciousness and before the patient left the recovery room.

Statistical methods

The sample size of 170 was arrived using the following calculation. Difference in pain intensity of at least = 1.5 VAS units; SD of VAS for Drug A = 3.0; SD of VAS for Drug B = 3.0; σ_1 and σ_2 =Standard Deviation of VAS for Drug A and Drug B; $\mu_1-\mu_2$ = Minimum mean difference in pain intensity; Drug A= MCT/LCT; Drug B = LCT. Based on these conditions, at 95% confidence level and at 90% power,

$$\text{Sample Size Formula} = \frac{(\sigma_1^2 + \sigma_2^2) \times [Z_{1-\alpha/2} + Z_{1-\beta}]^2}{(\mu_1 - \mu_2)^2}$$

$$(3^2 + 3^2) \times [1.645 + 1.282]^2 (1.5)^2$$

Calculated sample size are 170 patients. The sample size was determined using "MedCalc" - sample size for comparing two means.¹⁰

The outcome measures studied were VAS scores at the onset of pain, time (in seconds) for the onset of pain on intravenous injection of the drug, presence or absence of pain at induction dose, recall of pain, and changes in hemodynamic parameters.

Statistical analysis

The data was recorded in MS Excel. Quantitative data, which includes the VAS scores and the hemodynamic parameters to the injection of two formulations was evaluated and analysed using paired t test or Wilcoxon Signed rank test based on normality testing. For continuous variables, results were presented as Mean±SD or median and range; categorical variables were presented by frequency counts. Graphical representations wherever applicable. All calculations were performed by using MedCalc v.15.8. Level of significance was considered as $p \leq 0.05$.

RESULTS

The demographic profile of the patients is presented in (Table 1). As observed, the p values of each of the comparisons were more than 0.05. There is no statistically significant difference between the groups and the two groups are comparable.

Table 1: Demographic profile.

Patient characteristics	Group A	Group B	t test (p value)
Age (years)	40.2±9.87	41.7±10.73	0.419
Weight (kg)	67.02±7.31	69.49±7.60	0.398
Gender(female/male)	39/46=0.84	41/44=0.93	0.878
ASA	1 34/85(0.4)	28/85(0.48)	0.426
	2 51/85(0.6)	57/85(0.52)	

Table 2: Distribution of onset of pain (in seconds) and distribution of VAS scores.

Onset of pain in seconds	Mean±SD	Std. Deviation
Group A 76	11.3289±3.48478	t-test for Equality of Means applied t value = 2.683; df=155; p value 0.008(significant)
Group B 81	9.8025±3.63462	
VAS score distribution		
VAS SCORE	Group A	Group B
0	9	4
1	1	1
2	4	4
3	19	4
4	20	12
5	14	20
6	10	18
7	6	15
8	1	7
9	1	4
	3.94±- 2.00	5.49±-1.96

The two-tailed p value equals 0.0018(statistically significant) 95% CI: -2.74 to -0.66 t = 3.2584 df = 64, SED = 0.52

Majority of the patients in both the groups were in the group of 46-55 years of age. The age ranged from 19 to 55 years. There was no statistical difference between the two groups and age distribution of the two groups were similar and comparable. Majority of patients belonged to the weight range of 61-70 kilograms. The weight ranged between 50 kg and 81kg in group A while it ranged between 51 kg and 89 kg in group B. There was no statistical difference between the two groups. The groups were comparable in the parameter of weight. There were more males in both the groups. Though the proportion of females was slightly higher in group B, there was no statistically significant difference between the groups. The two groups were comparable with respect to gender. The number of patients belonging to ASA grade 2 was slightly higher. However, this difference was not statistically significant, and the two groups were comparable with respect to ASA grades.

The proportion of patients who experienced pain in group A was 76/85 =89.41%. The proportion of patients who experienced pain in group B was 81/85 = 95.29%. When the difference was statistically analysed, using Chi square test, p value = 0.247., and the difference is not statistically significant.

Table 2 shows the time taken for onset of pain upon injection in both groups, measured in seconds. Patients in group A took a longer time for onset of pain (11.3

seconds) as against 9.8 seconds in group B; and this difference was statistically significant (p value = 0.008).

The average and the range of VAS scores were higher in group B compared to those of group A, and the difference was statistically significant. In group A, the number of patients experiencing pain with an intensity higher than VAS score of 5 was 64; while in group A, only 32 patients experienced a VAS score of higher than 5. When analysed quartile wise, 63/85 = 74.1% in group A reported VAS scores in the range of 3-6, whereas in group B, 65/85 = 76.4% experienced VAS scores between 4-7. (Table 2)

A much lesser proportion of patients in group A experienced pain at full dose when compared to group B; and this difference was statistically significant. (Table 3)

Recall of pain: More patients of group B recalled pain when asked for the same at the time of recovery. However, this difference between the groups were not significant. (p value= 0.203).

Table 3: Distribution of pain at full dose.

Pain at full dose	A	B
Yes	28 (32.9%)	42 (49.4%)
No	57(67.1%)	43(50.6%)

Fisher's exact test: The two-tailed p value = 0.0424 (statistically significant)

Table 4: correlation between pain at full dose and recall of pain and correlation between VAS score and recall of pain: both groups.

Group A	No	Yes	
Pain at full dose	No	47	10
	Yes	11	17
Total	58	27	85
Group B	No	Yes	
Pain at full dose	No	37	6
	Yes	12	30
Total	49	36	85
Recall of pain	VAS Score		Mann-Whitney U
	Group A	Group B	
Yes	5.48±1.5	6.31±1.43	U value 268, p value ≈0.00
No	3.22±1.8	4.90±2.08	U value 536, p value =0.002

There was no correlation between those who had pain at full dose and those who had recall of pain. Further, there was no relationship between age or gender on the recall of pain. (In both, p value >0.05) As shown in (Table 4), there is a significant difference between the VAS scores of those patients who could recall their pain and those who could not in both groups A and B. Those who

recalled pain had higher VAS scores during induction of anaesthesia in both groups.

In both groups, those who experienced pain had a significantly higher VAS score (during induction) compared to those who did not experience pain at full dose (Table 4).

There was no statistically significant difference between the ages of the groups (p value >0.05) in patient of group

B. Whereas among patients of group A, age had a significant influence over the pain at full dose. (Table 5

Table 5: Correlation between VAS score, age and gender with pain at full dose: both groups.

Pain at full dose	VAS SCORE			
	Group A			
	Number	Mean	SD	
Yes	57	3.43	1.77	p value = 0.001
No	28	4.96	2.08	
Group B				
Yes	43	4.77	2.15	p value = 0.002
No	42	6.24	1.41	
Age				
	N	Mean	SD	
No	57	42.49	9.93	t-Test, t= 2.142, p value = 0.035
Yes	28	37.71	9.07	
Group B				
No	43	40.21	10.93	p value= .169
Yes	42	43.26	10.42	
Gender				
Group A				
	Female	Male		
No	32	25	57	Pearson Chi-Square value-7.333, df =1, P value= .010
Yes	7	21	28	
Group B				
	Female	Male		
No	21	22		Pearson Chi-Square; value= .013, df =1, p value= 1.0
Yes	20	22		

Table 6: Heart Rate: both groups.

Heart rate (bpm)	Group A (Mean ±SD)	Intra group p value (Kolmogorov-Smirnov)	Group B (Mean±SD)	Intra group p value (Kolmogorov-Smirnov)	t test p value <0.05 significant
At 1 minute	77.14±9.283		81.45±8.294		0.9482
At 2 minutes	77.06±8.629	0.022	81.42±7.999	0.035	0.8755
At 3 minutes	76.51±8.037	0.000	82.20±5.383	0.016	0.1551
At 4 minutes	74.87±7.23	0.017	80.25±6.45	0.022	0.3247
At 5 minutes	74.96±6.50	0.061	80.22±7.45	0.067	0.0872
At full dose	70.56±7.286	0.001	77.28±8.267	0.001	0.0621
Mean Arterial Pressure (mmHg)	Group A (Mean±SD)	Intra group p value (Kolmogorov-Smirnov)	Group B (Mean±SD)	Intra group p value (Kolmogorov-Smirnov)	t test p value <0.05 significant
At 1 minute	97.02±7.90		97.64±6.345		0.692
At 2 minutes	96.15±7.805	0.016	97.65±5.367	0.200	0.143
At 3 minutes	93.08±7.065	0.067	95.70±5.67	0.200	0.087
At 4 minutes	93.02±6.54	0.002	94.49±6.171	0.002	0.400
At 5 minutes	93.01±5.805	0.000	94.14±5.012	0.087	0.325
At full dose	82.32±5.95	0.200	84.14±4.98	0.009	0.438

There was a significant impact of sex on the pain at full dose in the patients of group A. Higher proportion of males experienced pain at full dose compared to females.

Whereas, there was no statistically significant difference between the pain at full dose among the sexes in those who belonged to group B. (Table 5)

The hemodynamic changes are tabulated in (Table 6). Though there was a decrease in the mean arterial pressure values as shown in table, there was no significant difference between these values over the observation period of 5 minutes and at full dose.

DISCUSSION

Wang et al, have also conducted a review titled “Is Propofol injection pain really important to patients?” and listed the interventions that are being sought for the same. Propofol injection pain figured sixth in the top 10 possible adverse effects of general anaesthesia as opined by the patients who had recently undergone surgery. It is sufficed to say that Propofol injection pain continues to be a specific problem and measures should be taken to reduce the same.¹⁰ Hence Propofol injection pain merits further study and this formed the focus of this dissertation.

The age range that author studied was 18 to 55 years. The average age was 40.2±9.87 years in group A and 41.7±10.73 in the other group, and the two groups were comparable in this parameter. In the study by Kim et al, the average age was around 40 years. In most studies, the age ranged between 18 and 65 years.¹¹

Younger the age, higher the possibility of Propofol related pain.¹² However, since the quantification of Propofol injection pain is very difficult in children, and answering of pain quantification questionnaires are difficult, very few studies exist. MCT/LCT reduces injection related pain even in children.¹³

In this study, the average weight in group A was 67.02±7.31 kg and that in group B was 69.49±7.60 kg; and the two groups were comparable in this parameter. Kang et al classified weight based on BMI and they found that there was no influence of weight on the pain due to Propofol injection.³

There was no effect of gender on the outcome parameters in this study. Lee BW et al, determined that the amount of remifentanyl required to obviate pain on micro emulsion Propofol injection was much higher in the male gender.¹⁴ Kang et al, concluded that female gender was more likely to be affected by Propofol injection.³

The ASA grades which were included in this study were grade 1 and 2. Almost all other reports have studied patients of ASA grades 1 and 2 only. Very few studies have utilized patients of grade 3. Examples of these are the ones by Alipour et al, However, ASA grade appears to be unrelated to the pain intensity.¹⁵

In this study, almost 90% in the LCT group and approximately 85% in the MCT/LCT group experienced pain on Propofol injection of 1 mL. The incidence of pain on injection of LCT Propofol has ranged between 60% and 96.7% in various studies.¹⁶⁻¹⁸

It is clear that only a small number of patients do not experience pain on Propofol injection. The proportion of patients who experienced pain at full dose was 49.4% in group B of THIS study. In the study by Mangar et al, the incidence of pain at full dose (2 mg /kg) was around 90% and on a 0-100mm VAS scale, the average VAS score was 75±28mm (p <0.05).¹⁹

Author quantified pain using the visual analog scale and the average VAS score was higher in those with MCT/LCT than those with only LCT. In THIS study, the mean VAS score in the LCT group was 5.49±1.96; whereas the MCT/LCT group had a VAS score of 3.94±2.00.

In a previous study by Liljeroth et al, where VAS units were used, the average VAS score in the LCT/MCT group was 3 (with a range of 0 to 6). In their study also, the intensity of Propofol induced pain was significantly lesser (p<0.0001) in the MCT/LCT group, which is similar to the findings in this study.¹⁰

In the study by Singh et al, the Mean VAS scores were 2.27±1.51.²⁰

In the study by Choi YJ et al, the Propofol saline group, which was the control group, the average VNRS score was 4.26.²¹

In the study by Sim JY et al, the median VAS score when lipid emulsion was used was 2.4. The severity of injection pain caused by microemulsion propofol and lipid emulsion propofol were compared. The incidence of injection pain caused by microemulsion and lipid emulsion propofol was 69.7 and 42.3% (p <0.001), respectively. The median VAS scores were 59 and 24 mm, respectively (95% confidence interval for the difference 12.5, 40.0).²²

The VAS score in the study by Madan et al, was 7.00±1.78 which is even higher than that noticed in this study.²³

In the study was conducted by Le Guen et al, who used a 6- point scale for rating pain, the group with LCT/MCT showed significantly lesser pain. The pain-diminutive effect remained consistently even after the use of lignocaine. This study by Le Guen et al, is one of the recently published studies which reiterates the advantage of LCT/MCT in pain reduction, which is in congruence to this study findings.²⁴

Sarkar et al, recently conducted a study in Indian settings which is very similar to this study. They found a 20% reduction in the incidence of pain and though they used the 10-point Visual Analog scale, 1.37±2.40(MCT/LCT) vs 2.6±2.93 (LCT). This finding are in agreement with theirs, establishing an advantage of pain reduction with MCT/LCT Propofol.²⁵

In the study by Ohmizo et al, who used the four-point scale, the reduced pain of MCT/LCT was very well noticed. In their study, 63.3% of patients were grouped "0" in the pain severity index. This is in agreement with this study, wherein the MCT/LCT group, 48% of them experienced VAS scores of 5 or less.²⁶

In this study, it was found that the pain intensity was lower with MCT/LCT but also the onset of pain was much later with the MCT/LCT group. This difference was also statistically significant. However, not many studies have dealt with the onset of pain after Propofol injection.

Overall 37% of patients in this study recalled pain, and this was similar in both groups. Boku et al, showed that 41.4% recalled the pain after injection with Propofol and also reported that midazolam can alleviate this pain recall.²⁷

Alipour et al, studied hemodynamic changes upon injection with Propofol. In their study and in the two groups of this study, there was a decrease in the mean arterial pressure upon injection with Propofol. In a separate study, Zahoor et al, also studied the hemodynamic effects of Propofol. They also found that there was a consistent decrease in the heart rate upon injection with Propofol, which is consistent with the findings of this study.²⁸

The limitations of this study include that a standard intravenous cannula of 22G was used, which may have contributed to increase in incidence of pain. The speed of injection and temperature of the drug were not considered in this study.

CONCLUSION

The following conclusions are obtained from this study. Pain on injection was higher and statistically significant in Propofol LCT group as compared to Propofol MCT/LCT. Pain observed occurred faster with LCT Propofol. Full induction dose of Propofol MCT/LCT produced significantly less pain when compared to Propofol LCT. Recall of pain was similar between LCT and LCT/MCT groups. Hemodynamic parameters (Heart rate and Mean Arterial Pressure) remained comparable in both groups.

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