

# PREVENTION OF PROPOFOL PAIN: A COMPARATIVE STUDY

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## Abstract

A common drawback of propofol is pain on injection and lignocaine is commonly mixed with propofol to reduce the incidence and severity of this pain. In this study we sought to draw a comparison between the effectiveness of propofol medium chain and long chain triglyceride (MCT/LCT) alone, propofol medium chain and long chain triglyceride (MCT/LCT) premixed with lignocaine, and propofol long chain triglyceride (LCT) premixed with lignocaine, in preventing propofol pain on injection. 300 patients were randomly divided into three equal groups. Group A received propofol-MCT/LCT premixed with normal saline, Group B received propofol-MCT/LCT premixed with 20 mg lignocaine and Group C received propofol-LCT premixed with 20 mg lignocaine. The incidence of pain in Group A was 63% compared to 15% in Group B ( $X^2 = 48.242$ ,  $p < 0.001$ ), whereas in Group C the incidence of pain was 24% compared to 63% in Group A ( $X^2 = 30.247$ ,  $p < 0.001$ ). There was no significant difference in incidence of pain between Groups B and C ( $X^2 = 2.5$ ,  $p = 0.11$ ). To conclude, propofol MCT/LCT alone provides no advantage to reduce pain on injection in comparison to propofol MCT/LCT premixed with lignocaine and propofol LCT premixed with lignocaine. Also, there is no significant difference in pain on injection between propofol LCT and propofol MCT/LCT as soon as lignocaine is added.

**Keywords:** lignocaine, propofol, pain on injection.

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## Introduction

Propofol is a popular intravenous anesthetic agent providing smooth induction and rapid recovery from anesthesia. However, pain on injection is a major disadvantage with a reported incidence of approximately 70% when a standard formulation of propofol is administered with no intervention to reduce pain<sup>1</sup>.

Several strategies have been applied to alleviate pain, such as previous administration of opioids or metoclopramide and adaptation of the temperature of the emulsion. The most frequently used method to reduce pain is the administration of lignocaine, either before propofol injection, with or without a tourniquet<sup>2</sup> or added to the propofol emulsion as a premixture<sup>1,3,4</sup>. The mechanism of pain relief can be two fold; first by reduction of propofol in the aqueous phase and second by lignocaine acting as a stabiliser in the kinin cascade<sup>5</sup>.

Injection pain has been attributed to the amount of free propofol in the aqueous phase of the emulsion. In 1997, Doenicke et al<sup>6</sup> advocated a reformulated lipid emulsion of propofol to alleviate injection pain. This reformulation of propofol contains both medium chain triglycerides (MCT) and long chain triglycerides (LCT) in equal proportions in contrast to usual LCT formulation. The amount of free propofol in a MCT/LCT emulsion is assumed to be less compared with propofol LCT thus causing less pain on injection. However, recent studies have suggested that propofol MCT/LCT emulsion when used alone causes more pain on injection, as compared to propofol LCT with lignocaine<sup>7,8,9</sup>.

The aim of the present study was to determine whether propofol in a reformulated MCT/LCT emulsion without further addition, was more effective in preventing pain on injection as compared to propofol MCT/LCT with lignocaine and more frequently used standard LCT propofol with a premixture of lignocaine.

## Materials and Methods

Following approval by the Institutional Ethics Committee and written informed consent, 300 ASA I-III patients, aged 18-65 years, scheduled for elective surgery under general anesthesia, were recruited into this prospective randomized double blind study.

Sample size was determined by performing a power analysis which showed that a minimum of 200 patients will be required for the study. Exclusion criteria consisted of patients with ischemic heart disease and neurological problems, pregnant or lactating patients, those who were taking any analgesics before surgery, or those with known hypersensitivity to propofol or to any of the constituents of the emulsion (soy-bean oil, MCT, glycerol, egg lecithin, sodium oleate or water for injection).

The drugs used were propofol-LCT (**Propofol™**, Claris Lifesciences, India), lignocaine hydrochloride 2% (**Xylocard<sup>®</sup>**, AstraZeneca, India) and propofol-MCT/LCT (**Propofol<sup>®</sup>-Lipuro**, B Braun Ltd, Melsungen, Germany).

The patients were assigned to 3 groups (100 each), using computer generated randomization. Group A received propofol-MCT/LCT premixed with normal saline (1 ml of normal saline added to 19 ml propofol-lipuro). Group B received propofol-MCT/LCT premixed with lignocaine (1 ml of 2% lignocaine added to 19 ml propofol-lipuro). Group C received propofol-LCT premixed with lignocaine (1 ml of 2% lignocaine added to 19 ml propofol). The investigators and patients were blinded to the study preparation being used.

Patients received no premedication. On arrival at the operation theatre, routine monitoring was applied and a 20G cannula was inserted into a suitable vein on the dorsum of non-dominant hand. A blinded investigator injected 5 ml of the propofol solution at a constant rate over 15 secs and patients were asked to grade any associated pain or discomfort using a four-point verbal rating scale that had been previously described to them (Table 1). Once the assessment of injection pain had been made, induction of anesthesia continued according to the anesthesiologist's routine practice.

*Table 1*  
*Verbal rating scale used by patients for assessment of propofol injection pain*

Pain Score	Description
0	No pain or discomfort at all.
1	Sensation of mild discomfort only.
2	Sensation of moderately severe pain.
3	Sensation of severe pain and/or grimacing or withdrawal of limb.

**Statistics**

Statistical analysis was conducted using SPSS version 11.5. Descriptive statistics such as mean, range and standard deviation have been used to summarize the baseline clinical and demographic profile of the patient. Categorical data was analyzed using Chi-square test and Fisher’s exact test. Parametric data was analyzed using analysis of variance (ANOVA) with post hoc analysis (least square difference).

**Results**

All the three groups were comparable with respect to age, weight and male: female ratio (Table 2).

*Table 2  
Demographic data*

	Group		
	A (n = 100)	B (n = 100)	C (n = 100)
Age (years)	42.02 ± 14.12	40.63 ± 13.71	41.5 ± 14.63
Weight (kg)	68.6 ± 9.46	65.4 ± 9.42	66.25 ± 8.17
Male: Female	59: 41	61: 39	49: 51

Values expressed as mean ± SD

MCT = medium-chain triglycerides; LCT = long chain triglycerides.

Group A = propofol MCT/LCT mixed with normal saline; Group B = propofol MCT/LCT mixed with lignocaine; Group C = propofol LCT mixed with lignocaine.

Patients in Group A had significant pain compared to patients in Groups B and C. In Group A the incidence of pain was 63% compared to 15% in Group B ( $X^2 = 48.242$ ,  $p < 0.001$ ), whereas in Group C the incidence of pain was 24% compared to 63% in Group A ( $X^2 = 30.247$ ,  $p < 0.001$ ) (Table 3). There was no significant difference in incidence of pain between Groups B and C ( $X^2 = 2.5$ ,  $p = 0.11$ ).

*Table 3  
Incidence of pain*

	Group		
	A (n = 100)	B (n = 100)	C (n = 100)
No pain	37	85	76
Pain	63	15	24

$X^2 = 58.021$ ,  $p < 0.001$

MCT = medium-chain triglycerides; LCT = long chain triglycerides.

Group A = propofol MCT/LCT mixed with normal saline; Group B = propofol MCT/LCT mixed with lignocaine; Group C = propofol LCT mixed with lignocaine.

There was significant difference in incidence of severity of pain between Groups A and B and Groups A and C. There was no difference in severity of pain between Groups B and C (Table 4).

*Table 4  
Incidence of severity of pain*

Pain score	Group		
	A (n = 100)	B (n = 100)	C (n = 100)
0 = no pain or discomfort	37	85	76
1 = mild discomfort	23	8	5
2 = moderately painful	32	7	15
3 = severely painful	8	0	4

$X^2 = 61.338$ ,  $p < 0.001$

MCT = medium-chain triglycerides; LCT = long chain triglycerides.

Group A = propofol MCT/LCT mixed with normal saline; Group B = propofol MCT/LCT mixed with lignocaine; Group C = propofol LCT mixed with lignocaine.

**Discussion**

In this study patients receiving propofol MCT/LCT premixed with lignocaine, and propofol LCT premixed with lignocaine, had significantly less pain on injection than LCT/MCT formulations of propofol.

Several mechanisms of pain on injection have been suggested, but investigations have shown that the free concentration of propofol in the aqueous phase may be the most important factor<sup>6,10,11</sup>. Emulsions of MCT/LCT, although maintaining similar pharmacological properties as standard propofol have smaller propofol concentrations in the aqueous phase<sup>5</sup>.

Rau et al.<sup>12</sup> reported that 37.8% of patients receiving propofol MCT/LCT were painfree and of the patients who had pain none graded it as severe. Kam et al.<sup>13</sup> have reported a similar incidence of pain on injection, 38% in patients receiving propofol MCT/LCT compared to 36% in patients receiving propofol LCT. Larsen et al.<sup>14</sup> have shown a lower incidence of pain on injection in patients receiving propofol MCT/LCT (37%) compared to patients receiving propofol LCT (64%). Yew et al.<sup>15</sup> have reported an incidence of 24% in patients receiving propofol LCT premixed with lignocaine and propofol MCT/LCT emulsion.

In our study, the incidence of pain with propofol MCT/LCT was 63%. Schaub et al.<sup>7</sup> have reported a 47%

incidence of pain with propofol MCT/LCT compared to 24% in patients receiving propofol LCT with lignocaine pretreatment. Nyman et al.<sup>8</sup> in their study in pediatric patients reported 33.3% patients having pain free propofol injection in the propofol MCT/LCT group compared to 61% patients having pain free propofol injection in the propofol LCT premixed with lignocaine group. Adam et al.<sup>9</sup> reported that patients receiving propofol MCT/LCT had a higher verbal analogue scale (VAS) as compared to patients receiving propofol LCT with lignocaine.

We found that mixing propofol MCT/LCT with lignocaine was effective in significantly reducing the incidence of pain from 63% in propofol MCT/LCT to 15% in propofol MCT/LCT with lignocaine.

Yew et al.<sup>15</sup> have reported a decrease in pain on injection from 24% to 4% in patients receiving propofol

MCT/LCT mixed with lignocaine. Kunitz et al.<sup>16</sup> have also suggested that addition of lignocaine to propofol MCT/LCT seems to have an additive effect to reduce propofol injection pain.

In our study, the incidence of pain with propofol LCT premixed with lignocaine was 24% which is in accordance with reported incidence in other studies<sup>1,15</sup>. We did not use propofol LCT without lignocaine as it was not ethically justified and studies have shown that propofol LCT used alone increases incidence of pain.

In conclusion, propofol MCT/LCT alone does not provide any advantage to reduce pain on injection in comparison to propofol MCT/LCT premixed with lignocaine and propofol LCT premixed with lignocaine. Further studies need to be done to establish the role of this new propofol MCT/LCT emulsion on propofol injection pain.

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