ORIGINAL RESEARCH PAPER
Volume - 10 | Issue - 12 | December - 2021 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

COMPARISON OF INJECTION PAIN BY MEDIUM PLUS LONG CHAIN TRIGLYCERIDE PROPOFOL VERSUS LONG CHAIN TRIGLYCERIDE PROPOFOL IN PEDIATRIC ELECTIVE SURGERY: A RANDOMIZED DOUBLE-BLIND INTERVENTIONAL STUDY

Anaesthesiology

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ABSTRACT

Background And Aims: Propofol is a one of the most popular drugs for anaesthesiologists but pain on injection is a perturbing issue in its use. Medium and long chain triglyceride (MCT-LCT) propofol had shown lesser injection pain in adults but in children its role remains debatable. The aim of the study was to compare the injection pain by medium plus long chain triglyceride propofol versus long chain triglyceride propofol in children. **Methods:** Total 226 patients, aged 4-8 years, posted for elective surgeries and randomly assigned to 2 groups of 113 each. Group A (n=113) received inj. 1 % Propofol MCT-LCT 2 mg/kg with inj. 2% lignocaine 0.2 mg/kg and Group B (n=113) received inj. 1 % Propofol LCT 2 mg/kg with inj. 2% lignocaine 0.2 mg/kg. Pain was assessed on 0-6 point pain scale. Unpaired Student's t-test and Chi-square test/Fisher's exact test were used to analyse results. **Results:** Propofol MCT – LCT had lower incidence of injection pain [22 (19.46%) versus 40 (35.39%); (P = 0.011)] and lower incidence of severe pain [0 (0%) versus 8 (7.07%); (P = 0.012)] in comparison of Propofol LCT. **Conclusion:** Propofol MCT-LCT premixed with lignocaine significantly decreases the incidence and severity of injection pain in children as compared to Propofol LCT.

KEYWORDS

Propofol, children, injection, pain, lignocaine

INTRODUCTION

With the development and improvement of surgical and anesthetic techniques, critical incidents such as cardiac arrest or death during the perioperative period have been obviously minimized. In turn, more attempts have been made to address minor but potentially distressing clinical anesthetic problems such as pain, postoperative nausea and vomiting to further improve the quality of anesthesia care.[1] Propofol injection pain is one of these problems and it was ranked seventh among the most important 33 low-morbidity clinical anesthesia problems by a panel of expert anesthesiologists.[2]

Propofol has become the most popular intravenous anaesthetic drug for smooth induction, sedation, faster recovery and anti-emetic effect than other drugs such as thiopental.[3] But pain on injection is a perturbing issue in its use. There are many methods to prevent or to reduce the pain of propofol injection like adding lidocaine to propofol, cooling or warming propofol, diluting the propofol solution, injection of propofol into a large vein, and pre-treatment with IV injection of lidocaine, ondansetron, metoclopramide, opioid, magnesium, or thiopental with or without tourniquet; all have been tried with variable results.[4-6]

In adults medium plus long chain triglyceride propofol (MCT-LCT) Propofol showed lesser pain on injection but in children it was not sufficiently researched. In previous studies only one pain scale was use for infants and children but all age groups children are not same in in vascular size, pharmacokinetic and pharmacodynamic of propofol so the same pain scale cannot be used for all ages.

With this background this study was designed to compare the pain on injection of medium plus long chain triglyceride (MCT-LCT) propofol versus long chain triglyceride (LCT) propofol in paediatric patients with attention on haemodynamic parameters and to evaluate side effects, if any.

Method:

After obtaining approval by the ethics committee we included 226 children aged 4-8 years, informed consent taken from parents, ASA physical status I or II patients, scheduled for elective surgical procedure under general anaesthesia. Children who had bradycardia, hypotension, allergic to Egg and anaesthetic agents and continued to cry or didn't calm down after 5 min of the pre-medication.

In this study randomization was done by sealed envelope method. A total of 226 envelopes 113 per group were made, each envelope mentioning a particular study group. Patient allocated to group mentioned on the envelope. A 22 gauge Intravenous (IV) cannula was inserted in antecubital veins in the ward. Inside the operation theatre, electrocardiograph, peripheral oxygen saturation (SpO2), heart rate, systolic and diastolic blood pressures were monitored and baseline values were noted. Glycopyrrolate 0.004 mg/kg, midazolam 0.02 mg/kg and fentanyl 2 µg/kg were administered intravenously to all children 5 min before the induction of anaesthesia. PR, BP parameters were recorded just before induction. Then after, induction of anaesthesia was carried out with freshly prepared (only taken out from the refrigerator) propofol 1%, either LCT propofol or MCT-LCT at a dose of 2 mg/kg administered over a period of 15 sec. along with preservative-free lignocaine in the proportion of 2% lignocaine 0.2 mg/kg.

Propofol MCT-LCT ampules were labelled as Drug A and Propofol LCT ampules labelled as Drug B. The drug solution administered by an anaesthesiologist who was blinded to the constituents of the drug. All patients who received Drug A labelled as Group A and patients who received Drug B labelled as Group B. Pain on injection of propofol was assessed in all patients until the loss of consciousness, by an anaesthesiologist who was unaware of the type of propofol being used. Pain scores were recorded with pain scale which included motor events scale and verbalization scale which is describe in Table 1. Total Pain score of ≥1 was considered as incidence of pain and of ≥3 was considered as severe pain. PR, BP parameters were recorded then Inj. Succinyl choline 2 mg/kg was administered then direct laryngoscopy was done and patient was intubated with appropriate size endotracheal tube. Bilateral air entry was checked & tube fixed. Anaesthesia was maintained with O_2 40%, N_2O 60% and neuromuscular blocker Inj. Atracurium 0.5 mg/kg loading then 0.1 mg/kg maintenance, At the end of the surgery patient reversed with Inj. Neostigmine (0.07 mg/kg iv) and Inj. Glycopyrrolate (0.01 mg/kg i.v.) & extubated after complete reversal. Patient was shifted to recovery room.

The primary outcomes of the study were incidence of pain and severe pain on injection and pain scores. The secondary outcomes studied were change in heart rate and systolic blood pressure and adverse events (if any). Adverse events such as rash, urticaria or myoclonic movements were noted. The sample size estimation was based on the assumptions from a previous study where severe pain in control group was observed to be in 7.1% of patients while that in experimental group, it was found to be in 0% of patients.[3] Considering 95% confidence and 80% power to verify the expected difference of 7% in proportion of cases who expressed severe pain in both groups. For statistical analysis of significance difference in Proportion of pain score chi square test was used, for significance difference in mean Hemodynamic parameters with unpaired 't' test was used, for significance difference in demographic data such as age, weight and

sex unpaired 't' test and Fisher's exact test was used. A value of P less than 0.05 was considered as statistically significant.

Table 1 : Pain Scale For Evaluation Of Propofol-induced Injection Pain

Response to propofol injection Pain	Score
Motor events	
No movement	0
Slight hand withdrawal	1
Marked withdrawal, rubbing, trying to tear off the line	2
Generalised restlessness	3
Verbalisation scale	
No vocalisation	0
Purposeless moaning	1
Explicit protest	2
Screams, cries	3

RESULTS

There were no statistically significant (*P > 0.05*) differences in the demographic parameters such as age, weight and sex among the study groups (Table 2). Propofol MCT – LCT had lower incidence of injection pain [22 (19.46%) versus 40 (35.39%); (*P = 0.011*)] and lower incidence of severe pain [0 (0%) versus 8 (7.07%); (*P = 0.012*)] in comparison of Propofol LCT (Table3). Propofol MCT-LCT had significantly lower Motor event score [Median 0 versus 0, IQR 0 versus 1, minimum-maximum (0-1) versus (0-2); (*P = 0.003*)] in comparison of propofol LCT (Table4). Propofol MCT-LCT had significantly lower verbal pain score [Median 0 versus 0, IQR 0 versus 1, minimum-maximum (0-1) versus (0-2); (*P = 0.003*)] in comparison of propofol LCT (Table 4). Propofol MCT-LCT had highly significant lower total pain score [Median 0 versus 0, IQR 0 versus 1, minimum-maximum (0-1) versus (0-4); (*P < 0.001*)] in comparison of propofol LCT (Table 4). There was no significant difference in heart rate and blood pressure at different time intervals between the groups following propofol injection (Table 5). No adverse effects were seen in any of the patients in both the groups.

Table 2: Demographic Characteristics Of Patients

Parameters	MCT-LCT Propofol	LCT Propofol	p value
Age in years (mean±SD)	5.93 ± 1.31	5.69 ± 1.30	*0.168*
Weight in kg (mean±SD)	16.70 ± 4.24	16.23 ± 3.66	*0.372*
Male, n (%)	84 (74.24)	84 (74.24)	*1.000*
Female, n (%)	29 (25.66)	29 (25.66)	
LCT – Long chain triglyceride; MCT – Medium chain triglyceride; SD – Standard deviation			

Table 3 : Incidence of pain and severe pain on injection

Pain	MCT-LCT Propofol (n=113), n (%)	LCT Propofol (n=113), n (%)	Total (n=226), n (%)	p value
Pain incidence ≥1	22 (19.46)	40 (35.39)	62 (27.43)	*0.011*
Severe Pain ≥3	0 (0.00)	8 (7.07)	8 (3.5)	*0.012*

Table 4 : Pain Score

Pain	MCT-LCT Propofol Median (IQR) (Min.-Max)	LCT Propofol Median (IQR) (Min.-Max)	p value
Motor	0 (0) (0-1)	0 (1) (0-2)	*0.003*
Verbal	0 (0) (0-1)	0 (0) (0-2)	*0.003*
Total	0 (0) (0-1)	0 (1) (0-4)	*<0.001*

Table 5: Difference of mean heart rate (BPM) at different time interval (Mean±SD)

Parameters	MCT-LCT Propofol	LCT Propofol	p value
Baseline vs. Just before induction	3.8 ±1.84	4.18 ± 1.63	*0.101*
Baseline vs. After propofol injection	8.77 ± 3.28	9.27 ± 2.24	*0.182*
Just before induction vs. After propofol injection	4.96 ± 2.74	5.09 ± 1.73	*0.670*
Difference of mean systolic blood pressure (SBP) at different time interval (Mean±SD)			
Baseline vs. Just before induction	2.88 ± 1.31	3.07 ± 1.25	*0.265*
Baseline vs. After propofol injection	7.31 ± 2.81	6.88 ± 1.95	*0.182*
Just before induction vs. After propofol injection	4.42 ± 2.48	3.81 ± 1.38	*0.155*

DISCUSSION

Nowadays propofol is the preferred intravenous general anaesthetic drug for induction of anaesthesia with a smooth induction, pleasant sleep, rapid recovery and low incidence of nausea and vomiting. [7] Despite these positive properties, pain on injection is one of the most common side effects of propofol. The mechanism of pain on injection of propofol is thought to be multifactorial but its exact cause is not clear. The most commonly identified mechanism is release of bradykinin as a result of the activation of the plasma kinin-kallikrein system by propofol. [8-9]

Although there were many methods used to reduce the pain of propofol injection like adding lidocaine to propofol, cooling or warming propofol, diluting the propofol solution, use different formula of propofol MCT-LCT, injection of propofol into a large vein, and pre-treatment with IV injection of lidocaine, ondansetron, metoclopramide, opioid, magnesium, thiopental with or without tourniquet.[3-6] But no method completely relieved the pain on propofol injection. **Tan et al** suggested to use a combination of techniques, such as alfentanil or fentanyl pre-treatment, mixing lignocaine with the propofol and injecting into a large vein with no carrier fluid in order to decrease the incidence and severity of propofol injection pain.[10] In our study we used fentanyl, premixed lignocaine with either propofol MCT-LCT or Propofol LCT which were injected in antecubital veins through 22 gauge cannula.

In previous studies the efficacy of MCT-LCT propofol to reduce pain on injection effectively revealed in adult patients. [11-16] But children are not little adult. They are different from adults in vascular size, pharmacokinetic and pharmacodynamic of propofol. According to **Larsen et al** [17] and **Öztürk et al** [18] 30- 90 % children experienced pain on propofol injection. However, the age distribution intervals in paediatric studies are wide. The study by **Nyman et al** [19] had studied on patients aged between 2 and 18 years, the study by **Varghese et al** [20] between 5 and 15 years, while the study by **Beyaz et al** [21] the ages were between 3 and 15 years, **Singla et al** [3] 6 month to 8 years, **Stefan Soltész et al** [22] 2 to 6 years, **Depue K et al** [23] 2 to 7 years and **Rochette et al** [24] had included preschool children. However, all age groups children are not same so the same pain scale cannot be used for all ages and it should rather be selected according to age.[21] Different pain scales should be used for different age groups. In our study pain scale was selected according to age group 4-8 years old children.

In several studies researchers used fentanyl as pretreatment to decrease incidence and severity of propofol injection pain. **Ahmed et al** [25] studied that when 100 µg fentanyl injected before the propofol premixed with lignocaine there was reduction in injection pain from 32% to 13%. **Helmers et al** [26] observed decrease in incidence on propofol injection pain from 40% to 16% with the use of fentanyl. In another study **Bahar et al** [27] assessed that there was abatement in the severity of pain but not in overall incidence of propofol injection pain when fentanyl 0.1 mg injected 3–5 min before propofol injection. In our study we gave 2 µg/kg inj. fentanyl in both groups.

Many studies discussed about the role of lignocaine in reducing the propofol injection pain. **Jinseok et al** [28] observed significantly lower incidence of injection pain from 83.3% to 36.7% in 90 patients, who received premixed lignocaine. **Amir M. Shabana** assessed that injection pain was dropped in 100 patients from 24% to 4% when lignocaine premixed with propofol.[29] **Scott et al** [30] studied that lignocaine mixed with propofol significantly lower the injection pain incidence than pre-treatment with lignocaine. But in another study by **Johnson et al** [31] there was no significant difference between a group of patients that received lignocaine pre-treatment and a group that received propofol mixed with lignocaine. **Cameron et al** observed in 100 children aged 1 to 10 years that the minimum effective dose of lignocaine required to prevent injection pain due to propofol was 0.2 mg/kg.[32] With this background, in this study we used 0.2 mg/kg lignocaine 2% premixed with propofol in both groups.

In many studies it was observed that Propofol MCT-LCT, which is

another formula of propofol in aqueous form relieved pain on injection in comparison of propofol LCT. [3,6,11,19,33-38] **Hiroshi et al** [12] observed that there was no role of bradykinin generation and complement activation in less injection pain by Propofol MCT-LCT than Propofol LCT. The decrease in pain when using LCT/MCT propofol is considered to be attributed to the lipid solvent that decreases the propofol concentration in the aqueous phase. [14,16-17,39] In our study we compared propofol MCT-LCT 1%, 2 mg/kg with propofol LCT 1%, 2 mg/kg in terms of injection pain.

In a previous studies sevoflurane required as supplementation in severe pain on injection [3] but in our study we didn't need the sevoflurane supplement for injection pain. Although the incidence of severe pain was 0% in MCT-LCT group, slight pain was present in 19.46 % of children in-spite of premixing with lignocaine and premedication with fentanyl. Therefore, there is a need to invent either different formulation or additive measures to overcome the pain.

CONCLUSION

From the present study, we conclude that 2 mg/kg 1% Propofol MCT-LCT premixed with 0.2 mg/kg 2% lignocaine significantly decreases the incidence and severity of injection pain in children as compared to 2 mg/kg 1% Propofol LCT. Systolic blood pressure and heart are unchanged with both type of Propofol. Propofol MCT-LCT is equally effective and easily available with same cost and has lesser adverse effects as compared to Propofol LCT. Therefore, Propofol MCT-LCT is more effective in reducing the pain on injection than Propofol LCT and can be used as preferable alternative to the traditional Propofol LCT for induction of anaesthesia in children.

Financial support and sponsorship - Nil.

Conflicts of interest - There are no conflicts of interest.

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