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Original Research Article

A Prospective Randomized Double-Blind Comparative Study of Pain on Injection and Hemodynamic Response between Long-Chain Triglyceride (LCT) Propofol and Medium-/Long-Chain Triglyceride (MCT/LCT) Propofol in Adult Patients Undergoing Elective Surgery under General Anesthesia

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Abstract

Background: Pain on injection is a common and distressing adverse effect of propofol administration during induction of general anesthesia. Conventional long-chain triglyceride (LCT) propofol formulations contain a higher free aqueous propofol fraction, which is thought to cause pain. Medium- and long-chain triglyceride (MCT/LCT) formulations reduce this free fraction and may decrease injection pain while maintaining equivalent anesthetic efficacy and hemodynamic stability.

Methods: In this prospective, randomized, double-blind study, 120 ASA I–II adult patients (18–60 years) scheduled for elective surgery under general anesthesia were randomized to receive either LCT propofol (n=60) or MCT/LCT propofol (n=60) for induction. Pain on injection was assessed using the McCrirrick and Hunter four-point pain scale (0–3). Hemodynamic parameters (heart rate, systolic blood pressure, diastolic blood pressure, and mean arterial pressure) were recorded at baseline and 1 minute after induction. Data were analyzed using the Mann–Whitney U test, Chi-square test, and repeated-measures ANOVA; $p<0.05$ was considered significant.

Results: Demographic characteristics were comparable between groups. The incidence of pain on injection (pain score >0) was significantly lower with MCT/LCT propofol (58.3%) compared with LCT propofol (81.7%; $p=0.0096$). Mean pain score was also significantly lower in the MCT/LCT group (0.75 ± 0.82 vs 1.53 ± 0.95; $p<0.0001$). Hemodynamic changes at 1 minute after induction (ΔHR, ΔSBP, ΔDBP, ΔMAP) were similar between the two formulations (all $p>0.3$). No serious adverse events occurred in either group.

Conclusion: MCT/LCT propofol significantly reduces both the incidence and severity of pain on injection compared with conventional LCT propofol while providing equivalent hemodynamic stability during induction of general anesthesia. MCT/LCT propofol is a preferable formulation for routine clinical use in adult patients undergoing elective surgery.

Keywords: Propofol; Pain on injection; MCT/LCT propofol; LCT propofol; Hemodynamic response; General anesthesia; Induction.

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Introduction

Propofol is the most widely used intravenous induction agent in modern anesthetic practice because of its rapid onset, smooth induction, short duration of action, and favorable recovery profile. [1] Despite these advantages, pain on injection remains one of its most common and distressing adverse effects, occurring in up to 70–90% of patients when injected into a peripheral vein without pretreatment. [2] This pain can cause patient discomfort, anxiety, and occasionally movement or withdrawal of the arm during induction, which may complicate airway management. The mechanism of propofol-induced pain is multifactorial. The free aqueous propofol fraction in the emulsion is thought to directly irritate the vascular endothelium and activate the kallikrein–kinin system, leading to the release of bradykinin and other pain mediators. [3]

Conventional long-chain triglyceride (LCT) propofol formulations contain a relatively high concentration of free propofol in the aqueous phase. In contrast, medium- and long-chain triglyceride (MCT/LCT) formulations incorporate medium-chain triglycerides, which increase the lipid solubility of propofol and reduce the free aqueous fraction, thereby potentially decreasing injection pain without compromising anesthetic potency. [4]

Several randomized controlled trials have compared LCT and MCT/LCT propofol formulations with respect to injection pain. Most studies have demonstrated a significant reduction in both the incidence and severity of pain with MCT/LCT propofol. [5-8] However, results regarding hemodynamic effects and overall induction characteristics have been inconsistent, and data from the Indian population remain limited. Furthermore, concerns have been raised that the altered lipid composition might affect the speed of onset or the magnitude of hemodynamic changes during induction.

Given these considerations, we conducted a prospective, randomized, double-blind comparative study to evaluate the incidence and severity of pain on injection as well as the hemodynamic response to induction with LCT propofol versus MCT/LCT propofol in adult patients undergoing elective surgery under general anesthesia.

Materials and Methods

Study Design and Setting: This prospective, randomized, double-blind, parallel-group comparative study was conducted in the Department of Anaesthesiology at a tertiary-care teaching hospital over a 12-month period. The study protocol was approved by the Institutional Ethics Committee, and written informed consent was obtained from all participants.

Participants

Inclusion criteria: Adults aged 18–60 years, American Society of Anesthesiologists (ASA) physical status I or II, scheduled for elective surgery under general anesthesia requiring intravenous induction with propofol, and providing written informed consent.

Exclusion criteria: Known allergy to propofol, egg, or soy; difficult intravenous access; chronic pain syndromes; regular opioid therapy; pregnancy or lactation; severe systemic disease (ASA III or higher); and emergency surgery.

Sample Size

Based on previous studies reporting a reduction in pain incidence from approximately 80% with LCT propofol to 50–60% with MCT/LCT propofol, a sample size of 55 patients per group was calculated to detect this difference with $\alpha = 0.05$ and power = 80%. Allowing for 10% attrition, 60 patients per group (total n = 120) were enrolled.

Randomization and Blinding: Eligible patients were randomized in a 1:1 ratio using a computer-generated random sequence with block randomization (block size 4). Allocation was concealed in sequentially numbered, opaque, sealed envelopes. Study drugs were prepared in identical syringes by an anaesthesiologist not involved in patient care or data collection. Both the patient and the outcome assessor were blinded to group allocation.

Intervention

Group LCT: Patients received conventional long-chain triglyceride propofol (1% propofol in LCT emulsion) at a dose of 2–2.5 mg/kg for induction.

Group MCT/LCT: Patients received medium- and long-chain triglyceride propofol (1% propofol in MCT/LCT emulsion) at a dose of 2–2.5 mg/kg for induction.

Anaesthetic Technique: All patients received standard premedication with midazolam 0.03 mg/kg and fentanyl 1.5 µg/kg intravenously 3–5 minutes before induction. A 20-gauge intravenous cannula was inserted in the dorsum of the non-dominant hand. Propofol was injected at a rate of 0.5 mL/s through this cannula without pretreatment. Immediately after injection, patients were asked to rate the pain using the McCrirrick and Hunter four-point verbal rating scale (0 = no pain, 1 = mild pain, 2 = moderate pain, 3 = severe pain). After loss of verbal response, vecuronium 0.1 mg/kg was administered, and tracheal intubation was performed after adequate neuromuscular blockade. Anesthesia was maintained with sevoflurane in oxygen–air mixture.

Outcome Measures

Primary outcome: Incidence (proportion of patients with pain score >0) and severity (mean pain score on the 0–3 McCrirrick and Hunter scale) of pain on injection.

Secondary outcomes: Changes in heart rate (ΔHR), systolic blood pressure (ΔSBP), diastolic blood pressure (ΔDBP), and mean arterial pressure (ΔMAP) from baseline to 1 minute after induction; incidence of adverse effects (hypotension, bradycardia, injection-site reactions).

Data Collection: Pain score was recorded immediately after propofol injection by a blinded observer. Hemodynamic parameters were measured non-invasively at baseline (pre-induction) and at 1 minute after completion of propofol injection using a calibrated monitor. All measurements and

assessments were performed by personnel blinded to group allocation.

Statistical Analysis: Data were analyzed using SPSS Statistics version 26.0 (IBM Corp., Armonk, NY, USA). Continuous variables are expressed as mean ± standard deviation and compared using the independent Student's t-test or Mann–Whitney U test as appropriate. Categorical variables are expressed as proportions and compared using the Chi-square or Fisher's exact test. Repeated-measures ANOVA was used to analyze hemodynamic trends. A two-sided p-value < 0.05 was considered statistically significant.

Results

A total of 120 patients were enrolled and randomized (60 per group). All patients completed the study protocol. Demographic characteristics (age, sex, ASA status, weight) were well balanced between the LCT and MCT/LCT groups (Table 1).

Table 1. Demographic characteristics

Parameter	LCT (n=60)	MCT/LCT (n=60)	p-value
Age (years), mean ± SD	39.1 ± 12.8	39.7 ± 12.4	0.78
Weight (kg), mean ± SD	68.3 ± 13.5	68.2 ± 12.8	0.95
Sex (Male/Female), n	28 / 32	31 / 29	0.71
ASA (I / II), n	32 / 28	30 / 30	0.85

SD = standard deviation; ASA = American Society of Anesthesiologists physical status.

Primary Outcome: Pain on Injection: The incidence of pain on injection (pain score >0) was significantly lower in the MCT/LCT group (35/60, 58.3%) compared with the LCT group (49/60, 81.7%; p=0.0096). The distribution of pain scores showed a clear shift toward lower severity with MCT/LCT propofol: 25 patients (41.7%) reported no pain (score 0) versus only 11 patients (18.3%) in the LCT group. Mean pain score was significantly lower with MCT/LCT propofol (0.75 ± 0.82) than with LCT propofol (1.53 ± 0.95; p<0.0001) (Table 2).

Table 2. Pain on injection scores (McCrirrick and Hunter scale)

Pain Score	LCT (n=60), n (%)	MCT/LCT (n=60), n (%)	p-value
0 (No pain)	11 (18.3%)	25 (41.7%)	—
1 (Mild pain)	18 (30.0%)	26 (43.3%)	—
2 (Moderate pain)	19 (31.7%)	8 (13.3%)	—
3 (Severe pain)	12 (20.0%)	1 (1.7%)	—
Incidence (score >0)	49 (81.7%)	35 (58.3%)	0.0096
Mean pain score ± SD	1.53 ± 0.95	0.75 ± 0.82	<0.0001

SD = standard deviation. Chi-square test for incidence; Mann–Whitney U test for mean score.

Secondary Outcomes: Hemodynamic Response: Changes in hemodynamic parameters from baseline to 1 minute after induction were comparable between the two groups.

There were no statistically significant differences in ΔHR, ΔSBP, ΔDBP, or ΔMAP (all p>0.3). Both formulations produced a mild decrease in blood pressure and minimal change in heart rate, consistent with the known cardiovascular effects of propofol (Table 3). No patient in either group experienced clinically significant hypotension, bradycardia, or other adverse events requiring intervention during the induction period.

Table 3. Hemodynamic changes at 1 minute after induction

Parameter (Δ from baseline)	LCT (n=60)	MCT/LCT (n=60)	Mean difference	p-value
Δ Heart rate (bpm)	0.0 ± 4.4	0.8 ± 4.2	+0.8	0.334
Δ SBP (mmHg)	−12.0 ± 4.0	−11.6 ± 4.2	+0.4	0.584
Δ DBP (mmHg)	−7.3 ± 2.7	−7.5 ± 2.9	−0.2	0.702
Δ MAP (mmHg)	−8.8 ± 2.3	−8.8 ± 2.3	0.0	0.720

Data presented as mean ± SD. Mann–Whitney U test used for all comparisons. SBP = systolic blood pressure; DBP = diastolic blood pressure; MAP = mean arterial pressure.

Discussion

In this prospective, randomized, double-blind study of 120 adult patients, MCT/LCT propofol significantly reduced both the incidence and severity of pain on injection compared with conventional LCT propofol. The incidence of any pain decreased from 81.7% to 58.3%, and the mean pain score was halved (1.53 to 0.75). Importantly, hemodynamic changes during induction were virtually identical between the two formulations, confirming that the pain-reducing benefit of MCT/LCT propofol does not come at the cost of altered cardiovascular stability.

Our findings are consistent with the majority of published randomized trials comparing the two formulations. [5-8] The reduction in pain is attributed to the lower free aqueous propofol concentration in MCT/LCT emulsions. By incorporating medium-chain triglycerides, a greater proportion of propofol remains dissolved in the lipid phase, reducing the amount available to irritate nociceptors in the vein wall. This physicochemical advantage translates directly into improved patient comfort during induction without compromising the speed or quality of anesthesia.

The hemodynamic equivalence observed in our study is clinically reassuring. Both formulations produced the expected mild decrease in blood pressure and minimal change in heart rate typical of propofol induction. There was no evidence of delayed onset or exaggerated cardiovascular depression with the MCT/LCT formulation. This supports the conclusion that the altered lipid composition does not meaningfully affect the pharmacodynamic profile of propofol during routine induction in ASA I–II patients.

An important practical implication of our results is that MCT/LCT propofol can be recommended as the preferred formulation for routine induction in adult patients undergoing elective surgery.

The reduction in moderate-to-severe pain (from 51.7% in the LCT group to only 15% in the MCT/LCT group) represents a meaningful improvement in patient experience. Given that propofol is administered to millions of patients worldwide each year, even a modest reduction in injection pain has substantial aggregate benefit.

Strengths and Limitations: Strengths of this study include the double-blind randomized design, standardized injection technique and assessment using a validated pain scale, and simultaneous evaluation of both pain and hemodynamic outcomes. The sample size was adequate for the primary endpoint. Limitations include the single-centre setting, restriction to ASA I–II patients, and assessment of pain only at the time of injection (without delayed assessment). Future studies could evaluate MCT/LCT propofol in higher-risk populations and explore combination strategies (e.g., with lignocaine pretreatment) for further pain reduction.

In conclusion, MCT/LCT propofol offers a clear advantage over conventional LCT propofol by significantly reducing the incidence and severity of pain on injection while maintaining identical hemodynamic stability during induction of general anesthesia. It should be considered the preferred formulation for routine clinical use in adult patients undergoing elective surgery.

Conclusion

MCT/LCT propofol significantly reduces both the incidence (58.3% vs 81.7%) and severity (mean score 0.75 vs 1.53) of pain on injection compared with LCT propofol during induction of general anesthesia in adult patients. Hemodynamic responses are equivalent between the two formulations. MCT/LCT propofol is a preferable choice for routine induction in elective surgical patients.

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