Propofol LCT vs propofol MCT-LCT: Randomized controlled trial

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Abstract

Background: Propofol formulation containing long chain triglycerides (LCT) elicits severe pain on intravenous injection. Newer formulation of propofol containing combination of medium and long chain triglycerides (MCT/LCT;50:50) with less concentration of free propofol may be beneficial in this aspect.

Methods: This prospective, randomized, double blind study included 116 ASAI/II adult patients undergoing short surgical procedures under general anesthesia. Patients in group M received 3 cc of MCT/LCT propofol (Fresofol 1%, Fresenius Kabi) and group L received LCT propofol (Diprivan 1%, Astrazeneca), both over 3 seconds (@1cc/sec to assess pain on injection using the VRS score. Induction time and requirement of additional dose of propofol was also noted. Heart rate (HR) and mean arterial pressure (MAP) were recorded at baseline, post intubation and 1, 3, 5 and 10 minutes thereafter. Serum triglyceride levels were measured 24 hours post-surgery and compared to preoperative levels.

Results: Group M reported reduced pain score after IV propofol injection (1.37+2.40 vs 2.60+2.93) along with overall less incidence of pain (34.5% vs 53.4%). No difference was found in preoperative and 24 hours postoperative serum triglyceride levels in both groups. Three patients in group L developed thrombophlebitis as compared to one in group M. Induction time and hemodynamics were similar in both groups.

Conclusion: MCT/LCT propofol produces less pain on intravenous injection. However, both formulations did not increase serum triglyceride levels after single induction dose.

Keywords: Propofol, Anesthesia, Triglycerides, Long chain, Medium chain

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Introduction

Propofol is the most popular intravenous (IV) anesthetic induction agent nowadays. It provides rapid, smooth induction and early clear headed recovery and used for variety of purposes like induction of general anaesthesia, sedation, total intravenous anaesthesia, anticonvulsant and as an antiemetic.[1] Conventionally, propofol formulation contains long chain triglycerides (LCT). But, the side effect of this formulation is a severe pain on intravenous injection.[2] Newer formulation of propofol containing combination of medium and long chain triglycerides (MCT/LCT; 50:50) have significantly less concentration of free propofol. Also, changes in the formulation may have an impact on the pharmacokinetics, pharmacodynamics or safety characteristics of a drug and hence can alter induction time.[3,4] Propofol also increases serum triglyceride levels which is associated with increased risk of pancreatitis, coronary artery disease etc.[5] So, we planned this study to determine differences in both formulations regarding severity of pain on injection, hemodynamic stability and the difference in serum triglyceride levels after single dose.

Material and Methods

After institutional ethics committee approval and obtaining written informed consent from each patient; this prospective, randomized, double blind study included 116 patients divided equally into two groups (n= 58 each) viz Group L and Group M by sealed envelope technique. All ASAI/II patients between 18 to 60 years of age undergoing short surgical procedures (less than 2 hours) under general anesthesia were included. Pregnant patients and those having known allergy to propofol, abnormal liver and renal function, history of drug abuse, chronic pain disorder were excluded from the study. Serum triglyceride levels were measured day before surgery along with all routine investigations. Before surgery, routine standard monitor viz. pulse oximetry, electrocardiography (ECG) and non-invasive blood pressure were applied. Venous cannulation with a 20 G cannula was done on the dorsum of the hand and verbal rating score (VRS) for pain (0 = no pain, 1-4 = mild, 5-7 = moderate, 8-10 =severe or worst pain imaginable) at cannulation was recorded. All patients were premedicated with fentanyl 1µg/kg and midazolam 1mg IV 10 minutes before induction. Anesthesiologist loading propofol was not involved in the management of patients to ensure blinding. Patients in group M received 3 cc of MCT/LCT propofol **(Fresofol 1%, Fresenius Kabi)**

and group L received 3 cc of LCT propofol (**Diprivan 1%, Astrazeneca**), both over 3 seconds (@1cc/sec) to assess pain on injection using the VRS score. Painful grimace (moderate pain) and hand withdrawal (severe pain) was also taken into consideration. Patients were then induced with the respective formulations of propofol with a total dose of 2mg/kg and induction time (till loss of verbal commands) was noted. Additional dose of propofol was also noted and the data was used to assess the cost effectiveness. Vecuronium 0.1mg/kg was used as muscle relaxant and patients were maintained on oxygen: nitrous oxide: isoflurane (MAC 1-1.2). Hemodynamic parameters such as Heart Rate (HR) and mean arterial pressure(MAP) were recorded at baseline, post intubation and 1,3,5 and 10 minutes thereafter. At the end of the surgery all patients were reversed with neostigmine 0.05 mg/kg and glycopyrrolate 10 mcg/kg IV and extubated after adequate recovery (TOF ratio>0.9) before shifting to the recovery room. Serum triglyceride levels were measured 24 hours post-surgery and compared to preoperative levels.

Statistical analysis

Statistical analysis was performed using SPSS 16 (SPSS, Inc, Chicago, IL) software. Demographic data & complications were analyzed using Student t-test and Chi-square test. Hemodynamic variables were analyzed using unpaired t-test. Intragroup comparison of triglyceride values was done with paired *t*-test. Ordinal data i.e. pain score was analyzed using Mann Whitney U test. All tests were two-tailed and $P < 0.05$ was considered as significant.

Results

All patients in the study were comparable with respect to age, sex, weight and ASA status. (Table 1) Mean VRS for pain on IV cannulation was similar [2.202±0.913(Group L) vs 2.089±0.896 (group M); p =0.413] in both groups. But, group M reported significantly reduced pain after IV propofol injection alongwith overall less incidence of pain (53.4% vs 34.5%). Three patients in group L developed thrombophlebitis as compared to one in group M. Induction time was similar (Table 2) and no difference was found in preoperative and 24 hours postoperative serum triglyceride levels in both groups.(Table 3) Both groups produced similar hemodynamics throughout procedures.(Fig 1 & 2)

Table 1: Demographic data

Parameter	Mean ± SD	
	Gr L	Gr M
Age	39.08±10.76	38.50±13.25
Sex (Male/Female %)	32/26(54.2/44.8%)	28/30(48.3/51.7%)
Weight	60.64±3.9	61.46±3.7
ASA I /ASA II	39/19	33/25

p>0.05

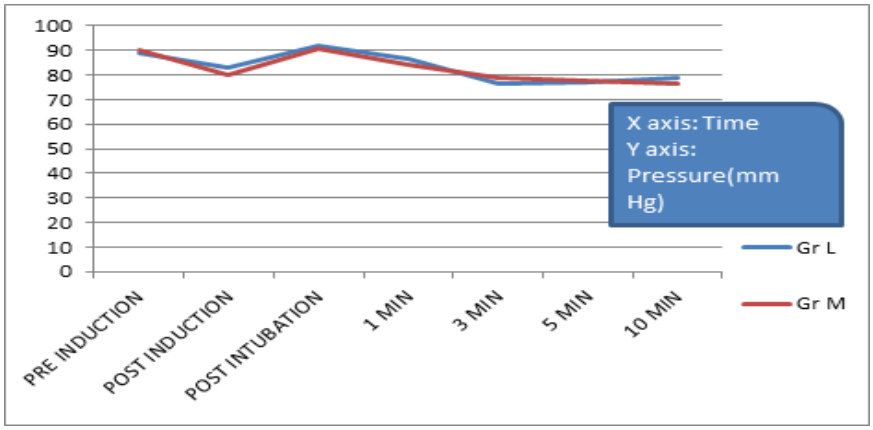

Fig. 1: Comparison of Mean arterial pressure

Note: No significant difference between groups

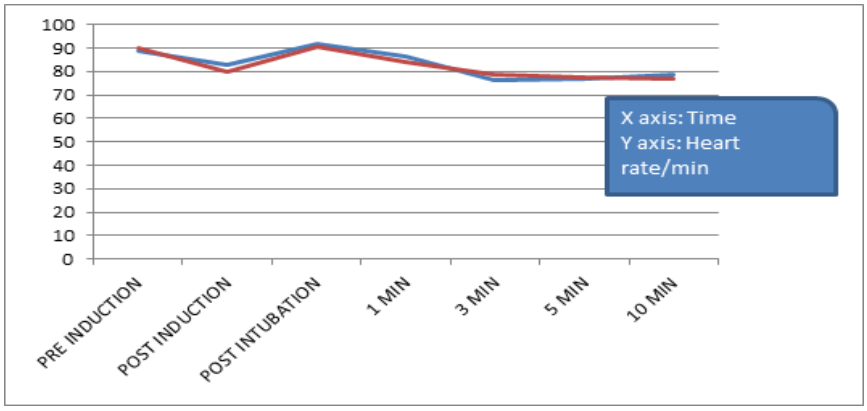

Fig. 2: Comparison of Heart rate

Note: No significant difference between groups

Table 2: Comparison of properties/adverse effects

Parameter	Mean ± SD		P value
	Gr L	Gr M	
Pain score on IV injection (VRS)	Sum of rank-4385 Mean-75.6	Sum of Rank-2401 Mean- 41.4	0.0001 (Mann Whitney U test)
Induction time (seconds)	33.75±12.92	32.10±11.91	0.475
Pain	31(53.4%)	20(34.5%)	0.0025
Thrombophlebitis	3(5%)	1(1.7%)	0.308

Table 3: Comparison of serum triglyceride levels before and after bolus doses of propofol

Groups	Pre-op Triglycerides (mg%)	Post-op Triglycerides 24 hrs. (mg%)	P value (paired t test)
Gr L	123.08±35.96	125.98±33.12	0.139
Gr M	130.22±31.88	126.48±31.63	0.055

Discussion

Pain on intravenous injection of propofol is an unpleasant anesthesia experience which is attributed to an aqueous phase containing free propofol.[2] This speculation is supported by the finding that dilution of the propofol emulsion with additional medium chain triglycerides decreases the incidence and intensity of pain.[6,7] Also, bradykinin and C3a levels were similar in the MCT/LCT propofol and the LCT formulations concluding that the reduced aqueous free form results in less severe pain.[8] We found reduction in the intensity and incidence of injection pain with MCT/LCT propofol (53.4 vs 34.5%; p=0.025). Similar incidence of injection pain with MCT/LCT propofol has been reported in the literature ranging from 37% to 62%.[7,9]

Also, MCT/LCT propofol had attenuated injection pain of LCT propofol when administered first.[10] Further reduction of pain has been shown with the lignocaine pretreatment prior to both LCT and MCT/LCT propofol.[11] Even one study showed similar incidence of pain with LCT propofol with lignocaine and MCT/LCT without lignocaine.[12]

But, an addition of lignocaine to both propofol MCT/LCT and propofol LCT produced similar incidence and severity of pain in pediatric patients.[13]Many adult studies show that the injection pain severity of intravenous propofol MCT/LCT is less than propofol LCT emulsion. [10,14-16]

However, Beyaz et al in their two studies in pediatric population found exactly opposite results where propofol MCT/LCT produced more pain than LCT propofol.[17-18] Authors suggest further studies in paediatric patients to validate these contrasting results.

Increased serum triglyceride level after propofol infusion is associated with increased risk of pancreatitis, coronary artery disease. It occurs in ICU patients who receive long term propofol infusion (>24 hrs).[5] There are no studies which cite increase in serum triglyceride levels after single dose of propofol except one case report of developing pancreatitis after bartholin duct excision in a 21 yr old patient 24 hrs after surgery despite having no other risk factors.[19]

Bhukal et al demonstrated that both LCT and MCT-LCT propofol cause significant rise in triglyceride levels in children when used for induction and maintenance of anesthesia. However, children in MCT-LCT group had lower triglyceride levels than children in LCT group at the end of propofol infusion and 4 hours after termination.[20]

In our study, both formulations of propofol failed to increase triglyceride levels to a significant level. So we conclude that despite the difference in the lipid content, single dose of MCT/LCT or LCT propofol does not increase serum triglyceride levels significantly to cause any adverse effects. However whether there is a significant transient rise during surgery or immediately after surgery is yet to be estimated or studied. One study demonstrated increase in triglyceride levels during administration of 2% MCT-LCT and 2% LCT propofol in adult patients mechanically ventilated for 48 hours but after stopping propofol infusion, rapid decrease in triglyceride levels was observed in MCT-LCT propofol group.[21] Ozlü et al reported significant rise in triglyceride levels in children administered propofol for induction and maintenance of anesthesia.[22]

We did not find any difference in the induction time between two groups. This suggests that the time taken to achieve therapeutic concentration in the brain is the same despite change in formulation. Our results are in agreement with studies done by Knibbe et al[23] and Suzuki et al.[24]

Regarding change in hemodynamics, we did not find significant difference between mean arterial pressures after giving the induction doses of both formulations. Larsen et al[7] and Song et al[25] studied the hemodynamic effects of both formuations of propofol and found no statistical differences in their effects.

There was no significant difference in the cost of the two different formulations with the average cost per kg of patient being Rs. 1.86 for LCT propofol and Rs. 2.04 for LCT/MCT propofol.

Limitations

We did not use propofol according to depth of anesthesia and possibly we could have used higher doses. We also excluded patients with liver disorder in which serum triglyceride levels would make a difference in the postoperative period.

Conclusion

MCT/LCT propofol is associated with less incidence and intensity of pain on injection than LCT propofol. However, we recommend use of other modalities to further reduce pain associated with injection of MCT/LCT formulation alone. Both formulations did not increase serum triglyceride levels after single induction dose.

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