A Comparison of Propofol-LCT with Propofol-LCT/MCT on Pain of Injection

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Background: *Propofol-Lipuro 1% is consisting of long-chain triglycerides (LCT) and medium-chain triglycerides (MCT) that have been reported to reduce injection pain.*
Objective: *To compare the incidence and intensity of injection pain with 1% Propofol-LCT with 1% Propofol-LCT/MCT in female populations for minor surgery under total intravenous anesthesia (TIVA).*
Material and Method: *One hundred and ten female patients were double-blind randomized into two groups. Group long-chain triglycerdes (L) received 1% propofol-LCT while group long-chain triglycerides/medium-chain triglycerides (L/M) received 1% propofol-LCT/MCT. All patients received no benzodiazepine pre-medication and fentanyl 1 µg/kg was given 3 minutes before propofol injection. The propofol 1 mg/kg was manually injected at 0.5 mL/sec. The verbal rating score (VRS 0-10) was recorded on pain of injection. VRS > 4 indicates a significant response to pain.*
Results: *There was a significantly greater incidence and intensity of injection pain in group L compared with group L/M ($p < 0.001$ and $p = 0.013$ respectively).*
Conclusions: *Propofol-LCT/MCT is superior to propofol-LCT on reducing pain of injection.*

Keywords: *Pain on injection, Propofol LCT/MCT, TIVA*

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Propofol is widely used as an IV anesthetic induction agent particularly intended for day surgery. However, pain on injection is a major disadvantage with a reported incidence of approximately 70% when a standard formulation of propofol (long-chain triglyceride-LCT) is administrated[1-3]. The large concentration of free propofol in the aqueous phase is thought to be particularly associated with injection pain[1,4,5].

Propofol-Lipuro 1% is a new formulation of propofol with a 10% fat emulsion consisting of long-chain triglycerides (LCT) and medium-chain triglycerides (MCT) with similar pharmacokinetics and efficacy as standard propofol-LCT[6-8]. Propofol-LCT/MCT formulations have been reported to reduce injection pain[9]. The studies, however, have limitations such as lack of control over site, speed of injection, propofol temperature, premedication, anesthetic technique, patient variability and gender.

The present prospective double-blind randomized study was carried out to compare the incidence and intensity of pain on injection of 1% Propofol-LCT with 1% Propofol-LCT/MCT in female populations for minor surgery under total intravenous anesthesia (TIVA).

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Material and Method

After approval of the Institutional ethics committee and obtaining written informed consent, the authors recruited 110 adult female patients, ASA physical status I-III, aged 18-60 yr, scheduled for elective obstetric and gynecological procedures, lasting about one hour duration and requiring general anesthesia (GA) without endotracheal intubation. The medications studied were administered for induction and maintenance of TIVA. Patients with allergy or seizure history,

chronic pain condition, renal insufficiency (creatinine > 1.5 mg/dL), hypovolemia and body weight > 100 kg, were excluded. All patients received no benzodiazepine premedication. Patients were randomly allocated to receive either 1%propofol-LCT (Group L) or 1% propofol-LCT/MCT (Group L/M) by means of random number table. All vials were stored at room temperature for 20 minutes before injection. Both patients and anesthesiologists were blinded with respect to the formulation used. On arrival at the operating room, routine monitoring was applied then a 22 G cannula was inserted into a dorsal hand vein with an infusion of 5% Dextrose and 0.45% normal saline at a rate of 6-10 mL/kg/hr. The pain verbal rating score (VRS) 0-10 (with 0 = no pain, 1-4 = mild, 5-7 = moderate, 8-10 = severe or the worst pain imaginable) at cannulation was recorded. Fentanyl 1 µg/kg was given 3 minutes before propofol injection. The propofol 1 mg/kg was manually injected at 0.5mL/sec. About 15 sec. after the propofol injection was completed, the patients were asked about pain of injection via VRS. The authors considered VRS>4 indicating that there was a significant response to pain. The verbal response and behavioral signs, such as facial grimacing and hand withdrawal were also noted. Maintenance of anesthesia with propofol was started at an infusion rate of 6-10 mL/kg/hr by using a syringe pump.

At Postanesthetic care unit (PACU), 60 min. after the procedure, patients were asked again to describe the VRS for recall of pain during injection by blinded anesthetist nurses.

Statistical analysis

Sample size was calculated by sample size for two sample test of proportion with $\alpha = 0.05$ and $\beta = 0.1$.

X^2 test or Fisher exact test was used for comparison of categorical variables, and Student's *t*-test was used for comparison of continuous variables between groups. Results were expressed as mean $\pm$ SD or number of patients (%). A value of $p < 0.05$ was considered statistically significant difference.

Results

One hundred and ten women completed the present study; fifty-five patients were assigned equally to group L and group L/M. There were no differences between the groups in demographic data with regards to body weight, height, age, dose of propofol, anesthesia time, as shown in Table 1.

The incidence of pain on needle insertion (Table 2) was comparable between the groups ($p = 0.463$). There was significantly greater incidence (Fig. 1) and intensity (Figure1) of propofol injection pain in group L than in group L/M ($p < 0.001$ and $p = 0.013$ respectively) (Table 3, 4). The intensity of recalled pain and pain during induction was similar in both groups (group L 61.8% and 60%; group L/M 27.3% and 16.4%). The incidence of facial grimacing and

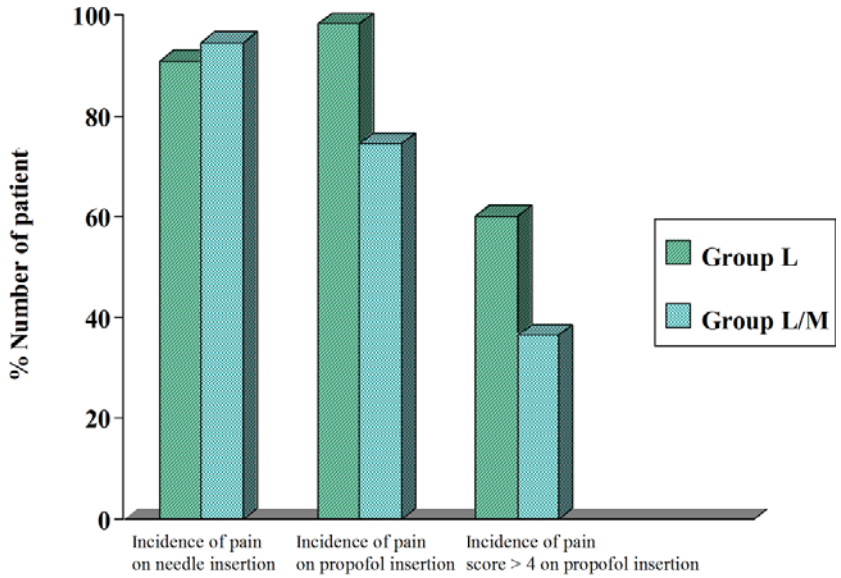

Fig. 1 Incidence of pain on needle insertion and propofol injection, intensity of pain (VRS > 4) on propofol injection

Table 1. Demographic data

	Group L (n = 55)	Group L/M (n = 55)	p-value
Body weight (kg)	58.22 ± 10.02	58.15 ± 10.16	0.973
Height (cm)	157.16 ± 4.96	157.37 ± 6.22	0.846
Age (yr)	37.47 ± 9.30	36.49 ± 8.65	0.569
Dose of propofol (mg/kg/hr)	10.36 ± 4.50	10.01 ± 3.60	0.653
Anesthesia time (min)	26.91 ± 13.82	26.36 ± 10.77	0.770
Obstetric patient	19 (34.50%)	16 (29.10%)	0.539
Gynecological patient	36 (65.50%)	39 (70.90%)	
ASA PS I	32 (58.20%)	38 (69.10%)	0.467
ASA PS II	21 (38.20%)	16 (29.10%)	
ASA PS III	2 (3.60%)	1 (1.80%)	

Values for body weight, height, age, dose of propofol, anesthetic time are mean + SD
Type of patient, ASA physical status (PS): values are numbers (%)
Group L = group receiving propofol-LCT, Group L/M = group receiving propofol-LCT/MCT

Table 2. Incidence of pain on needle insertion

	Group L (n = 55)	Group L/M (n = 55)	p-value
No pain (VRS = 0)	5 (9.1%)	3 (5.5%)	0.463
Pain (VRS > 0)	50 (90.9%)	52 (94.5%)	

Values are numbers (%)

Table 3. Incidence of pain on injection of propofol

	Group L (n = 55)	Group L/M (n = 55)	p-value
No pain (VRS = 0)	1 (1.8%)	14 (25.5%)	<0.001
Pain (VRS > 0)	54 (98.2%)	41 (74.5%)	<0.001

Values are numbers (%)

Table 4. Intensity of pain on propofol injection

	Group L (n = 55)	Group L/M (n = 55)	p-value
None to mild pain (VRS 0-4)	22 (40.0%)	35 (63.6%)	0.013
Moderate to severe pain (VRS 5-10)	33 (60.0%)	20 (36.4%)	

VRS > 4 is considered a significant response to pain

hand withdrawal in group L was significantly greater than in group L/M ($p < 0.001$).

Discussion

Pain following injection of propofol is a common problem and one important source of patient dissatisfaction. It may be distressing for the patient and interfere with the smooth induction of GA. Based on the proposed mechanisms and factors associated with propofol injection pain, several methods for the prevention of pain have been tried with varying degrees of success. The incidence and intensity of the

pain are affected by many factors including: cannula size and site of injection, volume, speed of injection, the use of local anesthetics, dilution of propofol, different temperature and premedication[3,10].

The use of lidocaine to prevent propofol injection pain is the most extensively studied technique and is the most common method used in clinical practice. However, the availability of plain lidocaine without preservative is still lacking in many countries including Thailand. Moreover, the mixing of propofol emulsion with any other drug is not recommended by the manufactures because emulsions are thermodynamically unstable despite the use of stabilizing agent[11]. The addition of lidocaine 20 or 40 mg to propofol 200 mg results in coalescence of oil droplets, which finally proceeds to a visible separate layer, indicating physicochemical incompatibility[11]. These methods also have the disadvantage of requiring additional manipulation, which may or may not alter pharmacokinetics and pharmacodynamics and makes delivery of anesthesia less efficient. There is also the potential of introducing contaminants into the emulsion, because LCT fat emulsion can serve as excellent growth media[12]. Propofol-LCT/MCT formulations have been reported to reduce injection pain. However, the incidence and intensity of injection pain of Propofol- LCT/MCT has not been compared previously with Propofol-LCT under multiple controlled conditions.

In the present study, the authors controlled the speed of injection, site of injection, needle size, propofol temperature, the speed of carrier of intravenous fluid, the use of lidocaine, premedication, anesthetic technique, duration of anesthesia and gender to examine the profile of two specific formulations of propofol to investigate the incidence and intensity of pain. The effect of gender on pain perception is also receiving increasing attention. Many studies have shown convincingly that women are more sensitive to different types of painful stimuli than men[13]. The authors excluded the patients who received benzodiazepine premedication because it may reduce recall of procedures such as insertion of the intravenous cannula and therefore reduce recall of unpleasant or painful injection during induction. In a previous study, the dose of 150 μg fentanyl was shown to reduce the injection pain but the analgesic was barely discernable when fentanyl 50 μg was given minutes before injection of propofol[14]. In addition, the residual hypnotic effect might render retrospective assessments of drug-induced pain intensity unreliable. Moreover, severe surgical pain could easily influence an assessment of injection pain in the early postoperative period. The type and duration of procedures in the present study was limited to minor surgery lasting only about one hour using TIVA. The short minor procedures did not cause severe pain and did not require very large amounts of propofol and fentanyl that may affect the rapid recovery.

The present results found that the incidence of pain on needle insertion was comparable between the groups. Reflecting that anxiety status of the studied populations was not different. The incidence of pain on injection with propofol-LCT (98.20%) was greater than propofol-LCT/MCT (74.50%) and was more frequent than that reported by other investigators using these formulations[5,8].The authors considered VRS > 4 (moderate to severe pain) indicating the pain intensity. The intensity of pain was significantly greater with propofol-LCT ($p = 0.013$). The intensity of pain with propofol-LCT (60%) and propofol- LCT/MCT (36.40%) was similar with the incidence of recalled pain in the study of Schaub et al (61% vs. 38%)[1]. The intensity of recalled pain was similar to the intensity of pain during induction in both groups. It meant that patients were not over sedated to answer about the pain intensity during induction or suffered from amnesic effect of the studied drugs. The incidence of facial grimacing and hand withdrawal in propofol-LCT was significantly greater than in propofol-LCT/MCT. Contrary to the authors' expectations, six patients had both facial grimacing and hand withdrawal, reporting of minimal pain on injection. Therefore, these reactions may not necessarily be related to the severe pain.

Almost 20 years after the advent of propofol, the injection of this anesthetic medication still causes a high incidence of pain, and the mechanisms of that pain are still obscure. It is hypothesized that the concentration of free propofol in the aqueous phase of the emulsion is responsible for the pain on injection. The lesser pain on injection by Propofol-LCT/MCT is most likely attributed to a decreased concentration of propofol in the aqueous phase[7,15,16] Many methods have been tried, with varying success, to reduce the incidence and severity of propofol injection pain.

Currently, another choice would be to use propofol-LCT/MCT in combination with other methods such as a mixture with lidocaine in order to decrease the incidence and intensity of pain on injection.

Conclusion

The incidence and intensity of pain on injection was significantly lower in patients receiving

propofol-LCT/MCT compared to propofol -LCT in nonpremedicated female populations. Since pain on injection is a common problem in clinical use, propofol-LCT/MCT is superior to propofol-LCT on pain of injection especially when the addition of lidocaine is undesirable.

References

1. Schaub E, Kern C, Landau R. Pain on injection: a double-blind comparison of propofol with lidocaine pretreatment versus propofol formulated with long- and medium-chain triglycerides. Anesth Analg 2004; 99: 1699-702.
2. Park JW, Park ES, Chi SC, Kil HY, Lee KH. The effect of lidocaine on the globule size distribution of propofol emulsions. Anesth Analg 2003; 97: 769-71.
3. Picard P, Tramer MR. Prevention of pain on injection with propofol: a quantitative systematic review. Anesth Analg 2000; 90: 963-9.
4. Larsen B, Beerhalter U, Biedler A, Brandt A, Doege F, Brun K, et al. Less pain on injection by a new formulation of propofol? A comparison with propofol LCT. Anaesthesist 2001; 50: 842-5.
5. Sun NC, Wong AY, Irwin MG. A comparison of pain on intravenous injection between two preparations of propofol. Anesth Analg 2005; 101: 675-8.
6. Doenicke AW, Roizen MF, Rau J, O'Connor M, Kugler J, Klotz U, et al. Pharmacokinetics and pharmacodynamics of propofol in a new solvent. Anesth Analg 1997; 85: 1399-403.
7. Ohmizo H, Obara S, Iwama H. Mechanism of injection pain with long and long-medium chain triglyceride emulsive propofol. Can J Anaesth 2005; 52: 595-9.
8. Rau J, Roizen MF, Doenicke AW, O'Connor MF, Strohschneider U. Propofol in an emulsion of long- and medium-chain triglycerides: the effect on pain. Anesth Analg 2001; 93: 382-4.
9. Nyman Y, von Hofsten K, Georgiadi A, Eksborg S, Lonnqvist PA. Propofol injection pain in children: a prospective randomized double-blind trial of a new propofol formulation versus propofol with added lidocaine. Br J Anaesth 2005; 95: 222-5.
10. Tan CH, Onsiong MK. Pain on injection of propofol. Anaesthesia 1998; 53: 468-76.
11. Masaki Y, Tanaka M, Nishikawa T. Physicochemical compatibility of propofol-lidocaine mixture. Anesth Analg 2003; 97: 1646-51.
12. Doenicke AW, Roizen MF, Rau J, Kellermann W, Babl J. Reducing pain during propofol injection: the role of the solvent. Anesth Analg 1996; 82: 472-4.
13. Cepeda MS, Carr DB. Women experience more pain and require more morphine than men to achieve a similar degree of analgesia. Anesth Analg 2003; 97: 1464-8.
14. Pang WW, Mok MS, Huang S, Hwang MH. The analgesic effect of fentanyl, morphine, meperidine, and lidocaine in the peripheral veins: a comparative study. Anesth Analg 1998; 86: 382-6.
15. Babl J, Doenicke A, Monch V. New formulation of propofol in an LCT/MCT emulsion. Approach to reduce pain on injection. Eur Hosp Pharm 1995; 1: 15-21.
16. Muller RH, Harnisch S. Physicochemical characterization of propofol-loaded emulsions and interaction with plasma proteins. Eur Hosp Pharm 2000; 6: 24-31.

การเปรียบเทียบความปวดขณะฉีดยาระหว่าง propofol-LCT และ propofol-LCT/MCT

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วัตถุประสงค์: *propofol-lipuro 1% ประกอบด้วย long-chain triglyceride (LCT) และ medium-chain triglyceride (MCT) พบว่ามีความปวดจากการฉีดยาน้อยลง การศึกษานี้ได้เปรียบเทียบอุบัติการณ์และความรุนแรงของความปวดจากการฉีดยาทั้ง 2 ชนิด ในผู้ป่วยหญิงที่มารับการผ่าตัดเล็กด้วยการให้ยาระงับความรู้สึกทางหลอดเลือดดำ (total intravenous anesthesia)*

วัสดุและวิธีการ: *ผู้ป่วยหญิง 110 คน แบ่งเป็น 2 กลุ่ม แบบสุ่มตัวอย่างเข้ากลุ่มทดลอง กลุ่ม long-chain triglyceride (L) ได้รับ 1% propofol-LCT, กลุ่ม long-chain triglyceride/medium-chain triglyceride (L/M) ได้รับ propofol LCT/MCT ผู้ป่วยทุกคนไม่ได้รับยากลุ่ม benzodiazepine สำหรับ premedication ก่อนการฉีด propofol 3 นาที ผู้ป่วยได้รับ fentanyl 1 ไมโครกรัม/กิโลกรัม และฉีด propofol ด้วยอัตราเร็ว 0.5 มิลลิลิตร/วินาที วัดระดับความปวดโดย verbal rating score (VRS 0-10) VRS ที่มากกว่า 4 ถือว่ามีระดับความปวดที่มีนัยสำคัญ (intensity of injection pain)*

ผลการศึกษา: *อุบัติการณ์ความปวดขณะฉีดยาและระดับความปวดที่มีนัยสำคัญในกลุ่ม L มากกว่าในกลุ่ม L/M อย่างมีนัยสำคัญทางสถิติ ($p < 0.001$ และ $p = 0.013$ ตามลำดับ)*

สรุป: *propofol LCT/MCT มีความปวดขณะฉีดยาน้อยกว่า propofol-LCT*