Does Addition of Lidocaine to Medium- and Long-Chain Triglyceride Propofol Emulsions Significantly Reduce Pain on Injection?

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Background: *Propofol formulated with medium- and long-chain triglycerides (MCT/LCT) causes less pain on injection than standard Propofol, but the incidence of pain persists between 28 and 67 percent. Such a broad range begs the question so the authors wanted to clarify whether the addition of lidocaine to medium- and long-chain triglyceride emulsion propofol results in any clinically significant lessening of pain on injection. The authors conducted a randomized, prospective, double-blinded study to compare the injection pain felt following the administration of propofol-MCT/LCT (Propofol-®Lipuro) to propofol-MCT/LCT plus 20 mg lidocaine for the induction of anesthesia.*

Material and Method: *The present study included 270 non-premedicated ASA I-II adult patients scheduled for elective surgery under general anesthesia. Patients were allocated randomly into two groups to receive either propofol-MCT/LCT alone or propofol-MCT/LCT plus 20 mg lidocaine. The study solution was injected at 1 mL/second by one anesthesiologist and patients graded any associated pain using a four-point scale.*

Results: *The overall incidence of pain on injection was 31/133 (23%) in the propofol-MCT/LCT plus lidocaine group vs. 45/135 (33%) in the propofol-MCT/LCT alone group. The difference in the incidence of pain on injection between groups failed to achieve statistical significance (p = 0.23) and no significant difference in intensity of pain between the two study groups occurred.*

Conclusions: *The authors concluded that the addition of lidocaine (20 mg) to the propofol-MCT/LCT does not significantly reduce the incidence or severity of the pain on injection.*

Keywords: *Anesthesia, Pain on injection, Propofol*

J Med Assoc Thai 2008; 91 (3): 383-7
Full text. e-Journal: *http://www.medassocthai.org/journal*

Propofol is the most commonly used intravenous anesthetic agent, providing smooth induction and rapid recovery; however, pain on injection, is experienced by 28 to 90 percent of patients[1,2], which is a major disadvantage. Previous studies[3,4] showed that the concentration of free propofol in the aqueous phase of an emulsion is associated with pain on injection. Therefore, many different approaches have been used in attempts to minimize propofol induced pain. The most common methods used in routine clinical practice are the adding of 10-40 mg lidocaine to the syringe of propofol immediately prior to use and lidocaine pretreatment, with or without the use of a tourniquet[5,6]. Notwithstanding, the use of propofol continues to be associated with an incidence of pain in up to 36% of cases[7].

Propofol-Lipuro (B Braun, Melsungen, Germany) is a new formulation of propofol emulsion containing medium- (MCT) and long-chain triglycerides (LCT), with similar pharmacokinetics and efficacy as

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standard propofol[7], but reduces the amount of free propofol in the emulsion. Previous observations have suggested that propofol-MCT/LCT causes less pain on injection than Dipivan® (Astra-Zeneca, Macclesfield, UK)[3,8,9], but the incidence of pain persists between 28 and 67 percent[9-13]. Evidently, clarification is needed so the authors planned and tested whether the addition of lidocaine to propofol-MCT/LCT would result in a clinically significant lessening of pain on injection. This randomized, double-blinded study was designed to evaluate the minimizing effect of lidocaine on injection pain of propofol-MCT/LCT.

Material and Method

After obtaining approval from the institutional Ethics Committee, 270 patients were included in the present study, ranging between 18 and 60 years of age, with an ASA physical status of I or II, and undergoing an elective surgical procedure with general anesthesia. Written informed consent was obtained from all patients.

Patients with a neurological or cardiovascular disorder, history of drug abuse, or egg lecithin or soybean oil allergies, as well as patients breast feeding at the time of surgery, taking sedatives or analgesics within 24 hr preceding surgery or requesting anxiolysis, were excluded from participating in the present study. No pre-medication was given.

Using computer-generated random numbers, patients were allocated into two groups to receive either propofol-MCT/LCT (*i.e.* 2 mL normal saline added to 19 mL Propofol-®Lipuro) or propofol-MCT/LCT plus lidocaine (20 mg) (*i.e.* 2 mL of lidocaine 1% added to 19 mL Propofol-®Lipuro) for the induction of anesthesia.

The propofol solutions were prepared by a nurse anesthetist in unlabeled syringes as per the patient's group allocation. As the physical appearances of the two study drugs were identical, the anesthesia providers and an investigator recording were unaware of the propofol formulation. In the present study, the investigator was limited to one anesthesiologist in order to eliminate inter-observer variability.

On arrival in the operating room, routine monitors were applied to the patients, for recording heart rate, mean arterial blood pressure, ECG and oxygen saturation values. All of the patients were cannulated with a 20-gauge venous cannula at the dorsum of the hand, flushed with 10 mL of normal saline over 5 sec to confirm that patient does not have any pain before the study drug is injected. The patients were also prepared for the present study and asked to indicate the pain experienced during injection of anesthetics, classifying its intensity as 'none', 'mild', 'moderate' and 'severe'.

Each patient was pre-oxygenated via a face-mask with a fresh gas flow of 6 L/min oxygen for 3 min. Anesthesia was induced with 2.5 mg/kg propofol at 1 mL/sec without a flowing intravenous fluid during and following the propofol injection. During the propofol injection, patients were questioned for pain on injection and observed for any vocal response, grimacing, arm withdrawal or tearing, all of which would suggest a pain reaction. If there was no answer or response, patients were repeated the questions about pain after 10 s.

Pain was then graded using a four-point scale: 0 = 'none'; 1 = 'mild' (*i.e.* in response to questioning without any behavioral signs); 2 = 'moderate' (*i.e.* in response to questioning *and* accompanied by a behavioral sign, *or* pain spontaneously reported that is without questioning); and, 3 = 'severe' (*i.e.* strong vocal response or grimacing, arm withdrawal or tearing)[14,15].

After the assessment of pain, the induction of anesthesia was continued as *per* routine practice. Fentanyl was administered only after induction of anesthesia. Within 24 h of the surgery, the injection site was checked for pain, edema, wheal and flare response by a nurse anesthetist not apprised of which drug had been administered.

Statistical analysis

In a previous study[9], the incidence of injection pain following the administration of propofol-MCT/LCT without added lidocaine was 28%. A sample size calculation indicated that 131 patients per study group would be needed to detect a statistically significant difference between the two groups with 80% power; assuming propofol-MCT/LCT mixed with lidocaine would decrease by 50% the incidence of pain on injection of propofol-MCT/LCT alone.

The Student's unpaired *t*-test was used to compare the continuous variables between groups. The difference in the incidence of injection pain because of propofol between the groups was evaluated using the χ^2-test or the Fisher's exact test where appropriate. A p-value of < 0.05 was considered statistically significant.

Results

Two patients from the propofol-MLC/LCT plus lidocaine group were excluded from the analysis due to protocol violation (midazolam given before

induction). The two study groups were comparable with respect to demographic characteristics (Table 1). The overall incidence of pain on injection in both groups was 31/133 (23%) in the propofol-MCT/LCT plus lidocaine group vs. 45/135 (33%) in the propofol-MCT/LCT alone group (Table 2). Patients who received propofol-MCT/LCT mixed with lidocaine had less pain during injection than patients who received Propofol-®Lipuro without lidocaine, but the difference was not statistically significant. There were no significant differences vis-à-vis the intensity of pain between the two study groups. No complications, such as pain, edema, wheal, or flare response were observed at any injection site within the first 24 h of surgery.

Discussion

Pain during injection of propofol is a common problem, which is sometimes very distressing to patients. In a study of 33 clinical problems, propofol-induced pain ranked seventh in priority when both clinical importance and frequency were considered[16]. Therefore, minimizing propofol injection pain is an important clinical goal. Propofol formulated in medium- and long-chain triglycerides (MCT/LCT) is thought to cause less pain on injection. Kam et al[7] reported that 38% of patients experienced pain or discomfort following propofol-MCT/LCT, while other researchers have reported the incidence of pain on injection after propofol-MCT/LCT was between 28 and 67 percent[9-11,16,17].

The broad range in incidence piqued the authors' curiosity. The authors hypothesized that the addition of lidocaine to propofol-MCT/LCT should decrease pain on injection. But, contrary to the authors' expectations, the difference in pain levels between the two groups was not statistically significant ($p = 0.23$). The 33% incidence of pain with propofol-MCT/LCT in the present study was in accordance with that of other studies[3,7,8]. The implication is that propofol-MCT/LCT alone could not reduce pain on injection perfectly because of the continued occurrence of free propofol in the aqueous phase of the emulsion.

The incidence in the present study of pain for propofol-MCT/LCT mixed with lidocaine (23%) was higher than that reported by other investigators using this formulation (16%)[11]. In that study, four groups of patients were randomized to receive either propofol-MCT/LCT or propofol alone, each with or without lidocaine pre-treatment. They observed that the severity of pain from the propofol-MCT/LCT was significantly reduced by the lidocaine pre-treatment. Possibly, the patients were too sedated to answer when asked about pain during the induction of anesthesia because they had also been pre-medicated with midazolam.

By comparison, in the present study, no pre-medication was given. The strength of the present study was that the authors assessed pain on injection and observed patient-reactions to the propofol injection recorded by an investigator unaware of the treatments. The present results strongly suggest that there is no significant difference in the incidence of propofol injection pain although there was a tendency for the injection-pain to be less in patients who received propofol-MCT/LCT mixed with lidocaine. The authors noticed that the clinical significance of such a difference is moot. However, the data sheet for propofol-MCT/LCT still recommends addition of lidocaine to alleviate injection pain. Importantly, the addition of lidocaine may destabilize the emulsion formulation of propofol

Table 1. Patient demographic data

	Propofol-®Lipuro (n = 135)	Propofol-®Lipuro mixed with 20 mg lidocaine (n = 133)
Age (yr)	43 ± 17	44 ± 16
Weight (kg)	59 ± 11	59 ± 10
Height cm)	161 ± 8	162 ± 7
Sex (M/F)	62/73	66/67
ASA class		
I	91	83
II	44	50

Data presented as mean ± SD or number (%)

Table 2. Assessment of pain during IV injection of propofol

	Propofol-®Lipuro	Propofol-®Lipuro + 20 mg lidocaine
Pain on injection		
No pain	90 (67%)	102 (77%)
Pain	45 (33%)	31 (23%)
Severity of pain on injection		
Mild	44 (32%)	30 (22%)
Moderate	1 (1%)	1 (1%)
Severe	0 (0%)	0 (0%)

Values are expressed as number (%)

with a subsequent risk of causing a pulmonary fat embolism[17].

In conclusion, the addition of lidocaine to propofol-MCT/LCT did not significantly reduce either the incidence or the severity of the pain on injection. The authors did not find any advantage in using lidocaine (20 mg) with that for propofol-MCT/LCT ensuring maximal patient comfort during induction of anesthesia using propofol.

Acknowledgements

The authors wish to thank Chaiyaphum Hospital for financial support and Mr. Bryan Roderick Hamman for his assistance with the English.

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การผสม lidocaine ใน propofol–MCT/LCT ลดความปวดขณะฉีดได้อย่างมีนัยสำคัญหรือไม่

บรรจง ครอบบัวบาน, ศิริวรรณ ดิเรกโภค, สุจริต คำแก้ว, มาลิน ถนอมสัตย์, ไกรสร แจ่มจำรัส, เครือวัลย์ ธเนศเศรษฐ์, สุรางค์รัตน์ โฆษิตธนสาร

ภูมิหลัง: *propofol–MCT/LCT สามารถลดความปวดขณะฉีดได้มากกว่า propofol ชนิดมาตรฐาน แต่อุบัติการณ์ของความปวดขณะฉีดยังคงมีอยู่ระหว่าง ร้อยละ 28-67 คณะผู้นิพนธ์จึงต้องการศึกษาการผสม lidocaine ใน propofol–MCT/LCT สามารถลดความปวดขณะฉีดได้อย่างมีนัยสำคัญหรือไม่ จึงได้ศึกษาเปรียบเทียบความปวดขณะฉีด propofol–MCT/LCT อย่างเดียวกับ propofol–MCT/LCT ที่ผสม lidocaine 20 มิลลิกรัม*

วิธีการศึกษา: *ทำการศึกษาในผู้ป่วย 270 ราย ที่เข้ารับการผ่าตัดแบบนัดล่วงหน้าภายใต้การให้ยาระงับความรู้สึกแบบทั่วไป ผู้ป่วยถูกสุ่มให้ได้รับ propofol–MCT/LCT หรือ propofol–MCT/LCT ที่ผสมlidocaine 20 มิลลิกรัม ในการนำสลบโดยฉีดด้วยความเร็ว 1 มิลลิลิตรต่อนาที และประเมินความปวดขณะฉีดของผู้ป่วยโดยใช้มาตราความปวด 4 ระดับ โดยผู้ให้ยาระงับความรู้สึกคนเดียวตลอดการศึกษา*

ผลการศึกษา: *อุบัติการณ์โดยรวมของความปวดขณะฉีด พบร้อยละ 23 (31/33) ในผู้ป่วยที่ได้รับ propofol–MCT/LCT ที่ผสม lidocaine และ ร้อยละ 33 (45/135) ในผู้ป่วยที่ได้รับ propofol–MCT/LCT อย่างเดียว แต่ไม่พบความแตกต่างที่มีนัยสำคัญทางสถิติ (p = 0.23) และมีความแตกต่างอย่างไม่มีนัยสำคัญทางสถิติระหว่างทั้งสองกลุ่มในระดับความรุนแรงของความปวดขณะฉีด*

สรุป: *การผสม lidocaine ใน propofol–MCT/LCT ไม่สามารถลดความปวดขณะฉีด หรือความ รุนแรงของความปวดขณะฉีดยาได้อย่างมีนัยสำคัญทางสถิติ*