Comparison on Pain on Injection of a Small Particle Size-Lipid Emulsion of Propofol and Standard Propofol with or without Lidocaine

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Pain on injection, reported in 28-90% of patients, is one of the most described side effects of the intravenous application of propofol. Many different approaches have been used in attempts to minimize propofol induced pain, with varied results. Using a randomized,double-blind protocol design, the author-section pain following the administration of two different particle size formulations of propofol with or without lidocaine in 388 nonpremedicated ASA I-II adult patients scheduled for elective surgery under general anesthesia. Patients were allocated randomly to receive either a small particle size lipid emulsion of propofol (Anepol : average particle size 140.5 nm), or standard propofol (Propofol : average particle size 193.3 nm), by dividing into 4 groups. Group 1 received 2 ml NaCl 0.9% and Propofol , group II received 2 ml lidocaine 2% and Propofol , group III received 2 ml NaCl 0.9% and Anepol and group IV received 2 ml lidocaine 2% and Anepol into a dorsal vein of the hand. Pain during propofol injection was evaluated over 5-10 seconds, until loss of conscious, using a four point scale. Sixty-seven patients(69.1%) complained of pain in group I, as compared with 50%, 41.2% and 39.2% in group II, III and IV ($p < 0.05$).The reported severity of injection pain was not significantly different between the groups. The authors conclude that small particle size propofol causes less pain on injection than standard propofol.

Keywords: *Propofol, Pain on injection, Particle size, Anesthesia*

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Pain on injection, experienced by 28-90% of patients[1,2], is a major disadvantage of propofol. Many different approaches have been used in attempts to reduce the incidence of pain. These include adding lidocaine to propofol, pretreatment with IV injection of lidocaine, ondonsetron, metoclopramide, pethidine, fentanyl, alfentanyl, remifentanyl, butorphanol, magnesium, or thiopental (with or without tourniquet), and injection of propofol into a large vein[3-6].

Commercially available propofol emulsions vary across different areas of the world in particle molecular size. Anepol (Hana pharm,Korea) is a new propofol formulation that contains small sized particles than the currently marketed formulations of propofol: Diprivan (Astra Zeneca) and Propofol (Abbott laboratories, North Chicago,IL). The average particle sizes are 140.5 nm, 188.9 nm and 193.3 nm for Anepol , Diprivan , and Propofol respectively (data on file at company). Anepol and Propofol are both formulated as a 1% solution in a fat emulsion containing 10% soybean oil long-chain triglycerides, and 1.2% egg lecithin. Anepol has pharmacokinetic and efficacy effects similar to Diprivan (data on file at company). Anepol is availiable on the market as the alternative of conventional propofol and were not developed to reduce pain on injection. From the authors' observation found that Anepol has been associated with less pain on injection.The authors hypothesize the particle size may be the decisive variable for the pain frequently associated with propofol injection. There had previously been no clinical studies comparing pain on injection between a small particle size lipid emulsion of propofol and the currently available propofol formulations.

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The randomized, double-blind study was designed to compare the pain on injection for these two propofol formulations, when used for the induction of anesthesia.The authors also investigated whether the additional administration of lidocaine before injecting Anepol had an additive effect on the reduction of pain.

Material and Method

After obtaining ethical committee approval, 388 patients were included in the present study, aged between 18-50 yr, ASA physical status I or II, and undergoing an elective surgical procedure under general anesthesia.Written informed consent was obtained from all patients. Patients with neurologic 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 preceeding surgery or requesting anxiolysis, were excluded from participating in the present study. No premedication was given. The authors had no sponsor or funding source from any drug company for the pre-sent study.

Using a computer-generated table of random numbers, patients were randomly assigned into 4 groups of 97 for propofol and 98 anepol. Patients in group I (NP) received 2 ml NaCl 0.9% and Propofol , group II (LP) received 2 ml lidocaine 2% and Propofol , group III (NA) received 2 ml NaCl 0.9% and Anepol , and group IV (LA) received 2 ml lidocaine 2% and Anepol for induction of anesthesia. The propofol solution was prepared by a nurse anesthetist in unlabeled syringes according to group allocation. As the physical appearance of the two study drugs were identical, the anesthesia providers and the investigators recording the data were unaware of the formulation.

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 patients were cannulated with a 20-gauge venous cannula at the dorsum of the hand, and flushed with 10 ml of normal saline over 5 s to ensure pain-free injection.

Each patient was preoxygenated via a facemask with fresh gas flow of 6 L/min oxygen for 3 min. Anesthesia was induced with 2.5 mg/kg propofol at a constant rate over 15 s. During the propofol injection, patients were continuously observed for vocal response, facial grimacing, arm withdrawal, or tearing, suggesting severe pain. Patients were questioned every 5-10s during induction regarding the presence of pain or discomfort. Pain was graded using a four-point scale: 0 = no pain, 1 = mild pain (pain reported only in response to questioning without any behavioral signs), 2 = moderate pain (pain reported in response to questioning and accompanied by a behavioral sign, or pain reported spontaneously without questioning), and 3 = severe pain (strong vocal response or response accompanied by facial grimacing, arm withdrawal, or tearing)[10]. After assessment of pain, remaining propofol was administered and general anesthesia was continued as per routine practice. Fentanyl was administered only after induction of anesthesia. Within 24 h after operation, the injection site was checked for pain, edema, wheal, and flare response by a nurse anesthetist who was unaware of which drug had been administered.

The sample size, 92 patients plus 5% of loss or exclusion per treatment group, was randomed so as to adequately ascertain the presence of statistically and clinically therapeutic difference.Calculations were based on the assumptions that (a) the incidence of pain on injection of propofol is 70% when a tandard formulation is administrated with no intervention to reduce pain, (b) the use of a small particle size lipid emulsion of propofol might reduce the incidence of pain on injection by approximately the same degree as pretreatment with lidocaine[7], and (c) $\alpha = 0.05$ with a power $(1-\beta)$ of 0.9. The authors planned to include 97 subjects per group, taking into account 5% exclusions.

ANOVA and Student's t-tests were used in comparisons between the groups along all continuous variables. The difference in the incidence of pain on injection of propofol between the groups was evaluated using the Chi-square test, or Fisher'exact test where appropriate. A p-value of less than 0.05 was considered to be statistically significant.

Results

One patient in group II (LP) was excluded from the analysis due to protocol violation (midazolam given before induction).

The four groups were comparable with respect to demographic characteristics (Table 1). The overall incidences (also, severity) of pain during the IV injection of propofol in the four study groups are shown in Table 2. The incidence of pain on injection was significantly lower in group II, III and IV (50%, 41.2%, and 39.8% respectively) than group I (69.1%). The severity of injection pain was not significantly different between the groups. No complications, such as pain, edema,

Table 1. Patient Demographic Data

	I (NP) n = 97	II (LP) n = 96	III (NA) n = 97	IV (LA) n = 97
Age (yr)	43.9±15.9	44.5±16.1	46.1±16.0	42.3 ±15.9
Weight (kg)	58.3±9.8	56.9±10.6	59.0±11.4	58.3 ±10.5
Height (cm)	158.3±8.0	158.3±8.2	158.8±7.1	159.5 ±7.4
Sex				
male	43 (44.3%)	38 (39.5%)	39 (40.2%)	43 (44.3%)
female	54 (55.7%)	58 (60.5%)	58 (59.8%)	54 (55.7%)
ASA class				
I	64 (66%)	69 (71.9%)	66 (67%)	66(68.1%)
II	33 (34%)	27 (28.1%)	31 (33%)	31(31.9%)

Data presented as mean ± SD or number (%)
Demographic data were no significant difference among the four groups

Table 2. Assessment of Pain During IV injection of Propofol

	I (NP) n = 97	II (LP) n = 96	III (NA) n = 97	IV (LA) n = 97
Pain				
no Pain	30 (30.9%)	48 (50%)*	57 (58.8%)*	59 (60.8%)*
Pain	67 (69.1%)	48 (50%)*	40 (41.2%)*	38 (39.2%)*
Severity of pain				
mild	54 (55.7%)	40 (41.7%)	31 (32%)	31 (32.0%)
moderate	9 (9.3%)	8 (8.3%)	9 (9.2%)	7 (7.2%)
severe	4 (4.1%)	0	0	0

* $p < 0.05$ intergroup comparison between control and other study group

wheal, or flare response were observed at any injection site within the first 24h after operation.

Discussion

In the present study, the authors observed that patients receiving Anepol with or without lidocaine Had a lower incidence of pain on injection than patients receiving Propofol ($p < 0.05$).

The mechanism of pain caused by propofol is not known with certaintly. Propofol belongs to the group of phenols that can irritate the skin, mucous membrane, and venous intima[5]. Propofol also, by an indirect action on the endothelium, activates the kallikrein-kinin system and releases bradykinin, thereby producing venous dilation and hyper permeability, which increase the contact between the aqueous phase of propofol and free nerve endings within the vein, resulting in pain on injection[8-10].

A large number of trials have identified several factors contributing to a high incidence of pain with propofol, and several strategies have evolved to minimize both the incidence and severity of pain. Currently, the most effective treatment is lidocaine, either mixed with the propofol,or as a separate injection[10-16]. However, the additional lidocaine may destabilise the emulsion formulation of propofol with a potential risk of causing pulmonary fat embolism[17].The alternative intervention to prevent pain should be identified. Early studies suggested that mixed medium and long chain triglyceride propofol emulsion are associated with decreased pain on injection, compared to Diprivan [18,19]. More recent studies have given the opposite result[20,21]. Anepol · like Diprivan and Propofol contains long-chain triglycerides. Anepol , however, has a smaller particle molecular size than Diprivan or Propofol . Interestingly, this smaller particle size emulsion formulation of propofol was associated in the present study with a somewhat less frequent incidence of pain on injection than standard Propofol . The present cannot explain the reason of reduction of injection pain in the

present study. The component of Anepol should be further studied to confirm the cause of less pain on injection.In the Anepol formulation, the propofol particle size was reduced by 28% compared with standard propofol. The present clinical trial showed that pain on injection is reduced with this small particle size lipid emulsion of propofol. The additional administration of lidocaine before injecting Anepol had no additve effect on the reduction of pain. The small particle size lipid emulsion of propofol could therefore be used to reduce pain on injection and to increase patient satisfaction with perioperative care.

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การเปรียบเทียบความปวดขณะฉีดยา propofol ชนิดที่มีขนาดโมเลกุลเล็ก กับ propofol ชนิดมาตรฐาน เมื่อผสมและไม่ผสม lidocaine

บรรจง ครอบบัวบาน, ศิริวรรณ ดิเรกโภค, สุจริต คำแก้ว, มาลิน ถนอมสัตย์

ความปวดขณะฉีดยาเป็นผลข้างเคียงที่สำคัญในการนำสลบผู้ป่วยด้วยยาฉีด propofol พบร้อยละ 28-90% ของผู้ป่วยที่ได้รับยานี้ แม้ว่ามีวิธีที่พยายามจะลดภาวะปวดขณะฉีดยาดังกล่าวหลายวิธี แต่ผลของการลดปวดแตกต่างกันไป การศึกษาครั้งนี้เป็นการศึกษาแบบ randomize, double-blind ที่ศึกษาเปรียบเทียบความปวดขณะฉีดยา propofol 2 ชนิดที่มีขนาดโมเลกุลแตกต่างกัน ในกรณีผสมและไม่ผสม lidocaine ในผู้ป่วย 368 ราย ASA physical status I-II ที่เข้ารับการผ่าตัดและให้ยาระงับความรู้สึก ผู้ป่วยจะถูกสุ่มเป็น 4 กลุ่ม คือกลุ่ม 1 ผู้ป่วยได้รับ 0.9% NaCl 2 มิลลิลิตร และยา propofol ชนิดมาตรฐาน กลุ่มที่ 2 ได้รับ 2% lidocaine 2 มิลลิลิตร และยา propofol ชนิดมาตรฐาน กลุ่มที่ 3 ได้รับยา 0.9% NaCl 2 มิลลิลิตร และยา propofol ชนิดขนาดโมเลกุลเล็ก (Anepol) และกลุ่มที่ 4 ได้รับ 2% lidocaine 2 มิลลิลิตร และยา Anepol ฉีดเข้าเส้นเลือดบริเวณหลังมือเพื่อนำสลบ ประเมินความปวดขณะฉีดยา ในเวลา 5-10 วินาที หลังฉีดยา โดยใช้ four point scale ผลการศึกษา พบว่าผู้ป่วยในกลุ่มที่ 1 มีความปวดขณะฉีดยาร้อยละ 69 ซึ่งแตกต่างอย่างมีนัยสำคัญทางสถิติเมื่อเปรียบเทียบกับผู้ป่วยในกลุ่มที่ 2, 3 และ 4 มีความปวดขณะฉีดยาร้อยละ 50, 41.8 และ 39 ตามลำดับ ($p < 0.05$) เมื่อเปรียบเทียบความแตกต่างของความรุนแรงของความปวดขณะฉีดยา พบว่าไม่มีความแตกต่างกันอย่างมีนัยสำคัญทางสถิติ จะเห็นได้ว่า propofol ชนิดที่มีขนาดโมเลกุลเล็ก เมื่อผสมและไม่ผสม lidocaine มีความปวดขณะฉีดยาน้อยกว่า propofol ชนิด มาตรฐาน