

Prevention of Propofol Injection Pain: A Comparison of Lidocaine Pretreatment and Lidocaine Pretreatment with the Diluted Propofol with Dextrose Water

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Introduction: Pain on propofol injection is commonly found. The intensity of pain relates to the concentration of free propofol.

Objective: We aimed to assess the effect of diluted propofol combined with lidocaine pretreatment on injection pain.

Methods: A prospective randomized controlled trial was conducted in patients scheduled for elective procedures under general anesthesia. The patients were allocated into 2 groups, the lidocaine pretreatment with diluted propofol (D) group and the lidocaine pretreatment with undiluted propofol (P) group. Lidocaine 40 mg was administered before the injection of propofol in both groups. In the D group, 1% propofol 30 mg was diluted with dextrose water into 0.5 % propofol before injection. In the P group, 30 mg of 1% propofol was injected. The severity of pain was evaluated by asking and observing behavioral

responses. The primary outcome was the incidence of pain. The intensity of pain and adverse events were recorded as secondary outcomes.

Results: We randomly allocated 328 patients to either D group (n=164) or P group (n=164). The incidence of pain in the D and P group was not different (42.1% and 44.5%, respectively; p 0.656). The reported mild, moderate, and severe pain was 34.1, 6.1, and 1.9% in the D group, and 36.6, 4.9, and 3% in the P group. There were no bradycardia and hypotension in both groups.

Conclusions: The dilution of medium chain and long chain triglyceride emulsive propofol with dextrose water did not potentiate the effect of lidocaine in reducing pain on injection of propofol.

Keywords: dilution with dextrose water, lidocaine pretreatment, propofol, pain on injection

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Introduction

Propofol has become the widely used intravenous anesthetic agent for general anesthesia due to its advantageous pharmacological effect such as rapid onset of action, short duration, easy titration and low incidence of postoperative nausea and vomiting.¹ It has been used for day care anesthesia, sedation, induction and maintenance of anesthesia. However, pain on injection is commonly found with a high incidence up to 90%² and can cause severe distress or discomfort. Additionally, propofol injection pain was ranked the

seventh most important problem to avoid in clinical practice.³

Factors affecting pain on injection of propofol included concentration of free propofol,⁴ site of injection,² speed of injection,⁵ temperature of solution,^{6,7} size of injection,² and rate of intravenous carrier fluid.⁸ Moreover, lipid-based emulsion was associated with propofol injection pain. Many studies showed that less pain was found in propofol in medium chain triglyceride (MCT) and long chain triglyceride (LCT) mixture compared to propofol in LCT emulsion.⁹ Several

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strategies have been investigated to prevent injection pain such as pretreatment with lidocaine,¹⁰ opioids,¹¹ non-steroidal anti-inflammatory drugs,² benzodiazepines,¹² steroids,¹³ microfiltrate,¹⁴ warm,⁷ or cold² propofol solution. The result of systematic review and meta-analysis¹⁵ revealed that the two most effective interventions for reducing pain were injection in antecubital vein and pretreatment with lidocaine along with venous occlusion in case of hand vein injection. However, these two methods are difficult in the practical manner. Lidocaine pretreatment is the convenient and common effective method used in clinical practice to prevent pain¹⁶⁻²⁰ but failure rate was found at 13-32 %.^{6,21}

Klement et al.⁴ showed that pain intensity increases with the concentration of propofol and it was related to the aqueous concentration. Dilution of propofol from 10 mg/mL to 5 mg/mL with 5% dextrose water significantly reduced the incidence of pain during injection.²² The effect of combined dilution of propofol and lidocaine pretreatment is still unknown.

We conducted a randomized controlled trial to evaluate propofol injection pain in adult patients who were scheduled for elective surgery under general anesthesia. We hypothesized that diluting propofol with dextrose water combined with lidocaine pretreatment can further reduce the incidence and severity of pain.

Methods

This prospective randomized controlled trial was reviewed and approved by the institutional review board of Mahidol university and registered in the Clinical Trial Registration www.ClinicalTrials.gov (ref: TCTR2018 0702004). Data was collected in the Department of Anesthesiology, Ramathibodi Hospital, Mahidol University, Thailand, between 1 May 2018 to 1 October 2019.

Population

We recruited 328 patients with the American Society of Anesthesiologists (ASA) physical status I-II age between 18 and 65, scheduled for elective procedure under general anesthesia. All patients had pre-induction mean arterial pressure higher than 65 mmHg

and anesthesiologists planned to administer propofol as an induction agent. Exclusion criteria included patients with chronic pain, history of allergy to propofol, egg, soybean, or lidocaine, and patients with communication difficulty. We also excluded patients who received any other sedative or analgesic drugs prior to induction and did not have 22G intravenous catheter on the dorsum of hand. Informed consent was obtained.

Randomization

Randomization was performed by computer generated block of 4. The patients were equally allocated into 2 groups, the lidocaine pretreatment with diluted propofol (D) group and the lidocaine pretreatment with undiluted propofol group (P) group.

Intervention

After standard monitoring, the pre-induction value of blood pressure, heart rate, and pulse oximetry were recorded. The patients were preoxygenated adequately and then 40 mg of 2% lidocaine was injected prior to administration of 30 mg of room-temperature 1% propofol in medium chain triglyceride (MCT) and long chain triglyceride (LCT) emulsion. In group D, propofol was diluted with 5% dextrose 3 mL while patients in P group received 1% propofol. Ten seconds after lidocaine pretreatment, propofol was manually injected within 3 seconds. The study drugs were prepared and injected by one of our investigator team who was aware of the patient group assignment but the patient and pain assessor were blinded. The pain was evaluated 10 seconds after propofol injection by observing patients behavior response and asking a standard question "Are you having pain at your intravenous site?" if the patients did not show any behavior response to pain. The incidence and severity of pain was assessed by using four-point pain response scale. The pain scale was no when patients reported no pain. The scale mild, moderate, and severe were documented when patient reported pain only in response to questioning and without behavioral signs, patients reported pain spontaneously without questioning, and patients expressed strong vocal or behavioral response eg.

facial grimacing, arm withdrawal or tears, respectively. The blood pressure and heart rate were recorded again after completion of pain evaluation. The induction of anesthesia was continued by administration of additional intravenous anesthetic, opioids and neuromuscular blocking agents. Type and dose of anesthetic drugs were at the discretion of the in-charge anesthesiologists.

Statistical analysis

Statistical analysis was performed using SPSS version 18.0. Continuous variables between groups were analyzed by Student t-test. Categorical variables were analyzed by Chi-square or Fisher exact test if 20% of expected frequencies was less than or equal to 5. P value less than 0.05 was considered as statistically significant. Continuous variables were presented as mean and standard deviation (SD). Categorical variables were presented as number of patients and percentages.

Sample size was calculated based on previous study published by Jalota et al.¹⁵ which demonstrated that the incidence of pain on propofol injection with 40 mg of lidocaine pretreatment was 27% and the study of Stokes et al.²² which showed the effect of dilution with dextrose water reduced the incidence of pain about 50%. A sample size of 148 patients per group was

estimated to provide an 80% power to detect such difference using a two-sided test with $\alpha = 0.05$. With adjusting 10% drop out rate, the total number of patients per group was 164.

Results

Demographic characteristics

Three hundred and twenty eight patients were equally randomized into two groups. No patient dropped out from the study. There were no significant differences between the groups in gender, age, ASA physical status, body weight, height, and body mass index. (Table 1)

Primary outcome

None of patients was heavily sedated and unable to communicate with the assessor. The overall incidence of propofol injection pain was shown in Table 2. There was no statistical difference on the incidence of pain between groups (42.1% and 44.5% respectively in group D and P; P 0.656).

Secondary outcome

There was no significant difference in intensity of pain. Mild, moderate, and severe pain were found 34.1%, 6.1%, and 1.9 % in the D group and 36.6%, 4.9%, and 3% in the P group. There was no bradycardia or hypotension in both groups.

Table 1 Demographic characteristics of 328 patients

Characteristics	P-group (n = 164)	D-group (n =164)	P-value
Sex, n (%)			0.678
Male	34 (20.7)	31 (18.9)	
Female	130 (79.3)	133 (81.1)	
Age (years), mean $\pm$ SD	46.68 $\pm$ 11.07	46.17 $\pm$ 10.96	0.678
ASA physical status, n (%)			0.902
Status I	46 (28.0)	45 (27.4)	
Status II	118 (72.0)	119 (72.6)	
Body weight (kg), mean $\pm$ SD	60.35 $\pm$ 11.59	61.82 $\pm$ 11.32	0.248
Height (cm), mean $\pm$ SD	158.24 $\pm$ 7.97	158.51 $\pm$ 7.27	0.756
BMI (kg/m ²), mean $\pm$ SD	24.10 $\pm$ 4.16	24.58 $\pm$ 4.08	0.285

ASA=American Society of Anesthesiologists; BMI=Body Mass Index.

Table 2 Incidence and severity of pain

	P group (n = 164)	D group (n = 164)	P-value
Incidence of pain, n (%)	73 (44.5)	69 (42.1)	0.656
Pain scale, n (%)			0.287
No pain	91 (55.5)	95 (57.9)	
mild pain	60 (36.6)	56 (34.1)	
moderate pain	8 (4.9)	10 (6.1)	
severe pain	5 (3.0)	3 (1.9)	
Adverse events, n (%)			-
Bradycardia (HR <50)	0	0	
Hypotension (SBP <90 mmHg)	0	0	

HR=heart rate; SBP=systolic blood pressure.

Discussion

Pain on injection of anesthetic agents are thought to be a direct irritant effect by the non-physiological osmolality or a pH of their preparations.⁴ However, propofol is nearly isotonic, nonhyperosmolar and has a pH from 6 to 8.5. So, this theory cannot explain the pain produced by injection of propofol.² Scott et al.⁵ postulate that the pain is likely to be an indirect irritant effect via the release of mediator such as kininogen from the kinin cascade and results in the stimulation of pain but the newer study²³⁻²⁴ found no relationship of propofol injection pain and kinin cascade substances. Based on the findings of many studies,^{4,23,25} the pain associated with propofol injection is directly related to propofol concentration in the free aqueous phase.

The use of lidocaine as a pretreatment to decrease propofol injection pain is based on its presumed local anesthetic effect on the vein.² From the recent systematic review and meta-analysis,¹⁵ the incidence of propofol injection pain after 40 mg of lidocaine pretreatment ranges from 10 - 55%. Like our study, incidence of pain on injection in the group P was 44.5 %.

Our study found that the effect of dilution of propofol with dextrose water does not potentiate the effect of lidocaine in reducing pain on injection. Several factors influence the outcome of the study. The speed of propofol injection is one of these factors.

Slow speed of propofol injection cause greater discomfort because the contact between the endothelium and the active component of propofol is more prolonged and results in mediators release.⁵ Speed of infusion of carrier intravenous fluid also modifies propofol concentration in the aqueous phase and the intensity of pain.^{2,8} In the present study, propofol was manually injected by many investigators therefore the speed of injection might vary. Speed of intravenous fluid carrier was not controlled. These might influence the incidence of pain. Additionally, lipid-based emulsions affect incidence of pain. LCT/MCT emulsive propofol causes less injection pain than LCT emulsive propofol due to lesser propofol concentration in the aqueous phase.²³ The free propofol content in MCT/LCT emulsive propofol is less by 30-45% compared to LCT emulsive propofol.²⁴

An insignificant difference of pain severity in our study can be explained by other strategies we applied together to alleviate the propofol injection pain. First of all, we use lidocaine pretreatment which is effective in reducing pain on propofol injection. The dosage of lidocaine pretreatment was an appropriate dosage to reduce propofol injection pain.²⁵ Moreover, we used the current propofol formulation with mixed MCT/LCT lipid emulsion which was launched in 1999 and many studies^{23,26-30} have proved that the mixed MCT/LCT lipid emulsion of propofol produce less pain on injection. Using both strategies has reduced the pain associated

with propofol injection. In our study the incidence of severe pain was only 3% in undiluted group compared to 32% in Stokes et al's study.²² Therefore, dilution of propofol with 5% dextrose water might not be able to decrease the pain any further. The dilution of MCT/LCT propofol with dextrose water might not significantly reduce propofol concentration in aqueous phase compared to 10% intralipid.⁴

Limitations of our study were method of pain intensity measurement, accuracy of injection speed and dose of study drugs. The intensity of pain was evaluated by using four-point pain response scale. Although it is easy method to evaluate the pain, it is not patient's self-assessment which is gold standard of pain and intensity measurement. The study drug was manually injected. Although we controlled the drug to be injected in 3 seconds, the injection rates might vary owing to human inaccuracy. The rate of intravenous fluid after propofol injection was not specific. We selected the dose to be 30 mg of propofol to avoid patient loss of consciousness before pain evaluation so we cannot assume that the more or less dose of drug will give to the same result even there is no current data show the correlation between dose and incidence of pain. The total volume of propofol in group D and P was not the same. It might be biased by the investigator. Furthermore, we did not measure free propofol in aqueous phase before and after dilution with dextrose. Finally, our study did not follow up the pain recall in the postoperative period.

Conclusion

Based on our study, there was no benefit of dilution of MCT/LCT emulsive propofol with dextrose water in reducing pain on injection of propofol when lidocaine pretreatment was used to prevent propofol injection pain.

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