Fentanyl Pre-treatment Alleviates Pain During Injection of Propofol-Lipuro® Premixed with Lignocaine

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SUMMARY

We studied the effect of fentanyl pretreatment on alleviating pain during the injection of Propofol-Lipuro®. One hundred and seventy patients were randomly allocated to receive either 100 mcg of intravenous fentanyl or normal saline (placebo) followed by intravenous Propofol-Lipuro® premixed with 20mg lignocaine. The incidence of injection pain was 32% and 13% in the placebo and fentanyl groups, respectively. We found a statistically significant reduction in incidence of injection pain in the fentanyl group when compared with the placebo group (p<0.003). The number needed to treat was 6 (3.2< 95%CI <15.1). In conclusion, fentanyl pretreatment is effective in alleviating pain during injection of Propofol-Lipuro®.

KEY WORDS:
Propofol, Injection pain, Fentanyl, Pretreatment, Lignocaine

INTRODUCTION

Pain during injection of propofol is a common clinical problem. It has been extensively investigated and various strategies have been employed to attenuate its severity and ensure patient comfort[1]. Recently, a new formulation of propofol (Propofol-Lipuro®, B Braun) has been introduced. It is thought that an emulsion consisting of long-chain triglycerides (LCT) and medium-chain triglycerides (MCT) would decrease the concentration of free propofol in the aqueous phase thereby reduce the pain on injection. Indeed, Propofol-Lipuro® has been associated with less pain on injection but the incidence is still significant.

Intravenous fentanyl is routinely administered before induction of anaesthesia. The effect-site concentration for fentanyl peaks at 3 to 4 minutes. Fentanyl has a central analgesic effect in reducing pain during injection Propofol-Lipuro®. Most studies investigating Propofol-Lipuro® injection pain omit the administration of opioids, which could be beneficial in alleviating injection pain. We embarked on a clinical study to evaluate the effectiveness of fentanyl pretreatment on further reducing injection pain associated with Propofol-Lipuro® premixed with lignocaine.

MATERIALS AND METHODS

This prospective, randomised, placebo-controlled, double-blinded study was carried out at Sultanah Aminah Hospital, Johor Bahru following approval from the Malaysian Research Ethics Committee, Ministry of Health Malaysia. After obtaining written informed consent, 170 patients between the ages of 18 and 65, ASA physical status I or II, undergoing elective surgical procedures requiring general anaesthesia were randomly allocated to Group A (n=85); who received 2 ml intravenous fentanyl 100mcg and Group B (n=85); 2 ml of normal saline as placebo. All patients received intravenous Propofol-Lipuro® (20ml premixed with 20mg lignocaine). Patients with chronic pain syndromes, neurological deficits, thrombophlebitis, difficult venous access and clinical conditions that contraindicate the administration of any of the drugs used in the study were excluded from the study. Patients who had received analgesic within the previous 24 hours were also excluded.

All patients were not given premedication. On arrival in the operating room, an 18-gauge intravenous cannula was inserted into the vein of the dorsum of the hand or cephalic vein of the forearm ensuring free flow by gravity of normal saline as intravenous fluid. All patients were monitored with routine non-invasive monitoring (electrocardiography, automated non-invasive blood pressure, pulse oximetry and end-tidal capnography).

All study drugs were prepared by the investigator in identical syringes and labelled with removable stickers. The syringes were kept at room temperature. The appropriate syringe was selected by another anaesthesiologist, according to the patient group allocation by using computer-generated randomised number in a sealed envelope and the syringe label was removed. The study drugs were administered through the injection port of the intravenous cannula with free flow of intravenous fluid. The test drug was given at time zero second by the investigator who was blinded to the study. After 120 seconds, Propofol-Lipuro® was injected at a rate of 400 ml/h delivered via a syringe pump connected to a three-way tap placed at the venous cannula. The patients were asked a standard question after 30 seconds "Is the injection comfortable?" The verbal response and behavioural signs, such as facial grimacing, arm withdrawal or tears were noted and recorded (Table I). The total dose of propofol to render loss of consciousness was also recorded. Any adverse effects were also noted. Once an assessment had been made, anaesthesia was continued as routine at the discretion of the attending anaesthesiologist.

Based on an estimated incidence of pain on injection of Propofol-Lipuro® mixed with lidocaine of 25%, a power analysis indicated that a sample size of 168 was sufficient to have an 80% power (Type II error $\beta = 0.2$) of detecting a 50%

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Table I: Assessment of Pain during Injection of Propofol

Pain score	Degree of pain	Response
0	None	Negative response to questioning
1	Mild	Pain reported in response to questioning only, without any behavioral sign
2	Moderate	Pain reported in response to questioning and accompanied by a behavioral sign, or pain reported simultaneously without questioning
3	Severe	Strong vocal response or response accompanied by facial grimacing, arm withdrawal, or tears

Table II: Demographic Data

	Group A	Group B
Age (yr)	40.3 ± 11.7	38.9 ± 11.1
Weight (kg)	63.9 ± 11.5	62.3 ± 12.5
Gender (M/F)	22/63	30/55
ASA (I/II)	61/24	60/25
Dose (mg/kg)	1.6 ± 0.4*	2.1 ± 0.4*

Values are expressed in mean ± SD, range, or number of patients, where appropriate.
* P< 0.05

Table III: Incidence of Pain on Injection Associated with Propofol-Lipuro®

Pain Score	Group A N= 85	Group B N= 85
0	74 (87%)	58(68%)
1	10(12%)	20(24%)
2	1(1%)	5(6%)
3	0	2(2%)

P<0.003 Pain Score 0 versus Pain Score 1+2+3
P<0.02 Pain Score 0 versus Pain Score 2+3

difference in incidence of pain between the two groups at 95% significance level (Type I error α = 0.05). Patients' characteristics were compared using one-way analysis of variance (ANOVA). The frequency with which any response (grade 1 or more) occurred was compared between the groups by using a Chi-squared and/or Fisher's exact tests. Statistical significance was defined as $p \leq 0.05$. Statistical analysis was conducted using Minitab for Windows version 11.

RESULTS

Both groups were comparable with respect to demographic data (Table II). The dose of Propofol-Lipuro® was lower in the fentanyl group which was statistically significant. Three patients in the placebo group developed mild clonus but no other serious adverse event occurred.

The incidence of pain was 32% and 13% (an absolute risk reduction of 19% (95% confidence interval 6.6 %-31.0%)) in the placebo and fentanyl groups, respectively (Table III). We found a statistically significant reduction in incidence of pain in the fentanyl group when compared with the placebo group (p<0.003). The number needed to treat to prevent pain was 6 (95% confidence interval 3.2-15.1).

DISCUSSION

In this study, we found that patients who received fentanyl pretreatment had significantly less pain during injection of Propofol-Lipuro® premixed with lignocaine than those who received placebo. The effect of opioid such as alfentanil and remifentanil had been investigated[2,3]. Iyilikci *et al* found that the remifentanil and alfentanil groups showed less frequency and severity of propofol injection pain than the saline group[2]. We chose fentanyl because it is the only fast-acting opioid available in our practice. Since we usually administer fentanyl before induction of anaesthesia, its central analgesic effect could be an added benefit to alleviate pain during injection of Propofol-Lipuro®, in addition to the effect of lignocaine. This is similar to the multimodal approach by Auoad *et al* using remifentanil and lignocaine[3]. They found that combination of remifentanil and lignocaine has a significantly lower incidence of propofol pain at induction (9.6%) compared with remifentanil and lidocaine alone (36% and 35%, respectively).

Lignocaine had been shown to reduce propofol injection pain[4, 5]. In this study, all patients received Propofol-Lipuro® premixed with 20mg lignocaine. Yew et al have shown that patients who were given a mixture of propofol-MCT/LCT and lignocaine had significantly less pain on injection than those given either propofol-MCT/LCT alone or the conventional propofol-lignocaine mixture[4]. In another study, Sethi et al found a 15% incidence of injection pain in patients receiving propofol LCT/MCT premixed with 20 mg lignocaine[5]. We found a 32% incidence of injection pain in our placebo group. It is unclear why we found a higher incidence despite using the same dose of lignocaine. Propofol and lignocaine mixtures are unstable; therefore the effect on injection pain may be unpredictable. We prepared our Propofol-Lipuro® /lignocaine mixture before each case.

In our study, fentanyl pretreatment significantly reduced the incidence of moderate and severe injection pain due to Propofol-Lipuro® and completely eliminated the incidence of severe pain. We believe this effect is clinically relevant

because it ensures patient comfort during injection of Propofol-Lipuro®. Furthermore, we noted that the fentanyl group required reduced dose of Propofol-Lipuro® which was statistically significant. This can explained by the synergistic effect of fentanyl with anaesthetic induction agents.

In conclusion, fentanyl pretreatment incorporated in anaesthesia induction technique is a simple and effective way to alleviate pain during injection of Propofol-Lipuro® in addition to premixing with lignocaine.

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