A Comparison of Pretreatment With Fentanyl and Lidocaine Preceded by Venous Occlusion for Reducing Pain on Injection of Propofol: A Prospective, Randomized, Double-Blind, Placebo-Controlled Study in Adult Japanese Surgical Patients

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ABSTRACT

Background: Pain on injection is a recognized adverse effect of propofol, an agent used to induce general anesthesia in surgical patients. Pretreatment with fentanyl has been reported to be effective in reducing propofol-induced pain.

Objective: The aim of this study was to compare the efficacy of intravenous pretreatment with fentanyl 50 μg, fentanyl 100 μg, and lidocaine 40 mg, preceded by venous occlusion, for reducing pain on injection of propofol in adult Japanese surgical patients.

Methods: This was a prospective, randomized, double-blind, placebo-controlled study. Adult Japanese surgical patients were randomized to 1 of 4 groups to receive intravenous fentanyl 50 μg, fentanyl 100 μg, lidocaine 40 mg, or placebo (0.9% isotonic saline). The drug administration was preceded by manual venous occlusion with a rubber tourniquet for 1 minute, followed by administering propofol 0.5 mg/kg injected into the largest dorsal vein of the hand through a 20-gauge intravenous cannula at the rate of 10 mg/sec. Pain on injection of propofol was assessed by an investigator who was blinded to group assignment. Patients were interviewed to assess pain intensity on injection using a 4-point verbal rating scale (0 = none; 1 = mild; 2 = moderate; and 3 = severe). Incidence and severity of pain were determined in each of the 4 study groups. Adverse events related to the study drug were recorded before the induction of anesthesia and after surgery. Patients were monitored for adverse events for 24 hours following surgery.

Results: A total of 120 patients (70 men and 50 women; mean [SD] age, 44 [11] years; height, 160 [7] cm; weight, 56 [10] kg) completed the study. Each group comprised 30 patients. No significant between-group differences in demographic characteristics were found. The overall incidence of propofol-induced pain was 77% (23/30 patients) with fentanyl 50 μg (P = NS), 37% (11/30 patients) with fentanyl 100 μg (P = 0.001), and 33% (10/30 patients) with lidocaine 40 mg (P = 0.001) compared with 83% (25/30 patients) with placebo. The median pain score was lower in patients who received fentanyl 50 μg (1; P = NS), fentanyl 100 μg (0; P = 0.001), or lidocaine 40 mg (0; P = 0.001) than in those who received placebo (2). The incidence and severity of pain were significantly different between the fentanyl 50-μg and 100-μg groups (incidence, P = 0.0[illegible] severity, P = 0.001). However, there was no significant difference in the incidence and severity of such pain between the fentanyl 100-μg and lidocaine 40-mg groups. Both study drugs were well tolerated.

Conclusions: Preceded by venous occlusion for 1 minute, fentanyl 100 μg was not significantly different from lidocaine 40 mg in reducing pain during injection of propofol in these adult Japanese surgical patients. Fentanyl 50 μg was ineffective in reducing such pain compared with placebo. (*Clin Ther.* 2009;31: 2107–2112) © 2009 Excerpta Medica Inc.

Key words: complications, pain, propofol LCT, fentanyl, lidocaine.

INTRODUCTION

Pain on injection is a recognized adverse effect of propofol, an agent used to induce general anesthesia in surgical patients.[1] Propofol is formulated as a 1% solution diluted in an emulsion of long-chain triglyc-

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erides (LCTs) containing 10% soybean oil. Among 33 low-morbidity clinical outcomes, as assessed by expert anesthesiologists considering clinical importance and frequency, pain during injection of propofol ranked seventh.[1] When a vein on the hand is used, this pain has been reported in up to 80% of patients.[2,3] Several studies have examined pharmacologic and nonpharmacologic strategies for the prevention of propofol-induced pain.[4,5] Pretreatment with lidocaine 40 mg, when administered in conjunction with a rubber tourniquet on the forearm, is an effective method used to reduce this pain.[4,5] Previously, 3 comparative studies evaluated the efficacy of fentanyl against placebo in reducing pain on injection of propofol. In a randomized, double-blind, placebo-controlled trial in 99 surgical patients, Helmers et al[6] found that fentanyl 100 µg was significantly more effective than placebo in reducing pain on injection of propofol (P = 0.006). Kobayashi et al[7] evaluated the analgesic efficacy of fentanyl 100 µg in preventing pain on injection of propofol compared with placebo (N = 40; P = 0.005). Similarly, Pang et al[8] compared the effects of fentanyl 150 µg on local analgesia in propofol-induced pain on injection when fentanyl was administered in conjunction with a rubber tourniquet on the forearm arresting blood flow for 1 minute. Their study found that fentanyl 150 µg was significantly more effective when administered in conjunction with a rubber tourniquet than was placebo (P = 0.001).

A search of the literature using MEDLINE and EMBASE databases for English- and non-English-language articles published between 1990 and 2008, containing key terms *complications*, *pain*, *propofol LCT*, *fentanyl*, *lidocaine*, and *venous occlusion*, identified 2 studies on the prophylactic use of fentanyl and lidocaine for reducing pain on injection of propofol.[4,5] However, no comparative studies were found.

The aim of this study was to compare the efficacy of intravenous pretreatment with fentanyl 50 µg, fentanyl 100 µg, and lidocaine 40 mg, preceded by venous occlusion, in reducing pain on injection of propofol in adult Japanese surgical patients.

PATIENTS AND METHODS

This prospective, randomized, double-blind, placebo-controlled study was conducted at the Department of Anesthesiology, Ushiku Aiwa General Hospital, Ibaraki, Japan. The study protocol was approved by the local institutional ethics committee. Verbal informed consent was obtained from all patients before enrollment. Japanese patients aged 22 to 69 years who were scheduled to undergo elective surgery were eligible. Patients with a history of adverse response to propofol, fentanyl, or lidocaine were excluded from the study. Patients were not allowed to receive analgesics or sedative drugs within 24 hours before surgery.

No patient received preanesthetic medication. On arrival in the holding area of the operating room, a 20-gauge intravenous cannula (Insyte Vocan Safety. B. Braun Inc., Bethlehem, Pennsylvania) was inserted into the largest dorsal vein of the hand and attached to an infusion of acetated Ringer's solution (Na^+ 130 mEq/L, K^+ 4 mEq/L, Ca^{2+} 3 mEq/L, Cl^- 109 mEq/L, and acetate 28 mEq/L; Yoshitomi-Fuso Yakuhin Kenkagaku Inc., Tokyo, Japan), which was administered at a rate of 10 mL/kg/h.

Using a computer-generated table of random numbers, patients were randomly assigned to 1 of 4 groups to receive fentanyl 50 µg IV, fentanyl 100 µg IV, lidocaine 40 mg IV, or placebo (0.9% isotonic saline). To ensure blinding, injections were administered using identical syringes that were covered with red tape. If the volume of the study drug to be administered was <2 mL, 0.9% isotonic saline was added to total a volume of 2 mL. The syringes were prepared by personnel not involved in the study.

Before injection of the study drug, all patients underwent venous occlusion (to retain the study drug within the vein), which involved manual compression of the forearm with a rubber tourniquet for 1 minute, an identical method described in previous studies.[8,9] The doses of the study drugs (fentanyl and lidocaine) selected were based on previous findings on the efficacy of these drugs for reducing pain on injection of propofol.[4–7] The study drug was injected over 10 seconds, after which the tourniquet was released, and propofol LCT 1%* (at room temperature, 23°C) 0.5 mg/kg was delivered through the intravenous cannula at the rate of 1 mL/sec.

Immediately after administering propofol, an investigator (M.I.) blinded to group assignment asked the patient about pain at the injection site and assessed pain intensity using a 4-point verbal rating scale (VRS), with 0 = no pain (negative response to questioning); 1 = mild pain (pain reported only in response to questioning without any behavioral signs); 2 = moderate

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