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Original Contribution

Impact of time interval between remifentanil and propofol on propofol injection pain☆,☆☆

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Abstract

Study Objective: To determine the most effective time interval between remifentanil and propofol ($Time_{RP}$) for the prevention of propofol injection pain in association with remifentanil dosage.

Design: Prospective randomized study.

Setting: Operating room of a university hospital.

Patients: Sixty American Society of Anesthesiologists physical status 1 and 2 patients scheduled for elective surgery under general anesthesia.

Interventions: Patients were randomly assigned to 1 of 3 groups to receive remifentanil at dosages of 0.25, 0.5, or 0.75 μg/kg over 30 seconds before the injection of 1% propofol 2 mg/kg. $Time_{RP}$ was defined as the time interval from the initiation of the remifentanil injection to the initiation of the propofol injection. $Time_{RP}$ for each subsequent patient was determined by the response of the previous patient using an up-and-down sequential allocation method. Injection pain caused by propofol was evaluated using a 4-point scale during the propofol injection.

Measurements: $Time_{RP}50$ was defined as the $Time_{RP}$ at which propofol injection pain was absent in 50% of patients, and it was estimated using isotonic regression for each dose group.

Main Results: $Time_{RP}50$ was significantly lower in the remifentanil 0.75 μg/kg group (38.6 seconds, 83% confidence interval [CI], 35.6-45.0) than in the 0.5 μg/kg group (65.0 seconds; 83% CI, 52.5-75.0) or the 0.25 μg/kg group (66.6 seconds; 83% CI, 57.1-76.5).

Conclusions: The efficacy of remifentanil pretreatment for preventing propofol injection pain can be influenced by the time interval between remifentanil and propofol as well as the remifentanil dose.

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1. Introduction

Propofol is a popular intravenous hypnotic for the induction and maintenance of general anesthesia because of its rapid onset and short duration of action [1]. However, the general incidence of propofol injection pain is approximately 60% [2], and it varies from 28% to 90%, depending on the size of the vein injected [3-5]. This has been recognized as an important problem in the current practice of anesthesia [6].

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☆☆ The English in this document has been checked by at least 2 professional editors, both native speakers of English. For a certificate, please see: http://www.textcheck.com/certificate/ZHYX7k.

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Many techniques have been investigated to reduce the incidence and severity of propofol injection pain [2,7]. The most efficacious nonpharmacologic intervention is selecting larger veins (eg, an antecubital vein instead of a hand vein) [2], although it is not possible to have an adequate vein in all situations. Pretreatment using lidocaine with a tourniquet has been postulated to be most effective among pharmacological interventions [8]; however, the technique failed to gain widespread popularity because of its complexity [2]. In addition, a recent Cochrane review demonstrated that both lidocaine admixture and pretreatment were effective similarly [9], but the overall incidence of pain and high-intensity pain were not low enough for comfortable induction (approximately 30% and 12%). Based on utility and convenience, intravenous opioids seem to be a reasonable intervention as a single or adjuvant pretreatment because opioids are used extensively as part of balanced anesthesia and can be possibly applied with other interventions [2].

Remifentanil is an ultra-short-acting opioid that can be titrated rapidly for various levels of surgical stimuli [10], and it is commonly used with other hypnotic anesthetics in general anesthesia. Several investigators have reported that administering remifentanil before the injection of propofol can effectively reduce pain due to the propofol injection [11-17]; the mechanism may be central, peripheral, or both. By whatever mechanism, it should take some time (not zero) for remifentanil to provide an optimal effect. However, time intervals between remifentanil and propofol administration in previous clinical studies varied from 0 to 90 seconds. Our hypothesis was that the timing of propofol administration after remifentanil may influence the incidence and severity of propofol injection pain. To our knowledge, there has been no reported study regarding the "effective time interval" between remifentanil and propofol. The purpose of the current study, thus, was to determine the most effective time interval between remifentanil and propofol ($Time_{RP}$) for preventing injection pain in association with the remifentanil dosage.

2. Materials and methods

With the approval of the institutional ethics committee, adult patients with American Society of Anesthesiologists physical status 1 and 2, aged 20 to 60 years, and scheduled for elective surgery under general anesthesia were enrolled. Exclusion criteria were as follows: known hypersensitivity to propofol or any other drug, neurologic deficits, psychiatric disorders, diabetes mellitus, peripheral vascular disease, body mass index greater than 30 kg/m^2, and receipt of analgesic or sedative drugs within 24 hours of the surgery. Written informed consent was obtained from all patients.

No premedication was administered to any patient. A 20-G cannula was placed in the largest vein of the forearm, and a 3-way stopcock was connected directly to the catheter. Its optimal function was examined by the free flow of fluid by gravity. Routine monitoring consisted of pulse oximetry, electrocardiography, and noninvasive blood pressure.

This trial was conducted with patients assigned to 1 of 3 groups to receive remifentanil 0.25, 0.5, or 0.75 μg/kg using a computer-generated randomization table. To achieve blinding, remifentanil (Ultiva, GlaxoSmithKline, Italy) was diluted with 0.9% saline to result in the same volume of 15 mL by an independent research nurse who did not participate in pain assessment. The research nurse injected the prepared remifentanil into a 3-way stopcock at a rate of 0.5 mL/s over 30 seconds. After a predetermined time interval ($Time_{RP}$), 1% long-chain triglyceride propofol (Anepol; Hana Pharm., Korea) 2 mg/kg was injected over 30 seconds. All study drugs were kept at room temperature and were injected with a slow constant speed using a stopwatch.

During the injection of propofol, pain at the injection site was evaluated by a study-blinded investigator using a 4-point verbal rating scale: 0 = no pain (negative response to questioning); 1 = mild pain (pain reported only in response to questioning without any behavioral sign); 2 = moderate pain (pain reported in response to questioning and accompanied by a behavioral sign or pain reported spontaneously without questioning); or 3 = severe pain (strong vocal response or response accompanied by facial grimacing, arm withdrawal, or tears). This verbal rating scale method has been used in other studies evaluating propofol injection pain [18-20]. The investigator first observed patients' behavioral signs for 10 seconds and then inquired, at 5-second intervals, whether patients experienced any pain in their arm. After loss of consciousness, anesthesia was conducted in the usual manner by an attending anesthesiologist. Remifentanil-related complications, including hypotension (>20% decrease compared with baseline value), bradycardia (heart rate <45 beats/min), chest wall rigidity (expressed as chest tightness and difficulty in breathing), desaturation (Spo_2 <95%), dizziness, nausea, cough, pruritus, and erythema, were also assessed until loss of consciousness.

$Time_{RP}$ was defined as the time interval from the initiation of the remifentanil injection to the initiation of the propofol injection. $Time_{RP}$ for the first patient in each group was 90 seconds because the half-time for equilibration between plasma and its effect compartment ($t_{1/2}k_{e0}$) is 1.0 to 1.5 minutes [21,22] in the case of remifentanil. $Time_{RP}$ for each subsequent patient was determined by the response of the previous patient using Dixon's up-and-down method [23]. If the patient had no injection pain (regarded as a success), $Time_{RP}$ for the next patient in that group was decreased by 15 seconds. If the patient had any injection pain (regarded as a failure), $Time_{RP}$ for the next patient in that group was increased by 15 seconds.

Based on the up-and-down method of Dixon [24], testing of different time intervals was carried out until 6 pairs of failure-success crossovers for each group had been collected. *$Time_{RP}50$* was defined as $Time_{RP}$ at which propofol injection pain was absent in 50% of patients, and it was calculated as the mean of the midpoint time interval of all independent crossover pairs for each group. To specify the precision of

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