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Original Article

EC50 of Remifentanil to Prevent Propofol Injection Pain

Hun Pyo Hong, Hyun min Ko, Ji Young Yoon, Ji Uk Yoon*, Kun Hyo Park†, Young Chea Roh†

Department of Dental Anesthesia and Pain Medicine, School of Dentistry, Pusan National University, *Department of Anesthesia and Pain Medicine School of Medicine, Pusan National University, †Department of Oral and Maxillofacial Surgery School of Dentistry, Pusan National University, Busan, Korea

Background: Various strategies have been studied to reduce the propofol injection pain. This study was designed to find out effect-site target concentration (Ce) of remifentanil at which there was a 50% probability of preventing the propofol injection pain (EC50).
Methods: Anesthesia was induced with a remifentanil TCI (Minto model). The Ce of remifentanil for the first patient started from 2.0 ng/ml. The Ce of remifentanil for each subsequent patient was determined by the response of the previous patient by Dixon up-and-down method with the interval of 0.5 ng/ml. After the remifentanil reached target concentrations, propofol was administered via a target-controlled infusion system based on a Marsh pharmacokinetic model using a TCI device (Orchestra®; Fresenius-Vial, Brezins, France). The dose of propofol was effect site target-controlled infusion (TCI) of 3 μg/ml.
Results: The EC50 of remifentanil to prevent the propofol injection pain was 1.80 ± 0.35 ng/ml by Dixon's up and down method.
Conclusions: The EC50 of remifentanil to blunt the pain responses to propofol injection was 1.80 ± 0.35 ng/ml for propofol TCI anesthesia.

Key Words: Injection; Pain; Propofol; Remifentanil

INTRODUCTION

Propofol is widely used for general anesthesia and ambulatory surgery because of its smooth induction of anesthesia, rapid onset and short action time [1,2].

However, pain or discomfort on injection of propofol is a common problem during induction of anesthesia. The incidence of pain on injection of propofol is reported to vary between 30 and 90% [3-5]. Furthermore, expert anesthesiologists ranked propofol injection pain during induction as seventh among 33 when both clinical importance and frequency were considered [6].

The mechanism of propofol injection pain is not fully understood [2,7]. The chemical mechanisms for propofol injection pain may be the direct irritation via the release of kininogens when propofol contacts with the vascular endothelium [7,8], but remain in part unclear. Klement & Arndt supposed that the afferent free nerve endings between the media and intima are the sensors for this pathway [9]. Several methods have been attempted to reduce propofol injection pain, including varying the injection speed and carrier fluid, dilution, cooling or warming the propofol, or concomitant use of drugs [6,10,11]. However, these methods have failed to become popular among anesthesiologists because preparations are difficult and they do not completely prevent the injection pain.

The use of opioids such as alfentanil or fentanyl has been found to prevent pain on injection of propofol [12-14]. Remifentanil is a synthetic, potent and selective μ-opioid receptor agonist with a rapid onset and

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Corresponding Author: Ji Young Yoon, Department of Dental Anesthesia and Pain Medicine, School of Dentistry, Pusan National University, Beomeo-ri, Mulgeu-eup, Yangsan-si, Gyung-sangnam-do 626-787, Korea
Tel: +82.55.360.5379 Fax: +82.51.242.7466 email: dryoonji@pusan.ac.kr
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ultra-short duration of action [15,16]. It has also been shown to prevent propofol injection pain in earlier studies [17-19].

There are few studies about effect-site target concentration (Ce) of remifentanil at which there is a 50% probability of preventing the propofol pain on injection (Ce50). In the current study, we aimed to evaluate the Ce50 of remifentanil to prevent the pain response associated with propofol injection in adult population.

MATERIALS AND METHODS

The study enrolled 40 male and female patients of ASA class I or II scheduled for oral surgery and aged 20-60 years. The institutional ethics committee approved the study and written informed consent was obtained from all patients. Exclusion criteria for the study were: ischemic heart disease, known allergy to any of the anesthetic medication, suspected or known pregnancy, disorders of the pancreas or liver (ALT or AST > 40 U/L; lipase > 30 U/L), renal problems, thrombophlebitis, history of major neurological or psychiatric problem, chronic pain being treated with sedative or analgesic medication, and use of an analgesic within 24 hours before surgery. Patients requiring a rapid-sequence induction were also excluded.

No premedication was administered to any of the patients and a 20-G cannula was placed in a vein on left forearm and a three-way tap was connected directly to the catheter for hydration and drug infusion. When the patients arrived at operating rooms, electrocardiogram, noninvasive blood pressure and SpO_2 were monitored. All patients were preoxygenated for 5 min before induction of anesthesia. The infusions of remifentanil were prepared using Ultiva inj., 2 mg vial (GlaxoSmithKline, Belgium). Remifentanil 2 mg was diluted into 20 ml of normal saline (100 μg/ml solution). A commercial TCI pump (Orchestra® Base Primea, Fresenius Vial, France) was used for the effect-site TCI of remifentanil. The pump used the Minto and colleagues models for remifentanil [20].

The target effect site remifentanil concentration for the first patient was 2.0 ng/ml. The target effect site remifentanil concentration for each subsequent patient was determined by the response of the previous patient. If a patient was adequately anesthetized (i.e., had no response to propofol injection), the target effect site remifentanil concentration for the subsequent patient was decreased by 0.5 ng/ml. If a patient had a response to injection ('response' defined as instances of excitation, spontaneous complaints of pain and complaints of pain after direct question about pain), the target effect site remifentanil concentration for the subsequent patient was increased by 0.5 ng/ml. After the remifentanil reached target concentrations, 1% propofol was administered via a target-controlled infusion system based on a Marsh pharmacokinetic model using a TCI device (Orchestra®; Fresenius-Vial, Brezins, France). The dose of propofol was effect site target-controlled infusion (TCI) of 3 μg/ml.

The Dixon up and down method was used to determine the mean and standard deviation of remifentanil EC50. The EC50 was determined by calculating the mean of the midpoint dose of all independent pairs of patients who manifested crossover from 'response to injection' to 'non response to injection' after eight crossover points. At least seven pairs of failure-success are necessary for the statistical analysis. Heart rate (HR) and mean arterial pressure (MAP) are recorded and compared between before drug infusion and after the target Ce of both drugs were reached. If the MAP decreases below 50 mmHg, ephedrine 0.25 mg/kg was scheduled. The changes of HR and MAP were analyzed with Paired t-test or Signed rank test. Data was plotted and analyzed using SPSS 12.0 (SPSS Inc., Chigago, IL,

USA). Values were expressed as mean ± SD, mean (95% confidence intervals; CI), or number of patients. A $p < 0.05$ was considered to be statistically significant.

RESULT

Forty subjects aged 20-60 yr were enrolled and all subjects completed the study protocol. No patient had bradycardia, hypotension or oxygen desaturation. The patient demographics are included in Table 1. No patient experienced clinically significant hemodynamic changes during the study. Even though HR and MAP decreased in statistical significance, the decrease of HR and MAP had no serious clinical meanings (Table 2). It did not decrease to as much as patients need inotropics like ephedrine.

The effect-site concentration of remifentanil reached the targets after start of infusion within 1 min 30sec, and the effect-site concentration of propofol reached the target after start of infusion within 3 min 40 sec, respectively. Dose-response data for each patient which was obtained by using the up and down method are shown in Fig. 1. The predicted EC50 of remifentanil was 1.80 ± 0.35 ng/ml by Dixon up and down method.

Table 1. Patient demographic

Characteristic	Data
Age (years)	44.6 ± 12.0
Height (cm)	164.2 ± 9.3
Weight (kg)	65.7 ± 11.8
Gender (M/F)	19 / 21

Data are shown as mean ± SD or frequency

DISCUSSION

The purpose of this study was to describe the effect site target concentration of remifentanil at which there is a 50% probability of preventing the propofol injection pain. Injection pain is a well-recognised problem during the intravenous administration of propofol [4].

The mechanism of pain on propofol injection remains unclear, although a number of mechanisms have been proposed [2,8,9]. Pain may be immediate or delayed within a latency of 10-20 sec. Immediate pain probably results from a direct irritant effect, whereas delayed pain may result from an indirect effect via the kinin cascade [2]. A variety of strategies has been tried for the pre-

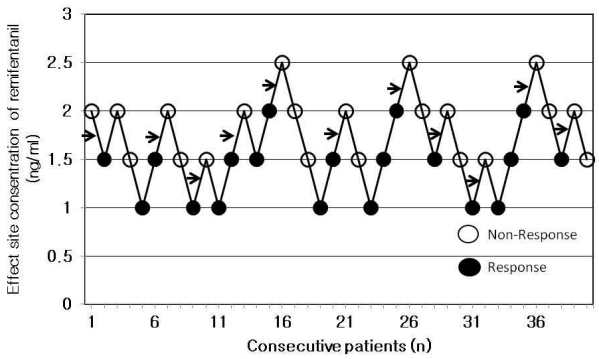

Fig. 1. Consecutive remifentanil concentration which is following Dixon up and down method. The arrow represents the mean remifentanil concentration when crossing from a response to a non-response for rocuronium injection. The average of these concentrations is ED50.

Table 2. Changes in mean arterial blood pressure and heart rate

	HR		MAP	
	Beats/minute	P value	mmHg	P value
Baseline	77.6 ± 17.5 (median, 76.5)		95.0 ± 16.4	
After infusion	78.6 ± 17.9 (median, 76.5)	> 0.05	93.3 ± 17.0	> 0.05

Data are shown as means ± SD.
HR heart rate, MAP mean arterial pressure.
Baseline, before administration of drugs; after infusion, after Ce(effect-site target concentration) of both remifentanil and propofol reached target concentration

vention of injection pain including varying injection speed and carrier fluid [10] dilution [9,11], temperature [21], or solvent [22,23], or the concomitant use of drugs.

Remifentanil has an analgesic potency 20-30 times of alfentanil and a rapid onset time. The use of remifentanil to prevent the pain of propofol injection has been studied by several investigators [18,19]. Remifentanil is an opioid of the phenylpiperidine group and could have a local anesthetic effect on nerves. Opioid receptors are found in the dorsal root ganglia, the central terminals of primary afferent nerves and peripheral sensory nerve fibres and their terminals. To have interaction with peripheral opioid receptors, opioids must remain in the body for a certain period of time. Roehm et al [18]. reported this period for remifentanil infusion to be 60 sec in the prevention of propofol-induced injection pain. In this study, remifentanil was administered over 90 sec with a TCI pump on running fluid without the venous occlusion technique; thus, the peripheral effect of remifentanil is less likely.

Regarding the dose of remifentanil, Roehm and colleagues[18] showed that remifentanil 0.25 μg/kg/min before propofol injection is as effective as lidocaine 40 mg prior to propofol injection in reducing the incidence of injection pain (30.2 vs. 62% for placebo). Basaranoglu and colleagues [19] used remifentanil 1 μg/kg/min before propofol, and the incidence of propofol injection pain decreased from 32% to 44%. Considering these result, a dose-dependent effect of remifentanil in attenuating propofol injection pain is suspected. Regardless of the mechanism, it is likely that pretreatment with remifentanil has resulted in a deeper level of anesthesia that increases the pain threshold and thus explains the decreased incidence of propofol injection pain. Further research to find out the optimal bolus dose of remifentanil required for the prevention of withdrawal movement with better hemodynamic stability, is needed.

As compared with these previous studies, we tried to maintain a relatively low target effect-site concentration of propofol to minimize hemodynamic instability [24,25]. The pharmacokinetics and pharmacodynamics of remifentanil are known to be influenced by patient age. We delivered remifentanil with effect-site TCI according to the Minto model. Minto et al [20]. stated that the pharmacokinetics and pharmacodynamics of remifentanil are influenced by age, not by gender, and they developed remifentanil dosing guidelines in consideration of age, sex, and lean body mass. This study was not focused on a specific population but on the general population including elderly patients. Even though the age of the population in this study varied from young to elderly persons, the study population passed the normality test of Kolmogorov-Smirnov, and the pharmacological effect of remifentanil on age was already reflected in the Minto's TCI model. The Dixon up-and-down method has been commonly used in anesthesia research and has advanced in regard to its methodology. To increase the precision of the final estimator, altering the test space could be done in the course of an up-and-down sequence. That is, this modified up-and-down sequence is composed of two stages. The first stage consists of an original up-and-down sequence on the predetermined equally spaced test levels until three to four changes of response type are observed. The second stage consists of reducing the initial test space and restarting the up-and-down sequence at the nearest level to the average and continuing the experiment at the next higher or the next lower level according to the response type on the reduced test space. Applying the foregoing modified up and down methods to this study, narrowing the gap between the doses after the fourth pairs of "response-nonresponse" would have resulted in a more precise confidence interval.

In conclusion, the EC50 of remifentanil to prevent the

withdrawal response was 1.80 ± 0.35 ng/ml with Dixon's up-and-down method.

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