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Original Article

Comparison of Efficacy of Propofol When Used with or without Remifentanil during Conscious Sedation with a Target-Controlled Infuser for Impacted Teeth Extraction

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Background: Clinical use of propofol along with remifentanil for intravenous sedation is increasing in these days, but there are not enough researches to evaluate proper target concentration when these drugs are infused by using target controlled infusion (TCI) pump in dental treatment cases. In this study, we compared efficacy of TCI conscious sedation and target concentration of propofol when it used with or without remifentanil during conscious sedation with the help of a TCI for the surgical extraction of impacted teeth.

Methods: After IRB approval, all the charts of patients who had undergone surgical extraction of impacted teeth under propofol TCI sedation for 6 months were selected and reviewed for this study. After reviewal of charts, we could divide patients in two groups. In one group (group 1), only propofol was selected for sedation and initial effect site concentration of propofol was 1 μg/ml (n = 33), and in another group (group 2), both propofol and remifentanil was infused and initial effect site concentration of each drug was 0.6 μg/ml and 1 ng/ml respectively (n = 25). For each group, average propofol target concentration was measured. In addition, we compared heart rate, respiratory rate, and systolic and diastolic blood pressure as well as oxygen saturation. Besides, BIS, sedation scores (OAAS/S), and subjective satisfaction scores were compared.

Results: Between group 1 and 2, there were no significant differences in demographics (age, weight and height), and total sedation time. However, total infused dose and the effect site target concentration of propofol was 163.8 ± 74.5 mg and 1.13 ± 0.21 μg/ml in group 1, and 104.3 ± 46.5 mg and 0.72 ± 0.26 μg/ml in the group 2 with 1.02 ± 0.21 ng/ml of the effect site target concentration of remifentanil, respectively. During sedation, there were no differences between overall vital sign, BIS and OAAS/S in 2 groups ($P > 0.05$). However, we figured out patients in group 2 had decreased pain sensation during sedation.

Conclusions: Co-administration of propofol along with remifentanil via a TCI for the surgical extraction of impacted teeth may be safe and effective compared to propofol only administration.

Key Words: Propofol; Remifentanil; Sedation; Target concentration; Target controlled infusion; Tooth extraction

INTRODUCTION

Controlling anxiety and pain in dental treatment is an important issue. Therefore, pain and/or anxiety management of patients is a huge concern in dentistry. Various sedation methods have been developed and used to control dental anxiety safely and effectively [1]. Especially, a number of more innovative sedation techniques have been investigated nowadays, including polypharmacy [2], intravenous sedation in children [3], inhalational sedation with sevoflurane, trans-mucosal sedation, and intravenous sedation with propofol.[1].

Propofol as an intravenous sedation agent is a phenolic derivative formulated as an oil-in-water emulsion. Propofol is highly lipophilic so rapidly crosses the blood brain barrier leading to a rapid onset of sedation. Its sedation level increases in a dose dependent manner. Compared with midazolam, it rapidly redistributes into

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peripheral tissues, which causes a rapid emergence from sedation [4]. And, we can predict recovery period from propofol better and control depth of sedation[5]. However, as propofol has a relative narrow therapeutic range, patients can quickly reach from moderate to deep sedation risking life-threatening respiratory problems. It means propofol must be carefully titrated to achieve moderate sedation without accidental deeper level of sedation. Propofol also causes injection pain, bradycardia and hypotension to patients.

Remifentanil, a 4-anilidopiperidine derivative of fentanyl, is a highly active, ultra-short acting, selective u-opioid receptor agonist [6]. Compared to other opioids, remifentanil shows rapid onset within 1 to 2 minutes, intense analgesia and extremely short duration of action having context-sensitive half life of 3 to 8 minutes. As a result, remifentanil is the best analgesic for brief painful stimuli [7].

A target controlled infuser (TCI) is a computer-assisted infusion pump to administer drugs intravenously [8]. TCI enables the drug concentration in the plasma or at the effect site such as the brain to be controlled continuously. For TCI, many researchers have developed their own pharmacokinetic models such as the Marsh (Diprifusor) and Schnider (Ochestra Base Primea) for propofol and the Minto and the Schnider for remifentanil. (AnestFusor Series II Standard, 2009). The use of propofol along with remifentanil via a TCI intravenous sedation for dental procedures is very limited and that is the reason why we could only find few articles [9,10].

To our best knowledge, there were only a few reports about the optimal target concentration of propofol co-administrated remifentanil via a TCI conscious sedation for impacted teeth extraction up to now. In this study, we compared the proper target plasma concentration of propofol when used with or without remifentanil during conscious sedation with a TCI for impacted teeth surgical extraction and wanted to suggest the safe and effective doses target plasma concentration of propofol along with remifentanil during TCI conscious sedation for the surgical extraction of wisdom teeth.

METHODS

After IRB approval, we reviewed all the charts of patients who had undergone surgical extraction of impacted teeth under TCI conscious sedation with propofol or propofol together with remifentanil at Seoul National University Dental Hospital from November 1, 2008 to April 30, 2009. Total 58 charts of patients were selected and reviewed for this study. The inclusion criteria were the age of 15 to 65 year and ASA physical status I and II. After reviewal of charts, we could divide patients in two groups. In one group (group 1), only propofol was selected for sedation and initial effect site concentration of propofol was 1 μg/ml (n = 33), and in another group (group 2), both propofol and remifentanil was infused and initial effect site concentration of each drug was 0.6 μg/ml and 1 ng/ml respectively (n=25). In order to maintain proper level of sedation, the target concentration has been increased or decreased during dental procedures.

In both group, TCI system that incorporate Schnider model for propofol and Minto model for remifentanil was used. Patients were instructed to fast 8 hours before their surgical appointment and to bring a responsible person to escort them home after sedation. After inserting a cannula into a vein, a continuous fluid therapy with Hartmann's solution was started to compensate dehydration during fasting. Before infusion of propofol, 2-3 ml of 1% lidocaine was injected through an intravenous cannula to reduce pain caused by propofol injection.

For each group, we compared demographic data, total infusion amount, time, and effect site concentration of

both propofol and remifentanil. To compare effect site concentration of propofol and remifentanil, we extracted initial concentration, average concentration, minimum and maximum concentrations. Vital signs such as heart rate, respiratory rate, and SpO_2 were recorded every minutes and systolic and diastolic blood pressure were recorded every 5 minutes. For comparing vital signs between each group, we extracted initial data, data at 10 minutes later, 20 minutes later, minimum and maximum one in each group except for SpO_2. As for SpO_2, we compared only minimum one between each group.

BIS and OAAS/S (Responsiveness scores of the modified observe's assessment of alertness/sedation scale) (Table 1) were compared in the same manner. We compared pain sensation degree in recovery room.

Table 1. Responsiveness scores of the modified observe's assessment of alertness/sedation scale (OAAS/S)

Response	Score level
Responds rapidly to name spoken in normal tone	5
Lethargic response to name spoken in normal tone	4
Responds only after name is called loudly or repeatedly	3
Responds only after mild prodding or shaking	2
Does not respond to mild prodding or shaking	1

Table 2. Demographic Data (n=58)

	Group 1 (n=33)	Group 2 (n=25)
Sex (M/F)	13/20	8/17
Age (yr)	27.4 ± 11.1	27.0 ± 9.2
Weight (kg)	58.8 ± 10.6	60.3 ± 13.1
Height (cm)	167.3 ± 9.7	162.5 ± 11.8
Surgery time	1 hr 3 min ± 14 min	1 hr 10 min ± 21 min

Data are mean ± S.D.

Student t-test and chi-square test were conducted to compare data in group 1 and 2, statistically.

RESULTS

In this study, 58 charts of patients were reviewed. There was no difference between age, weight, height and total surgery time of 2 groups (Table 2). Group 1 was composed of 13 males and 20 females. 8 male patients and 17 female patients were assigned in group 2 ($p > 0.05$, chi-sqaure test). When propofol was administered only, total amount of infused propofol was higher than when propofol was administered with remifentanil ($p < 0.05$) (Table 3).

As we expected, the effect site concentration of propofol when it used solely was higher than group 2 ($P < 0.05$) (Fig. 1). Target concentration of infused propofol was 1.13 ± 0.21 ㎍/ml in group 1, 0.72 ± 0.26

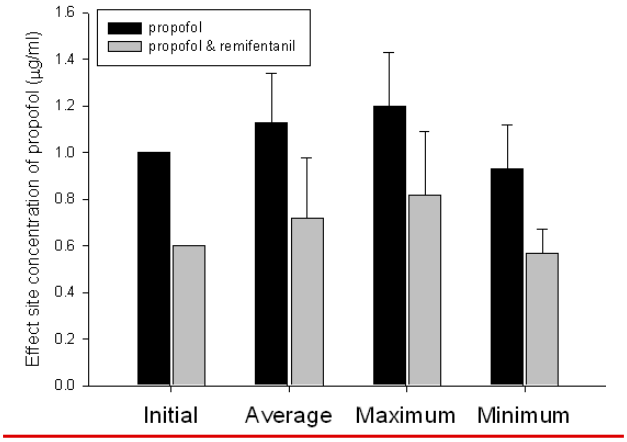

Fig. 1. Effect site concentration of Propofol – Effect site concentration of propofol when it was used only was higher than group 2. ($P < 0.05$).

Table 3. Total infusion amount and time

	Group 1	Group 2
Total amount of infused propofol (mg)	163.8 ± 74.5	104.3 ± 46.5
Total amount of remifentanil (㎍)		159.1 ± 87.9
Total time of propofol infusion (mg)	50 min ± 28 min	44 min ± 14 min
Total time of remifentanil infusion (㎍)		52 min ± 19 min

Data are mean ± S.D.

μg/ml in group 2 ($P < 0.05$). Maximum concentration in group 1 and 2 was 1.20 ± 0.23 μg/ml and 0.82 ± 0.27 μg/ml, respectively ($P < 0.05$). Minimum concentration was 0.93 ± 0.19 μg/ml and 0.57 ± 0.10 μg/ml, respectively ($P < 0.05$). The effect site concentration of remifentanil of both groups was set 1.00 ng/ml initially. Target concentration of infused remifentanil was 1.02 ± 0.21 ng/ml. Heart rate between two groups didn't show any significant difference ($P > 0.05$) (Fig. 2). And two groups showed no difference in respiratory rates ($P > 0.05$) (Fig. 3). As for minimum SpO_2, in group 1 it was 95.86 ± 4.65, and 95.26 ± 4.72 in group 2. It had no difference, neither. As for systolic and diastolic blood pressures of two groups, there were no significant

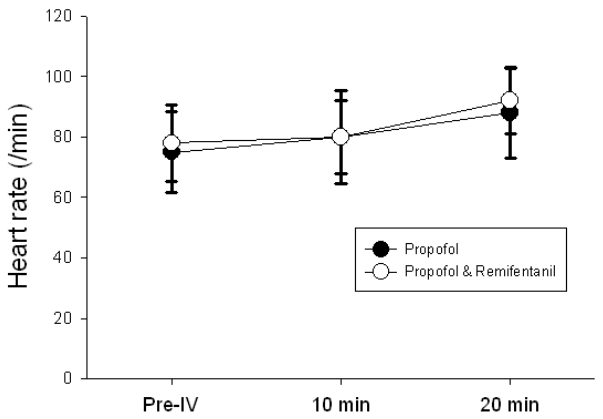

Fig. 2. Heart rate: There was no difference concerning heart rate between two groups ($P > 0.05$).

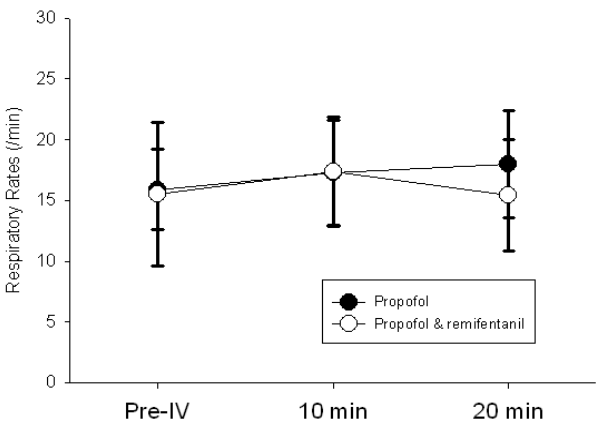

Fig. 3. Vital sign – Respiratory rate; No significant difference of respiratory rates between two groups existed ($P > 0.05$).

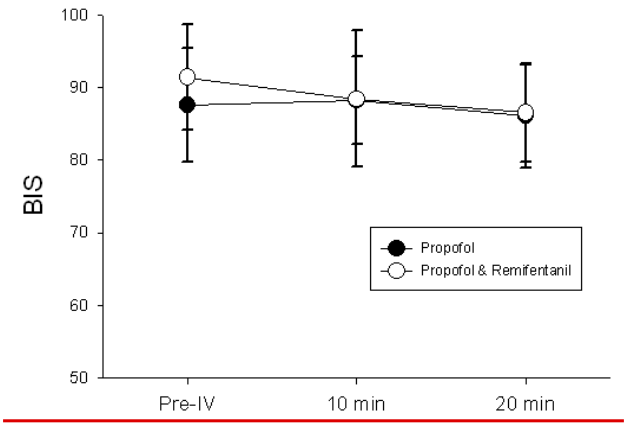

Fig. 4. BIS. Overall BIS in 2 groups were similar and were not different between 2 groups ($P > 0.05$).

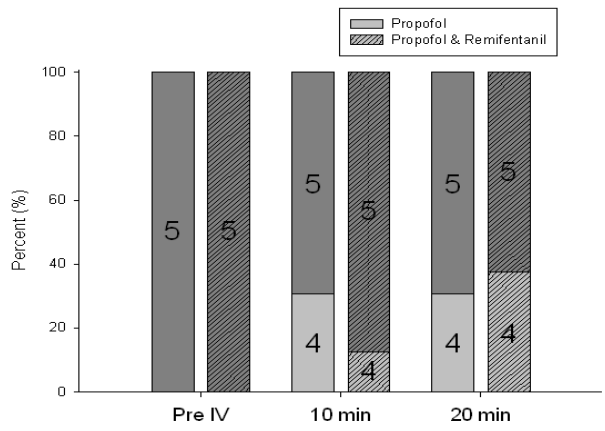

Fig. 5. Sedation scale (OAAS/S). OAAS between two groups were not different ($P > 0.05$). At each interval, answered score was indicated at the middle of each bar.

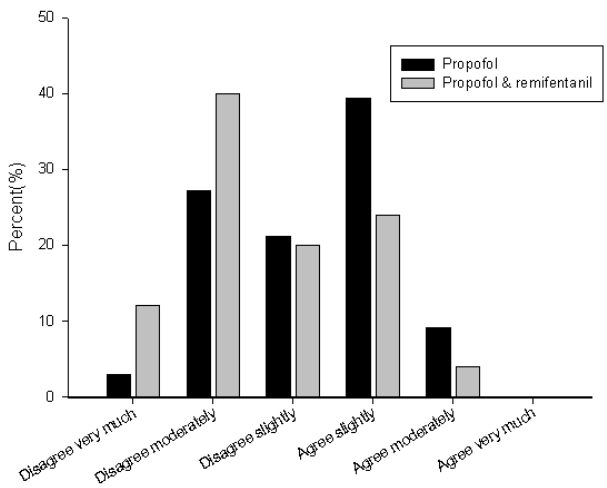

Fig. 6. Proportion of patients' response at the question "I felt pain during surgery".

differences ($P > 0.05$).

BIS in 2 group were similar on the whole and were not different ($P > 0.05$) (Fig. 4). Average BIS in group 1 was 87.18 ± 5.74 and average BIS in group 2 was 88.38 ± 7.06. OAAS between two groups has been shown no difference ($P > 0.05$) (Fig. 5). And we used a questionnaire which was utilized to assess patient's subjective satisfaction with sedation. Especially, the differences in pain sensation of 2 groups during procedure were statistically significant ($P < 0.05$) (Fig 6).

DISCUSSION

The objectives of this study were to compare the efficacy of TCI conscious sedation with propofol and propofol combined with remifentanil and to suggest the proper target effect site concentration of propofol and remifentanil for the surgical extraction of impacted teeth. Target concentration of propofol when used only was higher than when used with remifentanil. Mean target concentration of infused propofol when used only was 1.13 ± 0.21 μg/ml, that of propofol when used with remifentanil was 0.72 ± 0.26 μg/ml. Vital signs between 2 groups were not different throughout sedation procedure.

Differences in BIS and OAAS/S between 2 groups were not significant. We investigated patients' subjective satisfaction score by a questionnaire and it showed patients' perception about pain decreased during sedation when propofol was administered along with remifentanil compared to a single use of propofol.

We didn't have any case that patient was administered remifentanil only. There are not many trials investigating remifentanil TCI doses required for conscious sedation [11]. Remifentanil itself doesn't have any anxiolytic or sedative effects at low doses. Remifentanil is a potent, synthetic opioid narcotic that has a rapid onset of action and a short duration of effect. It showes few cardiovascular side effects, however, it can induce respiratory depression and spontaneous respiration block. So, remifentanil is recommended to use with concurrent administration of a pure sedative [12].

Remifentanil, used to produce general anesthesia, is known to interact with propofol synergistically. Increased concentrations of opioids led to less propofol requirements to maintain a satisfactory anesthesia. In one study, the effect of altering the blood remifentanil concentration during anesthesia to be dose-dependent. And the effect of reducing the required amount of propofol and altering the cardiovascular response during anesthesia was most prominent with a relatively high remifentanil concentration [13].

Both propofol and remifentanil are short acting anesthetic agents, so it would be safe to say that this is a promising combination. In total IV anesthesia, remifentanil is frequently combined with propofol for this reason. In one study, the predictive performance of the available remifentanil pharmacokinetic parameter sets in TCI of remifentanil during total IV anesthesia with propofol was evaluated. There could be bias and inaccuracy between target remifentanil concentration and measured concentration; they said it is acceptable [14].

Hypotension and respiratory depression are major side effects of propofol. In one study, propofol in dosages of 0.5-1.5 mg/kg decreased the systolic and diastolic blood pressure and heart rate during the GI procedure and increased after an initial value [15].

As for target plasma concentration of propofol, there could be various factors such as ages, anxiety and so on. Propofol extraction rate by is high, so clearance is dependent on liver blood flow. In addition, propofol itself has been shown to decrease cardiac output leading to decrease hepatic blood flow and decreased clearance. We can induce that older patient who has reduced

cardiac output would lower propofol clearance. Besides, one study showed that there was no statistical significant different dose of propofol infused between anxious and non-anxious patients during dental treatment [16].

Propofol has rapid onset and sedation induction and lower frequency of vomiting and tremor, so it is a widely used drug. But when used only, side effects such as pain and unpleasant feeling and unvoluntary movement and depressed blood pressure and bradycardia could be appeared. Pain mechanism when propofol infused is not clearly determined. However, it was suggested that propofol activates kinin cascade from vessel wall, Klement and Arndt said it is relevant to aqueous concentration of propofol [17]. Methods to decrease pain and unpleasant feeling were studied. Propofol infusion along with opioids such as remifentanil is said to be one of the appropriate methods [18]. Our present study assessed patients' satisfaction score with sedation by using a questionaire and found out patient felt less pain during sedation using propofol with remifentanil rather than propofol only.

In conclusion, we could induce effective conscious sedation with lower effect site target concentration of propofol when propofol was combined with opioids such as remifentanil in dental treatment. In this case, vital sign, BIS, OAAS/S were not different compared to single use of propofol. However, subjective pain perception during sedation was lower in case of combined infusion with remifentanil rather than when only propofol was infused.

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