

Target Controlled Conscious Sedation with Propofol and Remifentanil for the Extraction of Impacted Wisdom Teeth

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Abstract

매복지치 발치 시, Propofol과 Remifentanil을 이용한 목표조절농도주입(TCI) 의식하 진정

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방보영 · 신터전 · 서광석 · 김현정

배경: 매복지치의 수술적 발치 시 propofol과 remifentanil을 이용한 목표조절농도주입(Target controlled infusion) 의식하 정주진정법의 적절한 주입농도를 제시하고 그 안전성을 평가하고자 하였다.

방법: 매복지치의 수술적 발치가 예정된 미국마취학회 신체 등급 분류 1, 2에 속하는 15-65세, 142명(여 83명, 남 59명)의 환자를 대상으로 소급 연구하였다. 환자는 수술 전 목표조절농도주입법을 이용한 의식하 진정법 사용에 관한 동의서를 작성하였다. 정맥내 삽관을 시행하고 수액을 공급을 시작하고, 4-5 L/min의 산소를 비관을 통해서 공급하였다. Propofol과 remifentanil의 초기 목표 혈중농도는 각각 0.5 µg/ml와 1.0 ng/ml로 정하였다. 수술 중, 환자의 불안 통증 정도에 따라 목표농도를 조절하였으며 최저 농도와 최대 농도, 평균 농도, 주입된 총 용량을 기록하였다. 또한 수축기 혈압과 맥박 수, 산소포화도, 호기 말 이산화탄소량을 수술 시작 전, 수술 중 5분 간격으로 확인하고 기록하였다. 모든 측정치는 평균 ± 표준편차나 환자의 수, 초기 측정치에서의 백분율 편차로 표시하였다.

결과: 수술 동안의 목표 혈중농도의 평균은 propofol은 0.54 ± 0.11 µg/ml이고, remifentanil은 1.11 ± 0.30 ng/ml였다. 수술 중 조절된 최대농도는 propofol은 0.6 ± 0.23 µg/ml이고, remifentanil은 1.3 ± 0.63 ng/ml였다. 이는 의식하 진정에 해당되는 범위의 농도라고 할 수 있겠다. 진정동안 환자의 언어적 의사소통은 유지 되었으며 산소 포화도는 4-5 L/min 의 산소 보충 하에 98%이상으로 유지 되었다. 수축기 혈압과 맥박은 대부분의 환자에서 정상변위범위(± 20%)내에서 유지되었다.

결론: 본 연구는 목표조절 농도주입 의식하 진정에서 사용된 농도(propofol 0.5 µg/ml, remifentanil 1.0 ng/ml)는 안전하게 의식하 진정을 가능한 것을 보여준다. 이는 치과 치료 시 목표조절농도 주입 의식하 진정법에서 적절한 목표농도를 제시한다. (JKDSA 2010; 10: 159~165)

핵심용어: Target controlled infusion; Propofol; Remifentanil; Teeth extraction

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INTRODUCTION

Pain and anxiety have been considered as main factors influencing patient's attitudes for dental treatments. According to serial UK Adult Dental Health Surveys, around half of the UK's adults were anxious

about dental treatment (Leitch et al, 2007). Moreover, uncontrolled pain and anxiety can evoke harmful responses such as hypertension and tachycardia during dental treatment. For controlling pain and anxiety effectively and safely, new sedation methods have been needed. Recently, a number of more innovative sedation techniques have been investigated including polypharmacy (Ganzberg et al, 2002), intravenous sedation with target controlled infusion (TCI) and patient maintained sedation (Chapman et al, 2006) in dentistry.

The popular intravenous sedatives in dentistry are benzodiazepine or propofol. Sometimes, opioids can be combined with propofol or benzodiazepine (Kwak et al, 2006), because they can minimize adverse reactions of drugs and improve pharmacological effects (Amrein et al, 1995).

Generally, potent opioids are excellent for pain control but not used alone in sedation because they do not provide adequate level of sedation and may produce undesirable side effects (Kwak et al, 2006) such as nausea, vomiting, bowel dysfunction, urinary retention, pruritus, sedation and respiratory depression or even arrest. On the other hand, a sedative alone can provide sedation, anxiolysis and amnesia (Kwak et al, 2006), but combining sedatives with opioids allows reducing dosage and synergism (Whitwam, 1995). Among them, considering unique pharmacokinetic and pharmacodynamic characteristics (Alvarez et al, 2000) as well as recovery profiles (Glass et al, 1993), propofol and remifentanil are considered as one of ideal drug combinations for sedation.

Target controlled infusion (TCI), a computer-assisted intravenous administration of drugs, allows the target plasma and effect-site concentration to reach equilibrium and may produce consistent pharmacodynamic effects (Rai et al, 2007). TCI was first described by Schwilden et al. in early 1980s (Paul et al, 2006). A microcomputer was interfaced to an infusion pump and drug was infused at a rate to replace drug eliminated and transferred to the peripheral tissue (Ronald et al, 2005). The algorithms calculate the infusion

rates required to obtain the desired plasma or effect site drug concentration by using pharmacokinetic modeling (Ronald et al, 2005). Since TCI has been introduced, many researchers have estimated parameters, creating their own pharmacokinetic sets 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). Now, open TCI systems are provided by many manufacturers, and there is a choice of different dosing models for propofol, remifentanil and other opioids.

TCI have been more rapid and accurate in achieving and maintaining desired levels of anesthesia (Glen, 1998) and more effective in maintaining cardiovascular stability compared to traditional weight adjusted infusions (Castro, 2003). Therefore, TCI sedation with propofol and remifentanil may allow us a safe and predictable sedation. However, the reports of TCI sedation with propofol and remifentanil are very rare in dentistry up to now.

Since 2006, TCI conscious sedation with propofol and remifentanil for daily clinical practice has been used in Seoul National Dental Hospital. The aim of this study is to describe one year experience of TCI sedation with propofol and remifentanil in order to establish suitable plasma target concentration of propofol and remifentanil for the extraction of impacted wisdom tooth.

PATIENTS AND METHODS

TCI conscious sedation with propofol and remifentanil for the extraction of impacted wisdom teeth was evaluated retrospectively by reviewing of patients' chart. The TCI system that incorporate the Schnider set for propofol and the Minto set for remifentanil was used. In this study, 142 patients (female 83, male 59) between the age of 15 and 65 yr, American Society of Anesthesiologists physical status grade P1 and P2, who were scheduled for surgical extraction of impacted teeth were participated in this study. The

Table 1. Demographic Data (n = 142)

Sex (F / M)	83 / 59
Age (yr)	26 ± 9
Weight (kg)	60 ± 12
Height (cm)	165 ± 8
ASA grades (P1 /P2)	119 / 23

Data are mean ± S.D.

exclusion criteria were history of drug addiction or current use of opioids, allergy to propofol and opioids and upper respiratory infection (URI) symptom.

Patients were instructed to fast 8 h before their surgical appointment and to bring a responsible person to accompany them home after sedation. A written consent about TCI sedation procedure was taken. After inserting a cannula into a vein, a continuous fluid therapy with Hartmann's solution was started to compensate dehydration. Oxygen saturation, end tidal carbon dioxide tension, systolic blood pressure and heart rate were recorded before starting TCI and at 5-min interval during sedation. During sedation, 100% oxygen was administrated via a nasal cannula at a rate of 4–5 L/min. Before starting remifentanil and propofol, 2–3 ml of 1% lidocaine was injected through an intravenous cannula to reduce injection pain of propofol. The starting target plasma concentration of propofol and remifentanil was set at 0.5 µg/ml and 1.0 ng/ml. During the procedure, the target plasma concentration level was changed according to patients' response and surgeon's request. The target plasma concentration and total infused dose and time were recorded.

For local anesthesia, 3–4 cartilages of 2% lidocaine containing 1 : 100,000 epinephrine for each wisdom teeth were injected at the operation site. At the end of the operation, patients were sent to the recovery room and postoperative data were collected. The patients were asked immediately after the operation if they were relaxed and satisfied with the sedation they received. After surgeon's evaluation to patients' condition, patients were discharged. Collected data are

Table 2. Changes of Target Controlled Infusion Level

	Propofol (µg/ml)	Remifentanil (ng/ml)
Initial	0.50	1.00
Terminal	0.56 ± 0.19	1.20 ± 0.56
High	0.60 ± 0.23	1.30 ± 0.63
Low	0.50 ± 0.05	0.96 ± 0.14
Mean	0.54 ± 0.11	1.11 ± 0.30

Data are mean ± S.D.

infused propofol and remifentanil dose, total infusion time, total operation time, oxygen saturation, end tidal carbon dioxide tension, systolic blood pressure, heart rate, and demographic information. Data are presented as mean ± SD, number of patients or % deviation from initial values and calculation was performed by SAS 9.2 β (SAS Institute Inc. Cary, NC, USA).

RESULTS

In this study, 142 patients were enrolled and their demographic data are presented (Table 1).

The mean target controlled infusion levels are shown Table 2. The mean concentrations were 0.54 ± 0.11 µg/ml of propofol and 1.11 ± 0.30 ng/ml of remifentanil throughout the procedure. The maximum concentrations were 0.6 ± 0.23 µg/ml of propofol and 1.3 ± 0.63 ng/ml of remifentanil. Total amounts of drug infused were 172.7 ± 89.67 mg remifentanil and 98.9 ± 83.30 mg propofol. The mean infusion time for propofol and remifentanil were 53.6 min and 49.8 min and the mean operation time was 46 min.

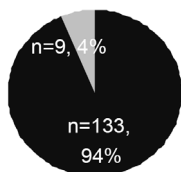
Oxygen saturation and end tidal carbon dioxide tension, systolic blood pressure and heart rate are summarized in Table 3 and 4. During sedation, oxygen saturation was maintained above 98% and the mean oxygen saturation was 100% with oxygen supplement as seen Table 3. Mean end tidal carbon dioxide tension was within normal range in all patients. Although 59 patients (42%) showed over 37 mmHg in their highest level, there weren't hypoventilation cases because all patients' oxygen saturation were over

Table 3. Oxygen Saturation and End Tidal Carbon Dioxide Tension

	Oxygen Saturation (%)	End Tidal Carbon Dioxide Tension (mmHg)
Initial	100 ± 0.7	32 ± 8
Terminal	100 ± 0.5	33 ± 9
High	100 ± 0.4	34 ± 10
Low	100 ± 1.0	27 ± 9

Data are mean ± S.D.

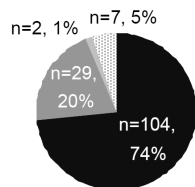
Systolic Blood Pressure (Low)



■ Within 20% ■ Out of 20%

Fig. 1. Systolic Blood Pressure Fluctuation I. (The highest level based on initial value, n = 142)

Systolic Blood Pressure (High)



■ Within 20%
 ■ Out of 20% - immediately after L/A injection
 □ Out of 20% - after stopping infusion
 □ Out of 20% - unstable

Fig. 2. Systolic Blood Pressure Fluctuation II. (The lowest level based on initial value, n = 142)

98%.

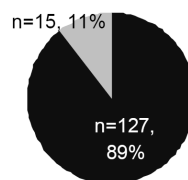
Systolic blood pressure was tried to maintain below 140 mmHg which means the upper normal limit of hypertension. Twelve (8%) out of total 146 patients were recorded high blood pressure as more than 140 mmHg and managed by labetalol or esmolol. Fifty six

Table 4. Changes of Systolic Blood Pressure and Heart Rate during Sedation

	Systolic Blood Pressure (mmHg)	Heart Rate (bpm)
Initial	123 ± 20	77 ± 14
High	144 ± 21	98 ± 15
Low	115 ± 18	71 ± 12

Data are mean ± S.D.

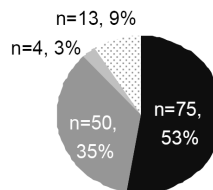
Heart Rate (Low)



■ Within 20% ■ Out of 20%

Fig. 3. Heart Rate Fluctuation I. (The highest level based on initial value, n = 142)

Heart Rate (High)



■ Within 20%
 ■ Out of 20% - immediately after L/A injection
 □ Out of 20% - after stopping infusion
 □ Out of 20% - unstable

Fig. 4. Heart Rate Fluctuation II. (The lowest level based on initial value, n = 142)

patients (35%) showed tachycardia, over 100 bpm, and 52 patients of those patients were controlled by increasing propofol, remifentanyl or propofol and remifentanyl level, up to 1.5 µg/ml of propofol and 2.5 ng/ml of remifentanyl.

An analysis of hemodynamic fluctuations based on

patients' initial systolic blood pressure and heart rate was conducted. The results are presented on Fig. 1, 2, 3 and 4. In the highest systolic blood pressure and heart rate value, 104 patients (73%) and 75 patients (53%) are within 20%. In patients' lowest systolic blood pressure and heart rate, 133 patients (94%) and 127 patients (89%) are within 20%.

DISCUSSION

In this study, the data of TCI conscious sedation and the changes of oxygen saturation, end tidal carbon dioxide tension, systolic blood pressure and heart rate during sedation, using propofol and remifentanyl, were analyzed retrospectively. According to the data, initial target plasma concentration as 0.5 $\mu\text{g/ml}$ of propofol and 1.0 ng/ml of remifentanyl may be safe for the extraction of impacted wisdom teeth.

To my best knowledge, TCI sedation with propofol and remifentanyl was used for the first time in dentistry although it is widely used in medicine, even though TCI sedation with only propofol or remifentanyl for dental patient could be found. Reports about conscious sedation are rare because almost previous studies about TCI have performed deep sedation and not designed clearly as conscious sedation. Although it is improper to compare them with my data because they are deep sedation, it is meaningful to establish this TCI procedure as a conscious sedation. In previous propofol TCI sedation for oral surgery, the mean concentration was 1.1 $\mu\text{g/ml}$ immediately before local anesthesia and 2 $\mu\text{g/ml}$ at the end of procedure (Leitch et al, 2003). In medical procedure like an awake fiber optic intubation, doctors apply propofol TCI, remifentanyl TCI or propofol and remifentanyl TCI sedation for procedure as well. In the case using remifentanyl TCI, the mean level of concentration was 3.2 ng/ml and in propofol TCI, that level of concentration was 1.3 $\mu\text{g/ml}$ (Rai et al, 2008) and up to 4.5 $\mu\text{g/ml}$ (Irwin et al, 1997). During the fiber optic procedure the mean concentrations of propofol and remifentanyl TCI ranged between 1.5 and 3.5 μg

/mL and between 1.0 and 5.0 ng/mL each (Cafiero et al, 2008). For nasotracheal intubation using propofol and remifentanyl TCI, the initial concentration setting was 2.5 $\mu\text{g/mL}$ of propofol and 1.5 ng/mL of remifentanyl (Lallo et al, 2009). Previous reports, fiber optic intubation or endoscopy, have shown higher level of amnesia and it has been suggested that this is dose related and a kind of deep sedation (Leitch et al, 2003).

In this study, the mean plasma concentration was $0.54 \pm 0.11 \mu\text{g/ml}$ of propofol and $1.11 \pm 0.30 \text{ng/ml}$ of remifentanyl throughout the surgical procedure. This means plasma concentration required for adequate sedation was lower than in previous medical studies and can be categorized into conscious sedation.

There is a large degree of pharmacokinetic and pharmacodynamic variability, producing a significant variability in the dose response relationship in clinical practice. Oversedation may result in cardiac or respiratory depression, whereas inadequate sedation may result in discomfort and potential morbidity. The regimen of TCI used in this study was adequate for anxiety and pain control and preventing side effects related to oversedation. All patients were under conscious sedation maintaining verbal communication throughout the procedure.

Propofol and remifentanyl is the ideal combination of intravenous anesthetics (Holas et al, 1999; Reyle et al, 2000; Kaidan et al, 2001). Propofol is the drug of choice when a rapid recovery is required (Paul et al, 2006). A carefully titrated propofol subhypnotic infusion of 0.5–0.6 $\mu\text{g/ml}$ (Dominique et al, 2002), following a propofol lethal dose (LD) of 0.25 to 0.5 mg/kg , produces a stable level of conscious sedation with minimal side effects and a short recovery period. The advantages of using propofol are the absence of hangover and less nausea and vomiting after sedation. The cardiovascular depressant may be appeared by propofol but can be minimized by titration and the use of TCI (Paul et al, 2006). Most frequent side effect of propofol is pain on injection but this pain can be controlled by lidocaine administration (Cillo

et al, 1999).

Remifentanil is characterized as an ultrashort acting opioid, therefore it is best administered in a continuous infusion and adjunct use for sedation or analgesia (Paul et al, 2006). Many studies showed the only use of remifentanil for conscious sedation could be associated with undesired side effects (Servin et al, 2002) and remifentanil had narrow therapeutic index. However, it can be beneficial when it is used with other sedatives because it has its additional analgesic and anti-tussive effect (Rai et al, 2008).

Nowdays, combination of drugs can provide an acceptable safety and ease of titratability. By acting synergistically, combination of drugs can reduce the dose of each single drug. For example, the combination of propofol and fentanyl has produced a more rapid recovery and better stress response than use of propofol only (Glass et al, 1991). The interaction between propofol and remifentanil can also be synergistic (Kaidan et al, 2001). The ability to combine propofol with potent, rapid and short acting opioid analgesics such as remifentanil enables the dose reduction of propofol (Morgan et al, 2006). Therefore, combination of remifentanil and propofol in dental TCI sedation seems to be optimal to minimize side effects by reducing doses of each drug and enhance their pharmacological effects.

In general, hemodynamics and oxygenation values are recommended remaining within a 20% range compared to basal line (Joseph et al, 2006). Sixty seven patients' heart rate values (47%) and thirty eight patients' blood pressure values (27%) are out of 20% range limit. Each Patient's chart was reviewed and the relation between the injection of local anesthetics and hemodynamic changes were checked. Fifty patients' heart rate (35%) and twenty nine patients' blood pressure (20%) increased immediately after the injection of local anesthetics containing 1 : 100,000 epinephrine and recovered within 10 min. Four patients' heart rate (3%) and two patients' blood pressure (1%) increased after stopping infusion of propofol and remifentanil and recovered before leaving

a post-anesthetic care unit. The rest of the patient (13 patients in heart rate and 7 patients in blood pressure) showed ongoing unstable data 10 min after the injection of local anesthetics. Therefore anesthesiologist and surgeons need to give vigilance to the patients when injecting local anesthetics containing epinephrine. Regarding to oxygenation values, all patients showed over the 98% oxygen saturation because the patients were applied 4-5 L/min of oxygen via a nasal cannula.

The aim of this study is to evaluate the safety of propofol and remifentanil TCI used in the SNU Dental Hospital for the extraction of impacted wisdom teeth. However there are some limitations that do not fulfill the high level of clinical trials. This study was performed retrospectively and the data about sedation satisfaction related to the efficacy of sedation were not collected. For more sophisticated investigation, the prospective, randomized, double blinded and multi-centered clinical trial is needed. It is also necessary that check the satisfaction score of anesthesiologists, surgeons and patients to evaluate the TCI efficacy statistically.

In conclusion the target concentration of propofol and remifentanil for the extraction of impacted wisdom teeth in healthy patients may be $0.54 \pm 0.11 \mu\text{g/ml}$ and $1.11 \pm 0.30 \text{ ng/ml}$ considering a safe dental conscious sedation without side effects, especially respiratory depression.

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