Report

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Propofol-remifentanil TCI sedation for oral surgery

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ABSTRACT

Background and objectives: To investigate the safety and efficacy of a propofol-remifentanil target controlled infusion (TCI) sedation technique for oral surgery.

Methods: This prospective study involved patient and registered nurse (RN) questionnaires to assess the efficacy of sedation during surgery. Outpatients having dental extractions in a private office-based practice with TCI sedation were monitored with a Sleep Apnoea Monitor (SAM) to measure the number of Oxygen Desaturation Events (ODEs), defined as a drop in blood oxygenation to below 94%.

Results: Patient- and RN-assessed questionnaires showed a high standard of perceived sedation efficacy, independent of patient BMI. The proportion of patients having one or more ODEs was greater in higher BMI categories: underweight (20.0%), normal (47.9%), overweight (68.2%) and obese (81.8%). The odds of at least one ODE was estimated to be 1.2 times greater for each unit increase in BMI (OR 1.2; 95% CI 1.1-1.3), and at a fixed BMI, the odds of at least one ODE was estimated to be 2.6 times as great for a male as a female (OR 2.6; 95% CI 1.2-5.52). Age, patient nervousness and American Society of Anesthesiologists (ASA) classification were not associated with ODEs.

Conclusions: The TCI technique had a high standard of efficacy, and there were no adverse safety outcomes. Higher BMI and male sex were found to be independently associated with predictors of ODEs during oral surgery under propofol-remifentanil TCI sedation.

INTRODUCTION

Ideal sedation should be both safe and effective. To be effective it must relieve the patient of pain and anxiety and provide for optimal operating conditions (Sims et al., 2012). Target Controlled Infusion (TCI) describes a drug delivery system using infusion pumps to achieve a desired plasma and brain concentration level. Propofol and remifentanil are suited to TCI because they have a fast onset and short half-life (Fono et al., 2007; Todd, 2005). The main concern about safety with potent intravenous anaesthetic agents such as these is the potential to over-sedate a patient and compromise their respiration. Propofol-remifentanil TCI sedation is carried out by simultaneous propofol and remifentanil infusion, administered by pumps with pre-programmed algorithms. A patient's height, weight, age and sex are entered into the algorithms, and a desired concentration in plasma or the brain is selected. The algorithms then calculate the drug dose to be administered and drive the pump to reach the desired concentration predictably and rapidly. TCI accommodates the patient's response to the drug dose, by allowing the operator to easily adjust the dosage as required (Höhener et al., 2008).

In the practice of sedation there is a conflict between safety and efficacy. Deep sedation naturally provides very effective sedation, but may be more dangerous. Light sedation is unlikely to compromise respiration but may leave dissatisfaction with its efficacy. Recently, higher Body Mass Index (BMI) has been linked with a greater risk of respiratory events during non-TCI continuous infusion propofol sedation during endoscopic procedures (Coté et al., 2010; Mehta et al., 2013; Wani et al., 2011).

The aim of this study was to investigate the safety and efficacy of propofol-remifentanil TCI during oral surgery, by use of questionnaires to assess efficacy and a Sleep Apnoea Monitor (SAM) to measure safety-related oxygen desaturation events (ODEs). This aim further involved exploring whether patient factors such as age, nervousness, American Society of Anesthesiologists (ASA) classification and Body Mass Index (BMI) had a significant impact on the safety or efficacy of TCI sedation.

METHOD

Ethical approval was granted by the Southern Regional Ethics Committee of New Zealand prior to commencement of the study. The prospective study was carried out in a private practice day-stay unit providing outpatient conscious sedation for Oral and Maxillofacial Surgery (OMS) procedures. A total of 174 patients were recruited into the study between February 2011 and December 2011. The two surgeons involved in the study carried out 67 (44.7%) sedations (JB) and 83 (55.3%) sedations (DC). The two surgeons (DC is an oral surgeon and JB an oral and maxillofacial surgeon) work in a joint private practice providing outpatient oral surgery. In addition, they each hold consultant appointments to the Tauranga Public Hospital. They have both been practising IV sedation for over 20 years and have both been using propofol for sedation for over 10 years. They began using remifentanil in combination with propofol in the method described in this paper 4 years ago. All of the patients in this study had dental extractions undertaken, either simple or surgical. No information on the complexity of the extractions was collected. At the time of the initial consultation, informed consent for the study was gained. The inclusion criterion for the study was limited to those over eighteen years of age who were scheduled for exodontia under propofol and remifentanil TCI sedation in the private practice setting. Complex medical patients in this private practice with an American Society of Anesthesiologists (ASA) classification of IV or V are routinely referred for hospital-based treatment, and therefore were not recruited into the study. Patients were not eligible for inclusion in the study if they could not provide informed consent, did not speak English, were administered midazolam during surgery or if they did not return their patient satisfaction questionnaire.

When indicated, pre-operative antibiotics (Co-Amoxy Clav 625mg or Clindamycin 300mg) were taken as an oral dose two hours prior to the procedure. Collection of patient height and weight measurements was done routinely as required

for use of the target-controlled infusion (TCI) pump system (Alaris Asena Pump, Carefusion), and these were later used to calculate individual BMI values using the formula of weight(kg)/(height(m))2. Patient sex, age, height and weight were entered into the Schnider effect site algorithm for propofol infusion, and the Minto effect site algorithm for remifentanil. A 1% solution of propofol (Fresofol® 1%, Fresenius Kabi New Zealand Ltd) was used undiluted as a 10 mg/ml solution, and a 1mg vial of remifentanil hydrochloride (Remifentanil-AFT 1mg, AFT Pharmaceuticals Ltd) was diluted with 50 ml of saline to provide a 20 µg/ml solution. Profound local analgesia was achieved using a single local anaesthetic or a combination of two or more local anaesthetics, limited to Lignocaine 2% with adrenaline 1:100,000 (Xylestein-A, 3M ESPE, 3M Deutchland GmbH), Articaine 4% with adrenaline 1:100,000 (Septanest, Ivoclar Vivadent, Septodont) and Bupivacaine 0.5 % (Marcain® without adrenaline, AstraZeneca Pty Ltd). If breakthrough pain occurred during surgery, further local anaesthetic was administered at that point to achieve local analgesia before continuing with the surgery.

Sedation efficacy was measured from two subjective perspectives; that of a registered nurse in the clinical team during surgery, and that of the patient after surgery. In our study the clinical team consisted of an oral surgeon and two registered nurses (RN), one acting as the surgical assistant and the other assisting in providing the sedation. The RN assisting with the sedation categorised the overall quality of sedation into one of four outcomes: excellent, good, satisfactory or poor. The guidelines for these categories are described in Table 1. In addition to the behaviours described in Table 1, behaviours such as reacting to the local anaesthetic injections, excessive talking, restlessness, crying or coughing were considered negative factors. High quality sedation desirable for surgery was indicated by a comfortable, still, settled and quiet patient. The subjective assessment of quality also took into account how persistent and difficult to control the negative factors were.

Table 1. Quality of Sedation for Outpatient Oral Surgery Procedures

Excellent	Surgery was not impaired by the patient's behaviour in any way. The patient was comfortable, still and content without talking.
Good	Minor disruptions occurred during surgery, but were easily and quickly dealt with. For example, the patient's behaviour may have included nose scratching, talking or moving their arms.
Satisfactory	Surgery occasionally needed to be momentarily stopped, but the overall momentum of the operation was not significantly slowed.
Poor	Continual disruption of the surgery occurred. Breaks in the operating time were required to manage the patient's behaviour.

A patient satisfaction questionnaire was used to obtain a subjective evaluation of sedation efficacy from the patient's perspective. It consisted of four simple questions (Figure 1), modified from those used by Lieblich in a study involving anaesthesia (Lieblich, 2004). Before leaving the practice after surgery, patients were provided with the questionnaire to fill out the following day. The questionnaire was either returned at their follow-up appointment or posted in a provided envelope if no follow-up appointment was arranged.

In-keeping with routine sedation protocols, oxygen was administered via a nasal cannula running at two litres per minute, and patient safety was closely monitored during surgery by use of continuous pulse oximetry, side stream capnography, intermittent automated non-invasive blood pressure and bispectral index (BIS) monitoring. In addition to the standard monitoring protocol, study participants were connected to a Sleep Apnoea Monitor (SAM) (PalmSAT® 2500, Nonin Medical). This was attached to patients by a finger clip on the opposite limb to the blood pressure cuff, to avoid false drops in saturations. The SAM took continuous measurements of oxygen saturation data. The SAM was not alarmed, hence the clinical team responded only to the other routine monitoring devices. Using nVision software (Nonin Medical), waveform and digital data was electronically retrieved from the SAM and was analysed after the surgery. An ODE was considered to be a drop in oxygen saturation below 94%. The SAM was attached to each participant for the complete duration of the surgery. This was defined as the time between starting the infusion pumps and the operator's removal of gloves.

DATA ANALYSIS

Following the computation of descriptive data, statistical analysis was undertaken to explore the relationship between oxygen desaturation events and patient age, sex, BMI and ASA classification. Bivariate analyses were conducted using t-tests, one-way analysis of variance and chi-squared tests of association. Binary logistic regression was used to model the joint effects of predictors on the probability of oxygen desaturation events. Diagnostic checks were carried out to confirm the appropriateness of these parametric procedures. All statistical analyses were performed using Minitab, version 17 (Minitab Inc, 2013), and a P value of less than 0.05 was considered to be statistically significant.

Figure 1. Patient Satisfaction Survey for Outpatient Sedation* *Please circle the appropriate number*

1. How nervous were you before your procedure?
   Not at all nervous 1.....2.....3.....4.....5 Extremely nervous
2. How much do you recall about the actual surgical procedure after the injection in your arm?
   No recollection 1.....2.....3.....4.....5 The entire surgery
3. Would you recommend this type of sedation to a friend or family member?
   Not recommend 1.....2.....3.....4.....5 Recommend
4. If you needed the procedure again would you choose the same type of sedation?
   Yes_____ No_____; if no, why not? _____

** Modified from S.E Lieblich (2004), with permission to publish from the author*

Figure 2. Estimated probability of one or more ODEs versus BMI.

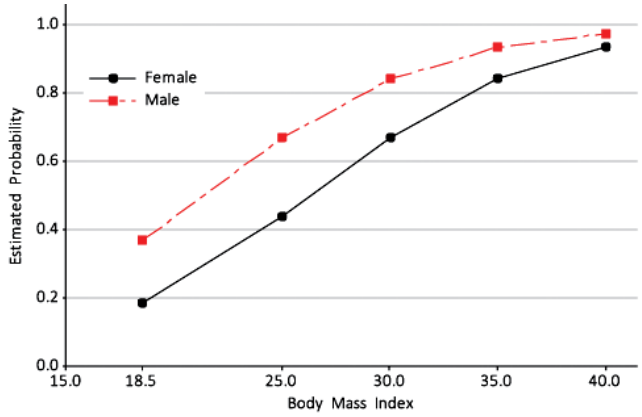
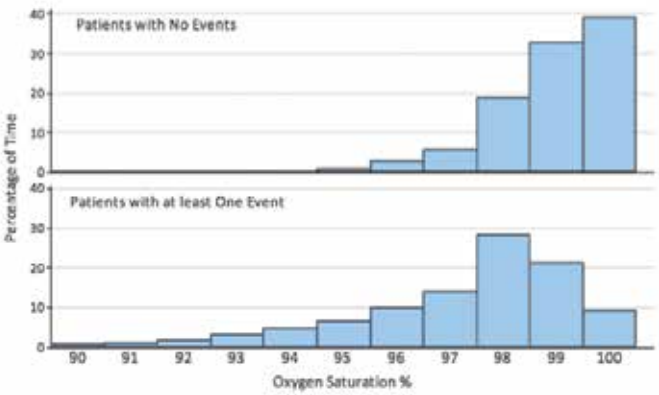


Figure 3. Pooled percentages of surgical time spent at different oxygen saturation levels.



RESULTS

Out of the 174 patients recruited, 21 did not return their questionnaire and 3 were administered midazolam during surgery. This resulted in a total of 150 patients included in the study and 150/174 (86.2%) included out of those recruited. Participants consisted of 100 (66.6%) females and 50 (33.3%) males. The average patient age was 38 years, and the age ranged from 18 to 73 years. There were 96 (64.0%) patients classified as ASA Class I, 52 (34.6%) patients classified as ASA Class II and two (1.3%) patients classified as ASA Class III. The Oral Surgeons involved in the study carried out 67 sedations (JB) and 83 sedations (DC). There were no adverse safety outcomes.

Sedation quality, assessed by the registered nurse present (Table 1) showed that the perceived quality of sedation was of a high standard. Of the 150 patient surgeries included in the study, 116 sedations (77.3%) were rated as excellent, 32 sedations (21.3%) were rated as good, 2 sedations were rated as satisfactory (1.3%) and no sedations were rated as poor. Although the two sedations rated as satisfactory were both in the overweight BMI group, the RN-assessed sedation quality data showed no statistically significant associations with patient BMI. Three patients were withdrawn from the study because they were administered midazolam, and these sedation sessions were rated as satisfactory by the RN.

The patient satisfaction questionnaire (Figure 1) results showed a high level of perceived efficacy of the TCI sedation. All participants answered 'Yes' when asked if they would choose the same type of sedation if they needed the same procedure again. The average score for recommending this type of sedation to a friend showed a high level of recommendation, averaging 4.9 on the scale of 1 to 5. A low level of recall regarding the surgical procedure after intravenous access was indicated by an average of 1.7 on the scale of 1 to 5. Participants showed a variable level of nervousness prior to the procedure: scores of 4/5 and 5/5 were recorded by 47 patients (31.3%), of which the majority (87.2%) were females. The average score for nervousness was 2.8 out of 5, and the greatest number (30.6%) of participants scored their nervousness as a 2 out of 5. Nervousness before surgery was not associated with sedation efficacy as assessed by the other three patient survey questions and the RN sedation quality rating; neither was it associated with patient BMI or number of ODEs.

Participants were grouped into underweight BMI (<18.5), normal BMI (18.5-24.9), overweight BMI (25-29.9) and obese BMI (≥30). The average age in each BMI group was similar for those with underweight and normal BMI, which were 34.4 years and 34.5 years respectively. The average age was higher in the overweight BMI group (41.8 years), and higher again in the obese BMI group (45.7 years). There was a statistically significant ($p<0.05$) difference in BMI distribution between females and males. Males were significantly more overweight and females were significantly more underweight.

Patients were also grouped into those having no events, a single event and multiple events. Higher BMI had a statistically significant association with ODEs. Patients who had no ODEs had an average BMI of 23.5, which falls within the normal range of 18.5 to 24.9. Patients who had a single ODE had an average BMI of 25.8, and those who had multiple ODEs had an average BMI of 27.2, both of which fall in the overweight BMI category. Each progressively larger BMI group was associated with a higher occurrence of one or more ODEs. In the underweight BMI group, 1 out of 5 patients (20.0%) had a single event and there were no multiple events. In the normal BMI group, 46 out of 96 patients (47.9%) had one or more events. In the overweight BMI group, 30 out of 44 patients (68.2%) had one or more events. In the obese BMI group, 18 out of 22 patients (81.9%) had one or more events.

There was no significant relationship between at least one ODE and the factors of age or ASA classification. BMI and sex did however have a significant association with the occurence of at least one ODE, each factor testing as significant after adjustment for the effect of the other. The odds of at least 1 event was estimated to be 2.6 times as great for a male as a female at a fixed BMI (OR 2.6; 95% CI 1.2-5.5), and to increase by 1.2 times for each unit increase in BMI regardless of sex (OR 1.2; 95% CI 1.1-1.3). Figure 2 presents the fitted logistic model for the probability of ODEs.

The digital oxygen saturation data from each patient procedure was recorded at one-second intervals by the SAM. This data was pooled and then grouped into patients having had no ODEs and those having had one or more ODEs. Patients who had at least one ODE spent a greater percentage of the surgery with oxygen saturation (SpO2) levels closer to the 94% threshold than those who did not have an ODE. This was statistically significant. For example, patients who did not have an ODE spent about 70% of their procedure time at an oxygen saturation level of 99-100%. In contrast, patients who had at least one ODE spent about 30% of their time at a 99-100% oxygen saturation level (Figure 3).

DISCUSSION

The present study measured propofol-remifentanil TCI sedation efficacy by questionnaire responses from patients and registered nurses present during outpatient office-based exodontia procedures. A high level of patient satisfaction and consistently good to excellent operating conditions were evident in the questionnaire responses. The study also measured an aspect of sedation safety, by use of a Sleep Apnoea Monitor (SAM) which recorded oxygen saturation data, specifically oxygen desaturation events (ODEs). A higher occurrence of ODEs was associated with larger patient BMI and male sex, and those who had one or more ODEs had lower oxygen saturation levels on average throughout the procedure.

Three patients entered into the study were withdrawn because midazolam was administered to these patients in addition to the propofol and remifentanil. Propofol can induce a euphoric talkative state in some young patients, and if this occurs then 1mg IV bolus doses of midazolam may be administered until the patient becomes more settled. The results therefore on the quality of sedation are reported slightly more favourably than they actually were, due to exclusion of three patients from the study. The overall measurement of ODEs was likely affected by two counteracting factors: the low male-to-female ratio of participants and potential inaccuracy of the SAM. The male:female ratio of study participants was 1:2 and this particularly low proportion of males (33.3%) may have affected the results of the study significantly. Males were found to have a higher chance of ODEs at a fixed BMI (OR 2.6; 95% CI 1.2-5.5), and thus a more even ratio of males to females would likely have produced results with a significantly higher overall occurrence of ODEs. The SAM was used because of its ability to record retrievable digital data, unlike the standard pulse oximeter routinely used in practice. However, ODEs may have been over-recorded by the SAM. It had a tendency to record a lower oxygen saturation levels than the standard pulse oximeter, and a small number of incidences when a false ODE may have been caused by a patient accidentally removing the SAM finger clip. No record was made of the difficulty of the extractions undertaken. Patients who had difficult extractions may have required a higher dose of sedative drugs, and thus may have had a higher likelihood of ODEs. Therefore we were unable to investigate a possible association between the difficulty of extractions and the occurrence of ODEs.

The findings of the study support recent papers investigating propofol sedation safety during endoscopic procedures. In these studies, higher BMI and male sex were reported as predictors of airway modifications, and higher BMI was also reported as a predictor of sedation-related adverse events (SRAEs) (Coté et al., 2010; Mehta et al., 2013; Wani et al., 2011). The present study differs considerably to these studies in that it was undertaken in an oral surgery context, a propofol-remifentanil TCI technique was used and the measure of safety involved ODEs measured by a SAM. Nevertheless, the results from this study show a stronger association between higher BMI and ODEs, and between male sex and ODEs. This is likely related to the use of a SAM to measure ODEs, which appears to have greater sensitivity in recording respiration-related events than measures used in afore mentioned studies. Less noteworthy is that our findings refute those of Coté et al. in relation to ASA Classification. Coté and colleagues stated ASA Class III or higher to be a predictor of airway modifications. Our results showed no association between ASA Class and ODEs, however there were only two ASA Class III patients in our study, and nil ASA Class IV-V patients.

The association in our study between higher BMI and ODEs supports literature stating that excessive adipose tissue within and surrounding the oral and throat regions, including a larger tongue, contribute to a more complicated airway; and that in obese patients, ventilation is further compromised by upward diaphragmatic pressure from heavy chest walls and abdominal contents (Chacon et al., 2004). The association between male sex and ODEs in our study (OR 2.6; 95% CI 1.2-5.52) supports literature on the topic of Obstructive Sleep Apnoea (OSA), a condition which causes a compromised airway and thus affects oxygen saturation of the blood. Males are more prone to Obstructive Sleep Apnoea (Jarzyna et al., 2011), possibly because of a male tendency to accumulate fat around the neck (Isono, 2012). This difference in fat distribution may partly explain the reason why males had a greater tendency towards ODEs than females in the present study.

Our study investigated propofol-remifentanil TCI sedation in oral surgery and found a high level of patient satisfaction, consistently good to excellent operating conditions and that higher BMI and male sex were associated with ODEs as a parameter of sedation safety. Average oxygen saturation throughout the procedure was lower in those who had one or more ODEs. Thus it appears that a higher BMI was associated with lower average oxygen saturation throughout the procedure, in addition to the likelihood of ODEs. These findings contribute to the existing literature on the topic of propofol sedation and are informative for dental practitioners who carry out sedation routinely. The use of a Sleep Apnoea Monitor to measure ODEs during sedation provided for an objective measurement of respiratory compromise. We would consider this to be a useful research tool which could be used to compare sedation techniques.

There is widespread awareness of the increasing prevalence of obesity. With regard to sedation, if indeed higher BMI impacts negatively on the safety parameter of blood oxygenation, determining the safest sedation technique for higher BMI patients would theoretically benefit the patient population as a whole. It has been suggested that propofol and remifentanil may carry some advantages over other drugs such as midazolam when used for obese patients. Remifentanil provides additional analgesia for oral surgery procedures (Gan, 2006), and has similar pharmacokinetics in obese and non-obese patients. It may be an ideal drug for obese patients because of a short half-life and lack of accumulation in the system (Todd, 2005). In contrast, the pharmacokinetics of propofol is affected by the volume of adipose tissue in an individual's body. Propofol has a higher volume of distribution and a longer half-life in the obese individual, resulting in a longer drug elimination and recovery time. It is recommended that the initial dosage of propofol is based on Ideal Body Weight (IBW), and the maintenance dosage based on Total Body Weight (TBW); remifentanil dosage is recommended to be based solely on IBW (Todd, 2005). The advantage of using the TCI technique for propofol-remifentanil sedation is that it deals with the inherent differences of these drugs. The operator is able to achieve and maintain specific effect site concentrations for both drugs individually, facilitating greater control and safety of sedation. TCI technique may therefore enable greater safety of sedation for all patients, particularly for males and those with

higher BMIs who appear to have a greater tendency towards oxygen desaturation events.

CONCLUSION

The patient and RN questionnaires revealed that propofol-remifentanil TCI sedation for oral surgery was effective for the patient and achieved good to excellent quality operation conditions. Use of a Sleep Apnoea Monitor to record oxygen saturation data revealed an association between the likelihood of ODEs and higher patient BMI. Males were more likely to have ODEs than females, and those who had one or more ODEs had a lower average oxygen saturation level during the procedure. No adverse safety events occurred during the study. The number of ODEs was not related to other parameters investigated such as pre-operative nervousness, age or ASA classification. The use of a Sleep Apnoea Monitor to measure ODEs could be considered to be a useful research tool for comparison of sedation techniques.

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