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SHORT COMMUNICATION

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Dental Sedation: The Advantages of Propofol and Remifentanil *via* Target Controlled Infusions

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Abstract

We prospectively audited 150 patients undergoing dental procedures with Target Controlled Infusion (TCI) of propofol and remifentanil to evaluate patient safety, adverse effects and post-operative discharge time and patient feedback. This anaesthetic technique provides for early recovery after surgery and allows for a 92% rate of "fast track" discharge within 20 minutes (mins) of completion of surgery. The technique proved safe with 14 patients (9.3%) experiencing a total of 14 adverse events, none of which were serious and all of which were easily managed. The adverse events were 8 cases of hypoxaemia (5.3%), 3 cases of paradoxical agitation/anxiety (2.0%), 2 cases of nausea (0.01%), neither of which required treatment and 1 case of generalised body itching, again not requiring treatment. Patient feedback was unanimously positive. We compared our rate of adverse events using TCI propofol and TCI remifentanil with our previous publication of 350 patients in which we used bolus alfentanil and TCI propofol. Additionally, we compared the effect target (Cet) propofol infusion levels required between the two groups. We advocate the use of remifentanil in combination with propofol in particular for longer duration cases and for those patients at risk of developing or who manifest an intraoperative paradoxical agitation reaction.

Keywords: Dental sedation; Sleep dentistry; Propofol; Remifentanil

Introduction

In a recent paper we described our experience with the use of the short-acting agents propofol and alfentanil for the intravenous conscious sedation of 350 patients undergoing dental surgery [1]. By utilising only shorter-acting agents, deliberately omitting the use of benzodiazepines and adding supplemental oxygen, we were able to achieve a low rate of adverse events, coupled with the capacity to achieve a fast-track discharge in 95% of our patients. We defined a fast-track discharge as spending 20 mins or less in the post anaesthesia care unit (PACU).

To date we have administered intravenous sedation to over 900 dental patients, using a TCI delivery system of propofol. Analgesia was originally provided by a bolus injection of alfentanil, but to provide greater flexibility to our technique, we have increasingly adopted the use of a combined infusion of TCI propofol with TCI remifentanil.

The combined administration of these two drugs has maintained high patient satisfaction rates, our desired fast track discharge time and a low rate of clinically non-significant, readily manageable adverse events. The ability to be able to manipulate the infusion rates of these two different drugs has enabled us to more effectively treat the uncommon, but troublesome adverse effects of propofol-induced anxiety or agitation reactions and the rare occurrence of myoclonus. Collectively, such events can be described as paradoxical reactions. Furthermore, the combination drug technique permits for a smooth sedation course should longer (more than one hour(hr)) surgical durations be desired, with the continuous delivery of a narcotic to be helpful should additional analgesia at times be required.

This audit describes our results and the technique we have adapted to safely administer the combination TCI technique of propofol and remifentanil to 150 patients at the Victorian Oral and Facial Surgery (VOFS) clinics in Melbourne and compares the results of this audit with our previously published data relating to 350 patients receiving bolus alfentanil with TCI propofol.

Materials and Methods

All patients scheduled to undergo elective dental procedures under intravenous (IV) sedation (or so-called "Sleep Dentistry") at VOFS after November 1, 2020 were entered into the audit, provided that their intended sedation technique was to be propofol and remifentanil. The target of 150 patients was met at the end of May, 2021. All cases were anaesthetised by the same practitioner (DW) and operated on by the VOFS surgeons (SV, BW or JS). The initial surgical consult, pre-operative telephone assessment by DW and completion of a pre-operative sedation questionnaire more than 24 hours prior to surgery was in accordance with the requirements of the Victorian Department of Health and Human Services (DHHS).

Written consent for anaesthesia and surgery was obtained from all patients; with all data being tabulated in a non-identifiable manner. A standard pre-operative examination of the cardio/respiratory system was performed. All patients with a history of reactive airways disease received their standard Beta 2 bronchodilator therapy immediately pre-operatively, and all patients with a history of symptomatic reflux, no matter how infrequent, received a three-day course of a proton pump inhibitor prior to surgery.

The monitoring of anaesthesia and conduct of surgery was in exact accordance with our previous publication [1]. All patients were monitored by blood pressure (BP) cuff, SPO2, nasal capnography, ECG when required and, most importantly, by a verbal contact, positive feedback hand holding process where the patients were frequently asked to squeeze the anaesthetist's hand twice "if they wished to be more asleep". Intranasal oxygen (3 L/min) was administered *via* a binasal oxygen delivery/capnographic system (Parker Medical Company).

American Society of Anesthesiology (ASA) 1 or 2 patients were considered suitable for sedation. Stable ASA 3 patients were considered provided only a brief surgical procedure was intended such as a single extraction. Exclusions included those patients with Barrett's oesophagus, BMI above 35 Kg/m^2 or weight above 115 Kg. Children under 12 years of age were excluded.

The sedation technique was intended to achieve a level where the patient was comfortable and relaxed but still able to respond purposely to verbal command, corresponding to a Modified Ramsay Sedation Level 3, not beyond level 4 (Table 1). A registered, anaesthesia trained nurse was present during the procedure and post-operatively in the PACU.

The patient characteristics are presented in table 2: Number of patients and gender, ASA status, age range, mean age, height, weight and BMI of the 150 Remifentanil *versus* 350 Alfentanil treatment groups.

Table 3 lists the operative procedures performed on 150 patients with Remifentanil *versus* 350 patients with Alfentanil.

Table 1: Modified ramsay sedation scale.

	Modified Ramsay Sedation Scale
1	Awake and alert, minimal or no cognitive impairment
2	Awake but tranquil, purposeful responses to verbal commands at a conversational level
3	Appears asleep, purposeful response to verbal commands at a conversational level
4	Appears asleep, purposeful responses to verbal commands but at a louder than conversational level, requiring light glabella tap, or both
5	Asleep, sluggish purposeful responses only to loud verbal commands, strong glabellar tap, or both
6	Asleep, sluggish purposeful responses only to painful stimuli
7	Asleep, reflex withdrawal to painful stimuli only
8	Unresponsive to external stimuli, including pain

Table 2: The patient characteristics.

Patient Characteristics	Remifentanil	Alfentanil
Number of patients	150	350
Sex - Female	102	235
Sex - Male	48	115
ASA Status 1 or 2	147	346
ASA Status 3	3	4
Age Range (years)	15-71	11-77
Height (cm)	169.32 ± 9.60	168 ± 9.9
Weight (kg)	72.52 ± 15.28	70.1 ± 15.2
BMI (Kg/m^2)	25.23 ± 4.57	24.6 ± 4.5

Table 3: Lists the operative procedures performed on 150 patients with Remifentanil *versus* 350 patients with Alfentanil.

Procedures*	Remifentanil	Alfentanil
Removal of third molars	126 patients	306
Other extractions	18 patients	55
Other procedures: Implants Sinus lift Clearance Alv. Ridge Augmentation	24 patients 13 patients 7 patients 1 patient 5 patients	3 2 1 0 0
*Note - many patients had more than one procedure performed		

Sedation technique

Our TCI sedation technique utilises the Alaris PK infusion pump (Alaris Medical, Alaris PK Carefusion System) set to Effect Target (Cet) mode *via* the Schnider model for propofol and Minto model for remifentanil. The addition of a Paedfusor propofol programme permits us to effectively administer propofol to children as young as 12 years of age, as the Schnider propofol model cannot be programmed below 16 years of age. The Minto model is able to be programmed to age as young as 12 years.

As described previously [1], we commence with a low-level propofol infusion to provide both anxiolysis and antiemesis. A remifentanil bolus is then administered, with the dose being dependant primarily on patient age- a typical range is a Cet of 2.5-5.0 nanograms/millilitre (ng/ml) (ie. at a level which gives an initial pre-determined remifentanil bolus dose of between 0.5-1.0 micrograms/kilogram (ug/kg)). The surgeon injects the local anaesthetic at the time of the patient acknowledging a narcotic euphoria, in combination with capnographic waveform evidence of narcosis. At this point, should it be required, the patients can readily respond to commands to breathe. Following the injection of local anaesthetic, the propofol TCI Cet is progressively increased in combination with a reduction in the dose of remifentanil TCI Cet. We have found that a satisfactory endpoint for the infusion of remifentanil is at a respiratory rate of around 10-14 breaths per minute (bpm) with the propofol dosage requirement being determined by the needs of the patient, in combination with the sedation level the anaesthesiologist is prepared to deliver. Using this combination technique it is possible, with experience, to tailor a sedation experience specifically to patient needs. Some patients prefer greater levels of sedation, whilst others prefer to be aware of their surroundings but require maximal analgesia.

Results

Table 4 describes the relevant sedation data and adverse events using TCI remifentanil and propofol, with a comparison rate using bolus alfentanil with TCI propofol. A total of 14 patients (9.3%) experienced 14 adverse events, all of which were readily corrected, with none proving to be serious. By comparison, the rate of adverse events with bolus alfentanil and propofol TCI was 8.3% (29 events in 27 patients).

Table 4: The relevant sedation data.

Sedation Data	TCI Remifentanil	Alfentanil
Time in OR (min)	30.36 ± 18.87	24.7 ± 8.4
Time in PACU (min)	15.57 ± 5.77	14.6 ± 5.5
Percentage discharge at/under 20 mins	92%	95%
Maximum Cet Propofol (mcg/ml)	1 .72 ± 0.46	2.0 ± 0.49
Cet Propofol Range (mcg/ml)	0.9-2.7	0.5-3.3
Cet bolus Remifentanil (ng/ml)	4.4 ± 0.80	
Cet remifentanil infusion level (ng/ml)	1.86 ± 0.70	
Adverse Events	14 (9.3%)	29(8.3%)
Hypoxaemia (SPO2<90%)	8 cases (5.3%)	10 cases (2.9%)
Bradycardia	0 cases (0%)	7 cases (2.0%)
Paradoxical Agitation/Anxiety	3 cases (2.0 %)	12 cases (3.4%)
Nausea	2 cases (.013%)	0%
Rigidity	0 cases	0%
Generalised body Itching	1 case (.006%)	0%

Whilst the overall incidence of adverse events was similar between the two sedation techniques, there was a difference in the type of adverse events. The most common complication with bolus alfentanil was an anxiety/agitation type of paradoxical reaction (3.4%), whereas with the combination infusion technique hypoxaemia occurred most commonly (5.3%).

Hypoxaemia: 8 cases, all transient, SPO2 ranging from 74%-89%. All cases occurred following the administration of the remifentanil bolus. All responded to simple measures such as instruction to breathe or increased oxygen flow rate. None required bag and mask ventilation. There was a definite "learning curve" with more cases of hypoxaemia occurring early with the introduction of the technique, *versus* later in the audit.

Bradycardia: zero cases. We do administer anticholinergics to those patients with pre-induction pulse rates less than 50 bpm.

Paradoxical agitation/anxiety: 3 cases in female patients, 2 with pre-existing anxiety and another with significant recreational drug abuse. All patients responded well to reductions in Cet propofol with a corresponding increase in Cet remifentanil, usually to a Cet remifentanil level of around 3 ng/ml or more.

Nausea: 2 cases. One in an anxious female at the commencement of the procedure. Her anti-emetic propofol TCI level was increased, and the commencement of remifentanil infusion delayed until symptoms abated. One case in a patient who insisted on leaving the centre *via* Uber- her request was refused. Some 20 mins later, whilst waiting for a relative to arrive and accompany her home, she had a single very small emesis. No treatment was required, and it was felt likely that this episode occurred for reasons of secondary gain.

Rigidity: zero cases.

Generalised body itching: 1 case, which settled in PACU with no treatment required. An itchy "narcotic" nose is common with both alfentanil and remifentanil prior to achieving a satisfactory sedation level.

As with the bolus alfentanil/propofol technique, there was universal acceptance by the patients of the combination infusion technique as evidenced by the "good" rating of their "sedation experience" on a linear analogue scale from "poor" to "fair" to "good".

Discussion

For reasons which are somewhat unclear to us, we observed an increased incidence of intra-operative paradoxical reactions in our sedated patients during the latter part of 2020. The occurrence over a brief period of time of five paradoxical reactions (three anxiety/agitation reactions, plus two patients who developed temporary myoclonic jerks of the lower limbs) leads us to modify our anaesthetic technique in the hope of reducing the occurrence of such adverse events. Our previous audit of 350 patients with bolus alfentanil/TCI propofol cited an intra-operative anxiety/agitation rate of 3.4% [1]. We suspect that the increased occurrence of these paradoxical reactions in the latter part of 2020 was in part a manifestation of the enormous societal pressures related to the widespread anxiety which accompanied the near-total 111 days (August- October) lockdown of the state of Victoria as measures were implemented to control the rapidly rising number of Coronavirus cases. We felt that a sedation technique that provided for a lower dose of propofol might reduce the incidence of these problem events and that such a technique should also allow for sedation to continue and any paradoxical reactions to be treated effectively should they occur.

We, therefore, modified the basis of our sedation technique from an initial bolus dose of alfentanil to an ongoing TCI remifentanil infusion, accompanying the TCI propofol infusion.

Both narcotics can be considered to be short-acting, but remifentanil, by virtue of its unique metabolism, discussed below, offers potentially more flexibility. Initially, we added a remifentanil TCI infusion when patients exhibited an intra-operative paradoxical reaction. Subsequently, we commenced the sedation process with combination propofol and remifentanil TCI infusions in all patients with pre-operative anxiety, before finally adopting the combination technique in nearly all of our patients as the primary sedation technique. We commence with a high Cet remifentanil level to achieve a bolus analgesic administration, and then reduce the Cet level to give a lower maintenance infusion as the propofol Cet is progressively increased.

The combination of propofol and remifentanil has been previously described for dental sedation [2-4], but many of these papers describe fixed-dose regimes, especially for the narcotic base. Coskun, et al., [5] described the combined use of TCI propofol and remifentanil for ovarian oocyte retrieval but used lower remifentanil target levels at the commencement than those that we utilised, in a surgical procedure expected to be far less stimulating than dental surgery.

It is clear that the technique of TCI propofol in combination with TCI remifentanil has been used in New Zealand for many years [6] and it is also apparent that ongoing New Zealand studies, in combination with Canadian researchers, are in progress [7]. Nevertheless, it does seem that the published data to date does not describe the manner of our use of an initial, high target level (Cet) of remifentanil, followed by a significantly lower baseline infusion Cet with which we strive to achieve a respiratory rate of around 10-14 breaths/min. Nor is there quantification of propofol and remifentanil TCI settings, but rather descriptive discussions of the technique and its desirable combination properties. We do acknowledge that there are many advocates of the synergistic properties afforded by the combined use of these two infusion agents plus qualitative descriptions of using them together in dental sedation.

Propofol is in many ways an ideal intravenous anaesthetic agent. With a fast onset of action, rapid awakening regardless of the length of infusion, and absence of nausea and vomiting, it also possesses the capacity to provide dose-dependent sedation. The context-sensitive half-life, the time for its concentration to fall by half, is little effected by the duration of infusion. At sub-hypnotic doses, propofol, *via* its action on central Gaba Amino Butyric Acid (GABA) receptors, provides potent anxiolysis and amnesia [8-11].

Remifentanil is an ultra-short acting narcotic agent, metabolised by non-specific plasma esterases. Its duration of action is independent of liver or renal dysfunction. Remifentanil acts on mu Opioid receptors and provides analgesia, sedation and a euphoric effect. It does not produce amnesia. The context-sensitive half time for remifentanil is four mins, and is little effected by age or duration of infusion, although there is greater variability in the elderly [12,13]. The fact that remifentanil's context-sensitive half time is independent of the duration of infusion is in stark contrast with other anaesthetic agents and makes it ideally suited for infusion purposes [14,15]. There is, however, a significant age-related dosage change whereby an 80-year-old patient requires approximately half the dose to achieve the same EEG effect as a 20-year-old patient, with the time to peak effect being doubled. The adjustment in bolus dose for age is far more important than the adjustment for weight. The infusion rate required to maintain a constant EEG effect in an octogenarian is approximately one third that required in a 20-year-old [13]. Used appropriately, remifentanil alone has been described for use for sedation in the elderly [16].

Administered together, the combination of propofol and remifentanil can be adjusted in order to provide sedation, anxiolysis, amnesia and analgesia. Higher levels of propofol contribute more to amnesia, whilst increasing the level of remifentanil adds a stronger analgesic effect. Acting together, the two drugs are known to be profoundly synergistic in their effects.

Patients undergoing sedation receive pharmacologic therapy in order to provide comfort with the reduction of stress, fear and anxiety. Many patients prefer to be amnestic. A myriad of drug cocktails and combinations are used in order to meet these requirements. The complexity of agents used should, and indeed must, reflect the training and expertise of the sedation practitioners involved.

In our previous article [1], we referred to disagreement and controversy concerning the credentialing requirements for those seditionists providing propofol TCI sedation (with a significant difference of opinion between the American Society of Anesthesiology and the American Society of Gastroenterology over the use of propofol) [17,18]. Our opinion was that propofol TCI sedation, in combination with bolus alfentanil, was probably best reserved for those practitioners having some familiarity with Total Intravenous Anaesthesia (TIVA).

With regards to the combination infusion of propofol and remifentanil, we strongly advocate this technique to only be utilised by anaesthesiologists, and only those anaesthesiologists with considerable experience in TCI TIVA. As with many aspects of contemporary medicine, there is a "learning curve" upon commencement of the use of this technique with hypoxaemia, in particular, being the most likely adverse event. With practice and increased familiarity, this complication becomes far less likely. In our case, the learning curve represented approximately 50 cases, after which the benefits of being able to either increase or decrease one component in comparison with the other simply made the process of administering sedation to be both more beneficial to the patient and extremely satisfying to the practitioner.

Longer duration cases are particularly suitable with this technique. Once a smooth base has been established, it is relatively straightforward to maintain the "status quo". With the constant drug levels provided by the Alaris PK TCI system, a commensurately constant depth of sedation is produced. An additional advantage of the addition of remifentanil to propofol sedation is the suppression of the gag reflex [2].

The development of intra-operative paradoxical reactions, a spectrum perhaps thought of as encompassing a variety of excitement type responses such as voluntary or involuntary movements, agitation, tremors and uncooperativeness has always concerned us and is an issue with some of the patients receiving propofol sedation. There is no exact definition of a paradoxical response. In our experience, these movements can range from fine tremulous motions, especially of the lower limbs, to more coarse, myoclonic-type jerks which can involve either the lower or all four limbs. In our original audit of 350 patients, we documented an increased incidence of paradoxical reactions in patients receiving higher Cet propofol, especially in the presence of pre-existing anxiety, female gender and in those individuals with a history of recreational drug abuse or heavy nicotine dependence.

Anxiety in sedated dental patients has been found to be more common in younger and female patients [19]. Ellis, found high levels of anxiety and intra-operative movement in third molar patients who received midazolam [20]. We have encountered several patients with significant, pre-existing levels of anxiety who have developed paradoxical agitation reactions after requesting progressively increasing amounts of propofol. As previously mentioned, we have found that the recreational abuse of illicit drugs, particularly heavy marijuana use, predisposes to higher intra-operative anxiety and agitation rates.

Paradoxical reactions occurring under benzodiazepine sedation range in incidence from 1.4-10.6% [21,22]. These authors describe male gender and older patients as being independent risk factors. Mancusco, et al., [23] cite a 1.0% incidence with benzodiazepines and describes them as being characterised by increased talkativeness, emotional release, excitement and excessive movement. Jeong, et al., [24] describe an increased incidence with either young or advancing age, degree of apprehensiveness of the patient and chronic alcohol abuse. They found that the highest rate was when propofol was titrated to a higher Cet level and caution against deeper sedation with propofol in patients with alcoholism. Jeong, et al., describe the incidence of paradoxical excitement response under sedation as being unknown, with a range of between 1-70% of patients. This wide discrepancy is reflective of the lack of diagnostic criteria for paradoxical excitement responses, and the wide variation in the type of responses. Lee, et al., [25] examined 421 patients receiving bolus propofol for upper endoscopy and found a paradoxical excitement rate of 16.1%. This finding correlated with pre-existing anxiety and younger age.

Our experience has taught us that higher Cet propofol levels are accompanied by an increased potential for a paradoxical response. Of note, our mean Cet propofol level in the bolus alfentanil patients was 2.0 ± 0.49 mcg/ml, *versus* 1.72 ± 0.46 mcg/ml in the remifentanil group. The presence of remifentanil in an ongoing manner lessens the requirement for propofol. A great advantage of the combination infusion method is the ability to quickly modify the propofol Cet level. Anxious patients who invariably wish to be, as they put it, "asleep", can be safely sedated with a predominantly propofol based sedation to amnestic levels. Should a paradoxical reaction begin to occur, a switch to sedation which is more remifentanil based can be initiated. In this

way the safety, comfort and needs of both patient and surgeon are best achieved. We were able to satisfactorily modify the paradoxical reactions, and continue the sedation process, in all three patients who developed such problems by reducing the Cet propofol and increasing the Cet remifentanil. (These outcomes have been further replicated outside of the audit group). This flexibility greatly enhances the potential benefits of using a combination propofol with remifentanil TCI technique for sedation purposes. Prior to the introduction of remifentanil, paradoxical reactions were treated with only a reduction in Cet propofol, which usually rendered the sedation process difficult for all involved.

As a standard precaution, we are now usually reluctant to proceed beyond a propofol Cet of 2.5 mcg/ml, finding that tremulous type reactions are more common with higher propofol levels, in particular when the propofol infusion rate accompanying the selected Cet is more than 6 mg/kg/hr. Those patients who insist on receiving more sedation beyond this level are titrated, by way of their respiratory rate, to higher levels of remifentanil. Should we encounter tremulous activity, we routinely reduce the propofol Cet and increase the remifentanil Cet. Perhaps the actual administration of propofol and remifentanil can be practically thought of as a "see-saw" type approach, where either reductions or increases in dosage of one of the drugs can be accommodated by an opposing change in the other, delivering the potential to hit a "sweet spot" where a constant sedation level ideally provides for optimal conditions for both patient and surgeon.

Conclusion

The addition of TCI Remifentanil to our TCI based Propofol sedation technique has proven to be safe and has resulted in potential advantages with regards to the increased ability to modify, at short notice, the basis of our sedation process. It allows us to more readily tailor intravenous sedation to the needs of an individual patient. We have adopted its use as a routine part of our current sedation process and, in particular, find it additionally helpful in longer duration cases and for those patients who demonstrate either pre-operative anxiety or actual intra-operative paradoxical anxiety/agitation reactions.

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