



# Comparison of the effects of target-controlled infusion-remifentanil/midazolam and manual fentanyl/midazolam administration on patient parameters in dental procedures

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**Background:** Moderate sedation is an integral part of dental care delivery. Target-controlled infusion (TCI) has the potential to improve patient safety and outcome. We compared the effects of using TCI to administer remifentanil/manual bolus midazolam with manual bolus fentanyl/midazolam administration on patient safety parameters, drug administration times, and patient recovery times.

**Methods:** In this retrospective chart review, records of patients who underwent moderate intravenous sedation over 12 months in a private dental clinic were assessed. Patient indicators (pre-, intra-, and post-procedure noninvasive systolic and diastolic blood pressure, respiration, and heart rate) were compared using independent t-test analysis. Patient recovery time, procedure length, and midazolam dosage required were also compared between the two groups.

**Results:** Eighty-five patient charts were included in the final analysis: 47 received TCI-remifentanil/midazolam sedation, and 38 received manual fentanyl/midazolam sedation. Among the physiological parameters, diastolic blood pressure showed slightly higher changes in the fentanyl group ( $P = 0.049$ ), respiratory rate changes showed higher changes in the fentanyl group ( $P = 0.032$ ), and the average  $\text{EtCO}_2$  was slightly higher in the remifentanil group ( $P = 0.041$ ). There was no significant difference in the minimum  $\text{SpO}_2$  levels and average procedure length between the fentanyl and remifentanil TCI pump groups ( $P > 0.05$ ). However, a significant difference was observed in the time required for discharge from the chair ( $P = 0.048$ ), indicating that patients who received remifentanil required less time for discharge from the chair than those who received fentanyl. The dosage of midazolam used in the fentanyl group was 0.487 mg more than that in the remifentanil group; however, the difference was not significant ( $P > 0.05$ ).

**Conclusion:** The combination of TCI administered remifentanil combined with manual administered midazolam has the potential to shorten the recovery time and reduce respiration rate changes when compared to manual administration of fentanyl/midazolam. This is possibly due to either the lower midazolam dosage required with TCI remifentanil administration or achieving a stable, steady-state low dose remifentanil concentration for the duration of the procedure.

**Keywords:** Fentanyl; Midazolam; Moderate Sedation; Remifentanil, Target-Controlled Infusion.



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## INTRODUCTION

Moderate procedural sedation (MPS), or conscious

sedation, includes techniques and medications used to help patients withstand unpleasant or painful dental procedures [1]. Local anesthesia is the basis of pain management and control during dental procedures,

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whereas decreasing the patient's perception of pain, lowering anxiety, and discomfort levels can be achieved through the administration of low-dose opioid analgesics, most commonly fentanyl, combined with a sedative agent, preferably a benzodiazepine agent, such as midazolam [2]. MPS allows patients to tolerate unpleasant or long dental procedures while breathing independently, maintaining protective reflexes, and response to verbal and tactile stimuli [3,4].

The effectiveness and safety of intravenous administration of benzodiazepines, including diazepam and midazolam, for conscious sedation, have been proven [5,6]. Their popularity in dentistry is attributed to their sedative and selective anxiolytic effects and wide safety margin [4]. Due to the lack of analgesic properties of benzodiazepines, a low-dose opioid agonist, such as fentanyl and remifentanyl, should be supplemented. The safety of this drug combination has been well documented in the scientific literature and clinical practice [7-9]. Regarding the order of drug administration, Lobb et al. [10] showed that administering low-dose opioid fentanyl before midazolam reduced the required dosage.

Fentanyl, a short-acting opioid that tends to be 60–80 times more potent than morphine, has a rapid onset of analgesia and sedation, with its duration of action being 30–60 min [11]. Based on its unique metabolic properties, remifentanyl has a rapid onset and offset of action and stable half-life compared with its alternatives [12]. Both agents are equipotent and provide similar analgesic and respiratory depressant effects while maintaining similar incidence and types of side effects [12,13].

Recently, the availability of precision administration technology, such as target-controlled infusion (TCI) pumps, has made it possible to administer stable, steady-state drug concentrations within the plasma and at the effect-site or brain. The drug dosage is adjusted automatically by the pump microprocessor and pharmacokinetic model specific to the drug chosen, and the operator only has to enter patient parameters including age, weight, height, sex, and the desired plasma concentration ( $C_p$ ). In this study, remifentanyl concen-

tration was fixed at  $\leq 1.0$  ng/mL [14,15].

The pharmacokinetic properties of remifentanyl coupled with precision drug administration technology such as TCI may make remifentanyl a preferred opioid for office-based ambulatory dental surgery, where decreased patient recovery time is required. Therefore, we aimed to compare the effects of TCI-remifentanyl/midazolam and manual fentanyl/midazolam administration on patient safety parameters (peripheral oxygen saturation [ $SpO_2$ ], end-tidal carbon dioxide [ $EtCO_2$ ], systolic and diastolic blood pressures [SBP and DBP], heart rate [HR], respiratory rate [RR], administered midazolam dosage, and patient recovery time).

## METHODS

Ethical approval for this study was obtained from the University Research Ethics Office (Pro00075457). A retrospective chart review was conducted in a general dentistry clinic in Edmonton, Alberta, Canada, which utilized a combination of midazolam and a remifentanyl TCI pump for procedures requiring moderate intravenous sedation over 12 months. These data were compared to those of patients who received fentanyl first without a TCI pump and then midazolam over a period of 9 months that was part of a previous study [10]. Chart data and sedation records were anonymized for data extraction, coding, and analysis. Appendix 1 presents the full sedation protocol used for both sedation approaches in the clinic.

### 1. Patients

The dental procedures performed on patients reviewed in this study were similar to those encountered at a general dental office that administers intravenous sedation: surgery; tooth removal; wisdom teeth removal; root canal treatment; restorative treatment such as fillings, crowns, and bridges; and cleaning. The procedures performed were recorded in the sedation monitoring documents for each patient. There were no selection or

assignment criteria for charts reviewed in the study, only the next person with sedation of a given protocol within the research study timeline.

All patients received 3–5 L/min of supplemental O<sub>2</sub> via a nasal cannula supplied by nasal prongs [16]. Capnography was performed and monitored using side-stream nasal prongs (Masimo Root Monitor, Masimo, California, USA). The most common amount of O<sub>2</sub> was 3 L/min.

All patients were sedated to the level of moderate sedation as defined by the American Society of Anesthesiologists (ASA) [17]: response to a loud voice or light touch or ability to give a thumbs up if the rubber dam was in place, and inconvenience to speak verbally. This is the same responsiveness score as the modified Ramsay score for sedation/anesthesia, part of the UA-HERB documentation [18]. All patients were at level 3 or 4 (moderate sedation), and no patient was sedated deeper than moderate sedation or a Ramsay score of 3 or 4.

## 2. Collected variables

Demographic information recorded included age, sex, smoking status, body mass index, ASA physical status classification, and blood SpO<sub>2</sub> and EtCO<sub>2</sub> levels. Patient indicators included pre-, intra-, and post-procedure SBP and DBP, RR, and HR.

Patients were monitored by an independent monitoring assistant, whose sole duty was to continuously observe the patient and monitor physiological changes using electronic monitoring equipment. The Masimo Root Monitor was used to monitor SpO<sub>2</sub>, CO<sub>2</sub>, capnography and capnogram, RR, HR, and noninvasive blood pressure, while a Philips MRx monitor/defibrillator (Phillips, USA) was used to control the three-lead electrocardiogram. The following data were recorded at 5-min intervals as the dependent variables for the study:

- RR
- Oxygen saturation rate – SpO<sub>2</sub>
- Capnography and end-tidal CO<sub>2</sub> values

- Three-lead electrocardiogram
- HR
- noninvasive blood pressure

Three time durations were calculated for each patient: procedure length (start to end of the procedure), end to discharge from the chair (end of the procedure to patient's ability to leave the chair to the waiting room), and end to discharge from office (end of the procedure to when the discharge criteria have been met).

After meeting the discharge criteria, patients stayed in the waiting room where additional observation was performed, instructions for care were given to patients' caregivers, and often, patients were escorted to their transportation by staff. The criteria to determine the discharge of patients were the Modified Aldrete Score [19], and patients were not discharged until he/she achieved a score of > 8 out of 10. None of the patients undergoing sedation was left unattended during or after sedation.

## 3. Sedation procedure

All anesthesia was achieved with local anesthesia administered in the same dental office by three staff members (a dentist holding permit for intravenous sedation with training in TCI administration, certified dental assistant, and dedicated sedation assistant for monitoring of patient vitals). Opioids (fentanyl or remifentanyl) were used for analgesia only and as part of the two-drug sedation regimen.

## 4. Fentanyl group

The administration of a single benzodiazepine (midazolam) and opioid analgesic (fentanyl) is a worldwide standard of care and is considered a traditional dental sedation regimen for moderate intravenous sedation in dental offices [20]. Fentanyl was administered at 5-µg/mL/min increments to a total of 25–50 µg. The dosage ranged between 25 and 50 µg based on the operator's clinical judgment and treatment required (50 µg for more stimulating procedures such as wisdom teeth

**Table 1.** Demographic data for continuous variables in patients receiving fentanyl and remifentanyl

Patient parameters	Groups	Number	Range	Minimum	Maximum	Mean $\pm$ SD	P Value
Age (yr)	Fentanyl	37	51	16	67	32.65 $\pm$ 17.07	0.920
	Remifentanyl	47	50	16	66	33.02 $\pm$ 16.55	
Weight (kg)	Fentanyl	37	82.2	49.3	131.5	74.07 $\pm$ 19.08	0.691
	Remifentanyl	47	66.7	49.4	116.1	72.58 $\pm$ 14.98	
BMI	Fentanyl	37	20.0	17.0	37.0	24.82 $\pm$ 4.59	0.993
	Remifentanyl	47	17.0	18.0	35.0	24.83 $\pm$ 4.21	

SD, Standard Deviation; yr, year.

removal and 25  $\mu$ g for less stimulating procedures such as fillings and root canals). Midazolam was administered at 1-mg/mL/min increments until patients reached a suitable sedation level of moderate sedation or a Ramsay score of 3 or 4. The dose of  $\mu$ g/kg of fentanyl or mg/kg of midazolam could be calculated; however, the results defeated the purpose of titration. The maximum dose of fentanyl administered was 50  $\mu$ g for each patient.

## 5. Remifentanyl group

Remifentanyl in combination with midazolam was administered by TCI pump technology using the Alaris PK infusion pump with TCI and a pharmacokinetic software model, Minto model, targeting plasma concentration (CareFusion, Basingstoke, UK). First, remifentanyl was administered at a fixed dose of  $\leq$  1.0 ng/mL. [21] The drug concentration maintained a stable steady-state concentration in the plasma and effect-site (brain) for the duration of sedation. The maximum remifentanyl was 1.0 ng/mL. Midazolam was administered by intermittent hand-bolus administration at 1 mg/mL/min until a suitable level of sedation was achieved. As time went by and sedation level waned, 1 mg of midazolam was administered every 15–30 min to maintain an adequate level of drug for patients. The maximum total dose of midazolam was 10 mg. The total midazolam dose administered was also recorded for each patient at the end of the procedure.

## 6. Analysis

Analyses were conducted using IBM SPSS Statistics version 24 (IBM Corp., Armonk, NY, USA). Data were

screened before statistical outliers were analyzed. Cases with outliers and potential entry errors were reviewed to determine whether single or all data points or entire cases were removed from the analysis. Differences pre-and post-procedure in SBP and DBP, RR, and HR were calculated as changes for analysis. Comparisons between the TCI-remifentanyl/midazolam and manual-fentanyl/midazolam groups were performed using an independent t-test with an alpha of 0.05.

## RESULTS

Eighty-four patient charts were reviewed. One chart from the fentanyl group was removed because the patient was less than 15 years old. For the chart information reviewed, 47 patients were included in the remifentanyl group, while 37 patients were included in the fentanyl group. No charts had missing key demographic information, except one patient who had a missing ASA classification.

### 1. Patient demographics and physiological measures

The demographic information for both patient groups is summarized in Tables 1 and 2. Of these patients, 39% were men and 61% were women. Only eight patients in both groups were reported as smokers. All patients met the ASA physical classification criteria of 1 or 2. Patients' ages ranged from 16 to 67 years, weight ranged from 49.3 to 131.5 kg, and body mass index ranged from 17 to 37. The groups did not significantly differ in any demographic variables (Table 1).

**Table 2.** Demographic data for categorical variables in patients receiving fentanyl and remifentanil

Patient parameters	Number (%)		Total	P-Value
	Fentanyl	Remifentanil		
Sex				0.812
male	14 (37.8)	19 (40.4)	33	
female	23 (62.2)	28 (59.6)	51	
Smoking status				0.275
No	32 (86.5)	44 (93.6)	76	
Yes	5 (13.5)	3 (6.4)	8	
ASA				0.603
I	30 (83.7)	37 (78.7)	67	
II	6 (16.7)	10 (21.3)	16	

ASA, American Society of Anesthesiologists.

**Table 3.** Summary of patient physiological parameters

Physiological Parameters	Fentanyl			Remifentanil		
	Mean $\pm$ SD	Min	Max	Mean $\pm$ SD	Min	Max
Average SpO <sub>2</sub> (%)	95.35 $\pm$ 1.79	92.70	100.00	97.41 $\pm$ 2.46	91.38	100.00
Average EtCO <sub>2</sub> (mmHG)	33.59 $\pm$ 5.05	21.00	42.00	38.09 $\pm$ 9.77	30.33	99.67
SBP (mmHG)	110.13 $\pm$ 10.59	94.33	141.00	119.29 $\pm$ 12.50	86.75	144.50
DBP (mmHG)	68.85 $\pm$ 9.69	56.00	100.33	74.71 $\pm$ 9.93	52.00	104.00
Average Heart Rate (beats/min)	72.65 $\pm$ 12.87	43.67	98.00	74.98 $\pm$ 11.94	54.33	104.00
Average respiration rate (breaths/minute)	16.29 $\pm$ 2.53	10.00	20.67	15.08 $\pm$ 2.23	11.33	20.00

DBP, diastolic blood pressure; EtCO<sub>2</sub>, end-tidal carbon dioxide; Max, maximum; Min, minimum; SBP, systolic blood pressure; SD, standard deviation; SpO<sub>2</sub>, peripheral capillary oxygen saturation.

**Table 4.** Comparison of changes in vital signs and average blood SpO<sub>2</sub> and EtCO<sub>2</sub> levels between fentanyl and remifentanil groups

Patient indicators	Groups	Mean $\pm$ SD	t score	P
SBP change	Fentanyl	8.83 $\pm$ 8.25	-0.909	.366
	Remifentanil	11.4 $\pm$ 12.65		
DBP change	Fentanyl	10.75 $\pm$ 9.71	1.996	.049*
	Remifentanil	7.51 $\pm$ 4.77		
HR change	Fentanyl	9.94 $\pm$ 7.39	0.181	.857
	Remifentanil	9.64 $\pm$ 7.80		
Respiratory rate changes per minute	Fentanyl	6.75 $\pm$ 11.20	2.179	.032*
	Remifentanil	2.87 $\pm$ 4.26		
Minimum SpO <sub>2</sub> (%)	Fentanyl	95.03 $\pm$ 2.75	0.383	.705
	Remifentanil	95.28 $\pm$ 3.11		
Average EtCO <sub>2</sub> (mmHg)	Fentanyl	33.59 $\pm$ 5.05	-2.077	.041*
	Remifentanil	38.09 $\pm$ 9.76		

\*P < .05

DBP, diastolic blood pressure; EtCO<sub>2</sub>, end-tidal carbon dioxide; HR, heart rate; SBP, systolic blood pressure; SD, standard deviation; SpO<sub>2</sub>, peripheral capillary oxygen saturation.

The patient physiological parameters are presented in Table 3. For blood SpO<sub>2</sub>, three of 47 remifentanil patients had a SpO<sub>2</sub> reading below 90. However, it quickly returned to safe oxygenation levels after patients were asked to take a deep breath; therefore, these were included in the analysis. The average reading was 95.35% and

97.41% in the fentanyl and remifentanil groups, respectively. The values of SBP and DBP are presented with the average, standard deviation, minimum and maximum.

**Table 5.** Comparison of recovery time and procedure length between fentanyl and remifentanil groups

Time	Groups	Mean $\pm$ SD	t score	P
End to discharge from office	Fentanyl	0:49:53.62 $\pm$ 0:18:22.96	-.884	.380
	Remifentanil	0:45:58.38 $\pm$ 0:22:17.20		
End to discharge from chair	Fentanyl	0:18:12.77 $\pm$ 0:09:18.09	-2.008	.048*
	Remifentanil	0:13:21.67 $\pm$ 0:12:42.82		
Procedure length	Fentanyl	0:31:44.21 $\pm$ 0:18:20.14	-1.549	.125
	Remifentanil	0:40:58.72 $\pm$ 0:32:51.30		

\*P &lt; .05

Notes: End to discharge from chair; The time required for discharge from the chair after completion of dental treatment

End to discharge from office; The time required for discharge from the office after completion of dental treatment

SD, standard deviation.

## 2. Vital sign changes

To analyze changes in vital signs, changes in each value (range of each patient) were measured throughout the procedure to determine differences in SBP, DBP, HR, and RR. The lowest blood SpO<sub>2</sub> value for each patient was recorded and compared. The average EtCO<sub>2</sub> levels were analyzed to determine the carbon dioxide concentration. The results of the evaluation of changes in vital signs are displayed in Table 4. Among the physiological parameters, DBP changes were slightly higher in the fentanyl group (P = 0.049), RR changes were higher in the fentanyl group (P = 0.032), and average EtCO<sub>2</sub> was slightly higher in the remifentanil group (P = 0.041). To ensure patient safety, verbal contact was maintained throughout the procedure. Oxygen desaturation (< 90%) occurred in three patients in the remifentanil group but was quickly reversed by asking patients to take a deep breath. Oxygen desaturation below 88% was not observed. Finally, no airway interventions were required. There was no significant difference in the minimum SpO<sub>2</sub> levels between the groups (P > 0.05).

## 3. Duration comparison

Three points of comparison were evaluated for the duration of patients between the two sedation groups and are presented in Table 5. There was no significant difference in the average procedure length between the fentanyl and remifentanil TCI pump groups (P > 0.05). The procedures completed between the two sedation groups were statistically comparable. However, a

significant difference was observed in the time required for discharge from the chair (P = 0.048), indicating that patients who received fentanyl required approximately 5 more minutes to be discharged from the chair. There were no differences in the time from the end of the procedure to discharge from the office (P > 0.05).

Finally, the total dosage of the drugs administered was compared with that of midazolam. The dosage of midazolam used in the fentanyl group (5.508  $\pm$  1.078) was 0.487 mg more than that in the TCI/remifentanil group (5.021  $\pm$  1.507); however, the difference was not significant (P = 0.095).

## DISCUSSION

This retrospective observational study revealed that the application of TCI in the administration of remifentanil/midazolam in adults was associated with a quicker recovery time of 5 min (P = 0.048) and lower respiration changes than was manual infusion of fentanyl/midazolam (P = 0.032). Moreover, a higher variation in DBP in the fentanyl group (P = 0.049) and higher EtCO<sub>2</sub> in the remifentanil group (P = 0.041) were found. Similar to our results, Hannam et al. found that administration of remifentanil combined with propofol results in a 16.7-mmHg increase in CO<sub>2</sub> pressure due to the inhibitory effect of remifentanil on pCO<sub>2</sub> removal [22]. Although a greater dosage of midazolam was required for patients who manually received fentanyl than for those who underwent the remifentanil/midazolam TCI technique, the



difference was not significant and clinically irrelevant.

TCI use was associated with prolonged operation time, although the difference was not significant, possible because of the additional time required for setting up and using the TCI device and the lower number of setting changes in the manual administration group. Hsieh et al. [23] also found that the administration of propofol using TCI is more time-consuming than manual infusion of a sedative agent for electroconvulsive therapy, as the former takes time to set up in each treatment.

The recovery time (end of the dental procedure to patient discharge from the chair) was approximately 5 min longer in patients who received fentanyl/midazolam anesthesia, which could be attributed to the lower dose of midazolam received by patients in the remifentanyl/midazolam TCI group. Similarly, a study conducted by Beers and Camporesi showed that remifentanyl has a faster onset and recovery than fentanyl. Minimal alterations of the pharmacokinetics in patients with systemic disorders and ease of drug administration were among other favorable pharmacological aspects of remifentanyl [24].

Changes in vital signs and average blood SpO<sub>2</sub> levels were not significantly different between the groups. RR significantly changed in patients sedated with manual administration of fentanyl/midazolam. This could be explained in part by both the greater midazolam dosage required for sedation of patients in the fentanyl group and the pharmacokinetics of fentanyl itself.

Our evidence supports that benzodiazepines such as midazolam decrease rr specifically when combined with opioids. The mechanism of action of midazolam in depressing respiration involves its agonist and antagonist effects on GABA and NMDA receptors, respectively. Despite the mild respiratory depressant effect of benzodiazepines, their combination with opioids results in additive or synergistic effects on respiration [25-28]. The application of TCI systems allows the computer's pump control algorithm to precisely calculate the infusion rate necessary to achieve a predetermined drug concentration known as the target (C<sub>p,target</sub>) in the plasma

[29,30]. In other words, this system allows clinicians to focus on the concentration domain for intravenous drug delivery [31].

Fentanyl and other opioid agonists can also depress respiration by reducing the response to elevated plasma levels of CO<sub>2</sub> and decreased plasma levels of O<sub>2</sub> by acting on  $\mu$ -opioid receptors at different sites, which leads to a reduction in the drive to breathe [25,32]. Slidharan et al. [33] demonstrated that the required dose of propofol combined with remifentanyl to induce general anesthesia was significantly lower than that in combination with fentanyl. Moreover, they found that intravenous infusion of fentanyl in humans is likely to produce respiratory depression by decreasing the drive to breathe and creating mechanical resistance.

Mu et al. compared TCI and manual administration of propofol in children and reported that the TCI use was associated with greater dosages of propofol required for anesthesia in the studied population [15]. This result contrasts with our findings that TCI required fewer sedative agents. Mu's finding can be attributed to the study population comprising children who require a high C<sub>p,target</sub> at induction. As mentioned, a high initial target for induction is required to achieve rapid induction of anesthesia in children because of their probable excessive movements. Moreover, the anesthetic drugs used in our study were different.

Similarly, Bilgin et al. compared the effects of intravenous infusions of alfentanil, fentanyl, and remifentanyl, finding that there were no significant differences in physiological parameters, including SBP, DBP, and HR at various stages of stereotactic brain biopsy [34].

In our study, oxygen desaturation (< 90%) occurred in three patients in the remifentanyl group but was quickly reversed by asking patients to take a deep breath. No significant difference was observed in the minimum SpO<sub>2</sub> between the fentanyl and remifentanyl groups. A convincing mechanism for this side effect is airway closure due to a decrease in lung volume. Indeed, opioids affect respiratory muscle actions in anesthetized patients

who can breathe spontaneously [35]. Our findings are consistent with the results of a study conducted by Maurtua et al. [36], who reported more oxygen desaturation in the remifentanyl group than in the fentanyl group. Owing to the short half-life of remifentanyl, this side effect does not appear to be clinically relevant.

Since the current study compared two methods of drug administration, it lacks information on other sedation strategies, which should be considered while interpreting the report's findings. Without various comparator groups, it is unclear whether the favorable safety outcomes are solely due to the target-controlled infusion of remifentanyl or midazolam.

Barends et al. [37] found that moderate-to-deep sedation (MDS) using propofol and remifentanyl TCIs provides adequate sedation associated with a low incidence of catastrophic events related to sedation, comparable to other methods used for MDS. The present study also provides further support for the use of remifentanyl TCI, a protocol-driven sedation method that, if provided by well-trained and equipped sedation practitioners under the indirect supervision of an anesthesiologist, is a safe and successful method of MDS for a wide range of patients and procedures. Moreover, the elimination of bolus injections reduces the potential for human error during administration.

In summary, the results of our study suggest that remifentanyl TCI combined with midazolam can shorten patient recovery time and significantly lower RR changes, possibly because of the smaller dosage of midazolam required than that typically used in the manual administration of fentanyl/midazolam. Additionally, the depressing effect of fentanyl on respiration through acting on  $\mu$ -opioid receptors at various sites can explain the greater RR changes among patients who received fentanyl/midazolam [25,32]. The availability of reversal agents for midazolam and remifentanyl may mitigate any potential concerns regarding adverse events in a non-hospital dental care setting [38]. Future studies should consider two short-acting drugs (propofol and remifentanyl) with precision drug administration by TCI

using a larger population of dental patients to make definitive conclusions and determine whether TCI should be incorporated into the standard of care for moderate sedation.

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#### AUTHOR CONTRIBUTIONS

**Doug Lobb:** Conceptualization, Data curation, Formal analysis, Resources, Writing - review & editing

**Nazila Ameli:** Formal analysis, Writing - original draft, Writing - review & editing

**Silvia Ortiz:** Data curation, Formal analysis, Methodology, Project administration, Writing - original draft

**Hollis Lai:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Software, Supervision, Validation, Writing - review & editing

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**Appendix 1.** Intravenous (IV) sedation protocols
 

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Intravenous (IV) Sedation Protocols - IV Drug Administration for Moderate (Conscious) Sedation in Dentistry

**Midazolam-First Administration – Titration to Effect (Moderate Sedation)**

Midazolam and fentanyl sedation protocol

Start sedation with midazolam

1. Draw 10 mg midazolam up to 10 ml with saline (1 mg/mL solution).
2. Administer 1–2 mg initially IV, then 1 mg at 1-min intervals until the patient is suitably relaxed and at sedation end-point of moderate sedation.

Start analgesia with fentanyl

3. Draw 50 mcg fentanyl up to 10 mL with saline (5 mcg/mL solution).
4. Administer 1 mL/min to a suitable end-point of 25–50 mcg. The level of fentanyl is based on the procedure stimulus – practitioner judgment. For more complex procedures or surgery (surgical extraction - impacted wisdom teeth removal or extractions requiring bone removal and/or tooth sectioning), 50 mcg is generally administered; less complex cases (restorations, root canal therapy, crown and bridge treatment, dental cleanings, patients with a high gag reflex that required sedation and routine periodontal treatment) generally require 25 mcg or less.
5. Continuously assess the patient and monitor SpO<sub>2</sub> levels.
6. Once the patient appears more relaxed and at a suitable sedation end-point, commence with local anesthetic administration.

Start anesthesia with local anesthetic administration

1. Wait for a local anesthetic to be effective and then proceed with the dental procedure.

Titration of Sedation during the Procedure

1. IV sedation is generally adequate for procedures of 30–45 min duration
2. If the procedure extends beyond this time frame and the sedation becomes inadequate, maintenance or supplemental titration may be required.
  - a. Wait 2 min after administering supplemental midazolam before administering either midazolam or fentanyl.
  - b. Wait 2 min after administering supplemental fentanyl before administering either fentanyl or midazolam.
  - c. Perform titration in 1.0-mL increments.

If the patient complains of

- Pain: assess the local anesthesia and re-administer
- Discomfort: increase the fentanyl for analgesia
- Awareness: increase the midazolam for sedation

Reasons to discontinue sedation or support patient

- No response to loud voice or shaking
- SpO<sub>2</sub> < 90%
- Airway support required
- Patient becomes unstable

If the patient becomes unresponsive and has entered a deeper level of sedation or general anesthesia, assess, support and observe the patient. Consider administration of antagonists or reversal agents (naloxone to reverse fentanyl or flumazenil to reverse midazolam).

**Fentanyl-First Administration – Titration to Effect (Moderate Sedation)**

Fentanyl and midazolam sedation protocol

Start analgesia with fentanyl

1. Draw 50 mcg fentanyl up to 10 mL with saline (5 mcg/mL solution).
2. Administer 1 ml/min to a suitable end-point of 25–50 mcg. The level of fentanyl is based on the procedure stimulus and practitioner judgment. For more complex procedures or surgery (surgical extraction - impacted wisdom teeth removal or extractions requiring bone removal and/or tooth sectioning), 50 mcg is generally administered, while less complex cases (restorations, root canal therapy, crown and bridge treatment, dental cleanings, patients with a high gag reflex that require sedation and routine periodontal treatment) generally require 25 mcg or less. In fentanyl-first administration, patients often mention that they feel something; however, there is no definitive endpoint, as observed with midazolam administration.
3. Wait 2 min after administering last increment of fentanyl before administering midazolam, and continuously assess the patient and monitor SpO<sub>2</sub> levels.

Start sedation with midazolam

1. Draw 10 mg midazolam up to 10 mL with saline (1 mg/mL solution).
2. Administer 1–2 mg initially IV and then 1 mg at 1-min intervals until the patient is relaxed and at the sedation endpoint of moderate sedation.
3. Once the patient appears more relaxed and at a suitable sedation end-point, commence local anesthetic administration.

Start anesthesia with administration of local anesthesia

1. Wait for the local anesthetic to be effective and then proceed with the dental procedure.
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#### Titration of Sedation during the Procedure

1. IV sedation is generally adequate for procedures of 30–45 min duration.
2. If the procedure extends beyond this duration and the sedation becomes inadequate then maintenance or supplemental titration may be required.
  - a. Wait 2 min after administering supplemental midazolam before administering either midazolam or fentanyl.
  - b. Wait 2 min after administering supplemental fentanyl before administering either fentanyl or midazolam.
  - c. Perform titration in 1.0-mL increments.

If the patient complains of

- Pain – assess the local anesthesia and re-administer
- Discomfort – increase the fentanyl dose for analgesia
- Awareness – increase the midazolam dose for sedation

Reasons to discontinue sedation or support patient

- No response to loud voice or shaking
- SpO<sub>2</sub> < 90%
- Airway support required
- Patient becomes unstable

#### **Single Pump TCI - Intravenous Drug Administration – Single Benzodiazepine by Intermittent Bolus Titration and Opioid Using Single Target-Controlled Infusion Moderate (Conscious) Sedation in Dentistry**

##### **Opioid-First Administration**

Start analgesia with remifentanyl target-controlled infusion (TCI)-Minto plasma level pharmacokinetic model in the Alaris PK infusion pump with TCI (CareFusion, Basingstoke, UK)

1. Start TCI plasma target concentration: Cpt of remifentanyl at 1.0 ng/mL.
2. Leave target concentration (Ce) at 1 ng/mL unless the analgesic level is insufficient.
3. Increase in 0.2-ng/mL increments, if necessary.
4. Wait 2 min, then assess the patient and SpO<sub>2</sub> levels before beginning midazolam administration.

##### **Start sedation with midazolam**

1. Draw 10 mg midazolam up to 10 ml with saline
2. Administer 1 mg initially intravenously and then 1 mg at 1-min. intervals until the patient is relaxed and at sedation endpoint of moderate sedation.
3. Once the patient appears more relaxed and at a suitable sedation endpoint, commence local anesthetic administration

##### **Start anesthesia with local anesthetic administration**

1. Wait for the local anesthetic to be effective and then proceed with the dental procedure

Titration of Sedation during the Procedure

##### **Remifentanyl titration for analgesia**

1. Leave target concentration at 1 ng/mL unless the analgesic level is insufficient.
2. Increase the dose in 0.2 ng/ml increments
3. Balance remifentanyl decrements if necessary to maintain SpO<sub>2</sub> levels.
4. If the patient is experiencing pain, then assess and administer additional local anesthetic

##### **Time limits for titration (both agents must never be titrated together)**

- Wait 2 min after starting or titrating midazolam with either midazolam or remifentanyl.
- Wait 2 min after titrating remifentanyl with either midazolam or remifentanyl.

If the patient complains of

- Pain - assess the local anesthesia and re-administer
- Discomfort – increase the remifentanyl dose for analgesia
- Awareness – increase the midazolam dose for sedation

Reasons to discontinue sedation or support patient

- No response to loud voice or shaking
- SpO<sub>2</sub> < 90%
- Airway support required
- Patient becomes unstable

If the patient becomes unresponsive and has entered a deeper level of sedation or general anesthesia, place the Alaris pump on hold or pause, then discontinue dental treatment, and assess, support, and observe the patient.

When the patient recovers to the level of moderate sedation, note the Ce drug levels on the pump, adjust the Cpt to equal the Ce reading, and recommence the infusion. If necessary, use a reversal agent for midazolam or remifentanyl. Flumazenil is the reversal agent for midazolam and naloxone is the reversal agent for remifentanyl. Follow the emergency treatment protocol as required.