Original Article

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Safety and efficacy of target controlled infusion administration of propofol and remifentanil for moderate sedation in non-hospital dental practice

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Background: Fearful and anxious patients who find dental treatment intolerable without sedative and analgesic support may benefit from moderate sedation. Target controlled infusion (TCI) pumps are superior to bolus injection in maintaining low plasma and effect-site concentration variability, resulting in stable, steady-state drug concentrations. We evaluated the safety and efficacy of moderate sedation with remifentanil and propofol using TCI pumps in non-hospital dental settings.

Methods: A prospective chart review was conducted on 101 patients sedated with propofol and remifentanil using TCI pumps. The charts were completed at two oral surgeons and one general dentist's office over 6 months. Hypoxia, hypotension, bradycardia, and over-sedation were considered adverse events and were collected using Tracking and Reporting Outcomes of Procedural Sedation (TROOPS). Furthermore, patient recovery time, sedation length, drug dose, and patient satisfaction questionnaires were used to measure sedation effectiveness.

Results: Of the 101 reviewed sedation charts, 54 were of men, and 47 were of women. The mean age of the patients was 40.5 ±18.7 years, and their mean BMI was 25.6 ± 4.4. The patients did not experience hypoxia, bradycardia, and hypotension during the 4694 min of sedation. The average minimum Mean Arterial Pressure (MAP) and heartbeats were 75.1 mmHg and 60.4 bpm, respectively. 98% of patients agreed that the sedation technique met their needs in reducing their anxiety, and 99% agreed that they were satisfied with the sedation 24 hours later. The average sedation time was 46.9 ± 55.6 min, and the average recovery time was 12.4 ± 4.4 min. Remifentanil and propofol had mean initial effect-site concentration doses of 0.96 μ/.ml and 1.0 ng/ml respectively. The overall total amount of drug administered was significantly higher in longer sedation procedures compared to shorter ones, while the infusion rate decreased as the procedural stimulus decreased.

Conclusion: According to the results of this study, no patients experienced adverse events during sedation, and all patients were kept at a moderate sedation level for a wide range of sedation times and differing procedures. The results showed that TCI pumps are safe and effective for administering propofol and remifentanil for moderate sedation in dentistry.

Keywords: Moderate Sedation; Propofol; Remifentanil; Target Controlled Infusion.

INTRODUCTION

Intravenous dental sedation is a treatment option for patients who are afraid, concerned about discomfort or pain, or find dental treatment intolerable without sedatives and analgesics. Moderate or conscious sedation uses drug-induced procedures to reduce patients' awareness and anxiety levels while maintaining responsiveness to verbal or tactile stimuli [1]. Several studies have

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demonstrated the safety of moderate sedation in dentistry [2-5].

Dentists use various sedation techniques and drug combinations to sedate patients. Sedatives/hypnotics, including, benzodiazepines (midazolam) and propofol, with or without opioid analgesics (remifentanil and fentanyl) are commonly used for moderate sedation [6,7]. Intermittent hand-bolus titration or target controlled infusion (TCI) pumps are the most common administration techniques, with TCI being the preferred method for administering propofol and remifentanil intravenously [8,9]. Although sedation is very safe, it is not without risk; comprehensive education and training reduce risk, while innovations and modern drug administration methods improve patient outcomes.

Propofol is a short-acting, sedative-hypnotic drug with limited analgesic effects. The onset of action is 0.5 to 1 min, and the effect lasts for 4–8 min from a single bolus injection [10] despite several favorable properties, including, significant anxiolysis even at sub-sedative doses, anti-emetic and positive mood alterations, rapid onset, faster recovery than midazolam, and less depression of psychomotor functions, the main adverse effects are respiratory depression and hypotension [11,12].

Owing to propofol's limited analgesic properties, a higher dose of propofol is required as a single anesthetic agent to reduce pain-induced movement, which may lead to deeper level sedation and longer recovery time. Several studies have reported that combining different types of drugs has synergistic effects on drug sedative potential [13,14]. Therefore, the addition of opioid narcotics reduces the required dose of propofol significantly [15-17]. Remifentanil is a synthetic short-acting opioid used to induce and maintain sedation [18]. Propofol and remifentanil are useful in moderate dental sedation. Sedation adequacy is dependent on maintaining stable brain or effect-site concentrations of propofol and remifentanil, with doses that are clinically appropriate for the patient and procedure, and in equilibrium with plasma levels [15,19]. TCI pumps outperform bolus injections in maintaining low plasma and effect-site concentration variability after drug injection, which results in stable, steady-state drug concentrations [20].

TCI pumps moderate the distribution of agents between compartments and allows for rapid adjustments to achieve the desired clinical effect [21]. The practitioner enters the drug, pharmacokinetic model, effect-site concentration, and patient characteristics, including sex, age, height, and weight, into TCI. The TCI pump then calculates and administers the bolus dose and infusion rate to achieve and maintain a steady-state drug concentration in the plasma and the effect site (brain) [5,21].

The use of propofol and remifentanil administered by TCI technology are regulated for use in over 95 countries for anesthesia and sedation. For intravenous dental sedation, Health Canada has approved the use of propofol, remifentanil, and TCI pumps (Alaris PK infusion pump with TCI, CareFusion/BD, UK) for on-label use in dental sedation and anesthesia. However, no Canadian dental college has issued a permit for the use of propofol and remifentanil with TCI technology for moderate sedation. To advance important and relevant Canadian clinical research, dental experts from New Zealand collaborated with the University of Alberta, researchers as part of this study examining the safety of this sedation method. We are unaware of any dentist/dental specialist in Canada administering propofol and remifentanil with TCI technology for moderate sedation nor any Canadian university involved in clinical research on this topic.

This study aimed to determine whether the controlled administration of propofol and remifentanil using TCI pump technology maintains a wide enough safety margin to render loss of consciousness/responsiveness unlikely in the dental clinic setting. We aimed to determine the safety and efficacy of this technique for moderate sedation in dentistry by establishing, identifying, and refining a study protocol in preparation for a more extensive study or replication study in Canada.

METHODS

1. Study design and settings

A prospective chart review of 101 patients was conducted in three dental offices in New Zealand, consisting of two oral surgeons and one general dentist. Oral surgeons in New Zealand have administered TCI sedation for over 15 years, and the two-pump TCI sedation process has become the Standard of Care in several dentist/dental specialist offices. The invited oral surgeons and general dentists had > 15 years of experience with TCI sedation. Furthermore, the population and demographic profile of New Zealand are quite similar to those of Alberta, as well as the types of dental surgery and general dentistry practiced. The participating oral surgeons/dentists abided by any research protocol established by the New Zealand Ethics Office and the University of Alberta Research Ethics Office.

2. Patients

In this observational study, we included 101 patients, recruited between August 1, 2019, and February 1, 2020. There were no specific inclusion or exclusion criteria for patient selection. The next patient scheduled for sedation and consented to the study protocol was included. Dental procedures normally performed with sedation in each New Zealand office were recorded in a sedation-monitoring document.

3. Safety measurements

The frequency of adverse events and side effects was recorded to evaluate the sedation procedure safety, using the Tracking and Reporting Outcomes of Procedural Sedation (TROOPS) Adverse Event Reporting [22]. A report is required for any event compromising the airway, circulation, neurophysiology, or patient experience on an intermediate or sentinel basis. A modified Ramsay score > 4 was used as a measure of concern for responsiveness, and values > 4 were considered deep sedation or general anesthesia. Hypoxia was defined as the sum of time intervals of oxygen desaturation (SpO_2) of < 90%, hypotension as MAP < 65 mmHg that lasts for more than 5 min and requires treatment, and bradycardia as a heart rate < 40 bpm that may require treatment [23].

Additionally, brain function monitoring with processed electroencephalograms (pEEG) using the Bispectral index (BIS™, Medtronics, Inc., Minneapolis, MN, USA) was in place for all patients as an objective guide to determine the depth of sedation. Values between 60 and 80 on the BIS index indicated moderate sedation. A score of 60 was used to determine the difference between moderate sedation and general anesthesia, and values < 60 were considered over-sedation [24,25]. All measurements were taken at 5-min intervals by a monitoring assistant.

4. Effectiveness measurements

A five-point scale was used to determine the anxiety level of the patients, ranging from not anxious to extremely anxious. For analysis, not anxious and slightly anxious were categorized as mild, fairly anxious as moderate, and very and extremely anxious as severe. A patient recall and satisfaction questionnaire, as a non-technical outcome measure, was used to provide researchers with information on patients' experiences and perspectives. Participants were asked a series of questions from the patient satisfaction questionnaire immediately following sedation and before discharge, and again 24 - 48 hours later in the follow-up portion of the study.

Four different sedation time measurements were recorded, including sedation time, procedure time, end of sedation to discharge, and end of the procedure to discharge. These measurement were calculated to evaluate the effectiveness of the procedure from a clinical perspective. Moreover, the total dosage of the drugs administered and the drug Ce (concentration of the drug at the effect site or the brain level) concentration range that met the desired level of moderate sedation for dental surgical procedures were measured.

5. Sedation procedure

Patient demographics, including sex, age, height, weight, body mass index (BMI), and ASA physical status category, were recorded, and written consent was obtained. All patients were moderately sedated according to the American Society of Anesthesiologists' definition [1]. This desired sedation level was equal to the modified Ramsay Sedation Score of three and four, where a patient is responsive to loud verbal and light tactile stimuli [26].

The study participants received the established TCI dental intravenous sedation consistent with each oral surgeon and general dentist's office protocol, which might be slightly different from each other. However, they all followed the same principles for their sedation technique [27-28]. Supplemental oxygen was administered to all patients. They were monitored by pulse oximetry, heart rate, nasal capnography and end-tidal CO_2, Non-Invasive Blood Pressure (NIBP) monitoring, brain function monitoring (pEEG), and ECG for patients > 60 years or patients with a cardiac history.

TCI sedation involved controlled administration of propofol and remifentanil using two Alaris PK infusion pumps with TCI. To control drug concentration during sedation, pharmacokinetic software models targeting effect-site (brain) concentrations were used (Schnider for propofol and Minto for remifentanil). An effective site-target concentration of 1 μg/ml for propofol and 1 ng/ml for remifentanil were commonly administered for commencing sedation, which could be altered based on the patient's response and adequate depth of sedation. Verbal communication and BIS monitoring provided information to the clinician during the titration of propofol and remifentanil to obtain the desired level of sedation. Two TCI-trained registered nurses assisted the practitioner during sedation, and one nurse was solely responsible for monitoring the patient. The sedation score was recorded throughout the sedation time at 5 min intervals.

Post-sedation, all patients were followed up with a phone call, and if there were any concerns, the patients were seen immediately. In the event of any problems or concerns after hours, the phone number of the oral surgeon/dentist was available on the post sedation instruction sheet.

6. Statistical analysis

The IBM SPSS Statistics ver. 26 (IBM Corp., Armonk, NY, USA) was used to conduct all analyses. A screening process was conducted before analysis to determine any data entry errors or outliers. The independent t-test was used to compare variables between general dentistry and oral surgeon clinics, and one-way ANOVA and non-parametric tests were used to compare variable means between the three dental clinics. Interpretation of the results was based on a significance level of 0.05.

The University Research Ethics Office approved this study, (approval number Pro00083505) and the study was registered at clinicaltrial.gov (NCT03995134).

RESULTS

During the study, 40 patients at surgeon site 1, 41 at surgeon site 2, and 20 at the general dentistry site were recruited and consented to participate successfully. A total of 101 sedation charts were reviewed, of which 54 and 47 patients were men and women, respectively. After reviewing the charts, one patient with ASA category 3 was excluded from the analysis. The mean age of patients was 40.5 ± 18.7 years, and the mean BMI, weight, and height were 25.6 ± 4.4, 76.8 ± 17 kg, and 172.8 ± 9.8 cm, respectively (Table 1). The reviewed patients underwent various procedures, including tooth extraction, implant placement, oral surgery, root canal therapy, restorations, and cleaning.

1. Safety measures

Five criteria for safety measures were collected from all patients in this study. 1) For a total of 4694 min under sedation, no patient had oxygen saturation below 90%. The minimum SpO_2 was 94%, and the average SpO_2 was

Table 1. Patients demographics and procedures details

Patient characteristics		N (% /SD)
ASA category	1	76 (76)
	2	17 (17)
	Missing	7 (7)
Gender	Male	46 (46)
	Female	54 (54)
Age	Mean	40.5 (18.7)
	Median	38
	Range	74 (12-86)
BMI	Mean	25.6 (4.4)
	Median	25
	Range	23.9 (14.2-38.1)
Weight	Mean	76.8 (17)
	Median	75
	Range	76 (46-122)
Height	Mean	172.8 (9.8)
	Median	173
	Range	52 (145-197)
Treatments	Aesthetic	3 (3)
	Extraction	61 (61)
	Restoration	9 (9)
	Hygiene	1 (1)
	Implant and Surgery	14 (14)
	Root canal therapy	2 (2)
	Unknown	11 (11)

ASA, American Society of Anesthesiologists; N, number; SD, standard deviation.

99.2% 2) None of the patients reported a responsiveness score > 4, which means no patient lost responsiveness (consciousness) at any point of the procedure. 3) The pEEG results, show no patient had a BIS score below 60. The average patient's minimum BIS was 77.2 ± 6.6, and the average BIS of all sedation times was 85.3 ± 5.4. 4) In terms of hemodynamic changes during sedation, no patients required treatment for hypotension, and the average lowest MAP was 75.1 ± 11.8 mmHg, while the average for the entire sedation was 83.7 ± 11.5. 5) The minimum reported heartbeat was 41 bpm, with an average of 60.2 bpm. As we did not observe any adverse events during the study, no TROOP report was utilized (Table 2). To investigate the effect of different procedures and patients' anxiety levels on vital signs during sedation, the procedures were categorized into extraction, surgery, and restorative, and anxiety level as mild, moderate, and severe. No statistically significant differences were observed in the different anxiety levels. However, the

Table 2. Summary of safety measurements

Safety measures		Number of patients (%)
Hypoxia		0
Hypotension		0
Bradycardia		0
Oversedation	Bispectral index	0
	Modified Ramsay score	0

average of the lowest SpO_2 and MAP values was significantly lower in the restorative group (Table 3).

2. Effectiveness measures

Patient satisfaction was recorded using a six-question survey (their level of recall, satisfaction, meeting needs, and willingness to use the procedure again). The survey was given immediately and 24 hours after the procedure using a 5-point Likert response scale. One hundred respondents completed both surveys. Of the responses, 96% of patients reported" agreeing or strongly agreeing" with the sedation technique meeting their needs in reducing their anxiety immediately after the procedure, which increased to 98% 24 h after the procedure. 95% of participants reported that they "agreed and strongly agreed" with being satisfied with the sedation immediately after, increasing to 99% 24 hours later. Eighteen% of patients reported recalling parts of the procedure immediately after, decreasing to 5% 24 h later.

3. Sedation timing

The timing of the procedure was evaluated in four ways: sedation time, procedure time, recovery time (sedation stop to discharge), and discontinuation of the procedure (Table 3). The modified Aldrete Scale was used as the discharge criterion. The results showed an average sedation time of 46.9 min with a standard deviation of 55.6 min. Of note, the median time was 26 min, meaning there was a bimodal distribution where one dentist (general dentist) tended to conduct procedures > 120 min (mean = 121.4 ± 84.8), and the surgeons (oral surgeons) tended to conduct procedures < 60 min (mean = 24.4 ± 15.8). However, there was no significant difference in the recovery time of patients in the three clinics (P = 0.34).

Table 3. Vital signs within different procedures and anxiety levels

	Procedures			P value	Anxiety			P value
	Extraction	Surgery	Restorative		Mild	Moderate	Severe	
	Mean (SD)				Mean (SD)			
BIS	85.2 (5.2)	87.2 (5.8)	86.7 (4.3)	0.370	85.2 (5.3)	86.9 (5.6)	82.9 (4.6)	0.061
Min BIS	77.2 (6.5)	80.3 (7.8)	77.1 (6.5)	0.345	77.5 (7.4)	78.2 (6.0)	75.1 (4.6)	0.305
SpO_2	99.3 (0.9)	99.0 (1.0)	98.9 (1.1)	0.222	99.0 (1.0)	99.4 (0.9)	99.5 (0.8)	0.066
Min SpO_2	98.7 (1.5)	98.2 (1.5)	97.4 (2.1)	0.032*	98.1 (1.6)	98.7 (1.8)	99.0 (1.2)	0.088
MAP	85.1 (10.9)	83.7 (14.7)	79.6 (7.6)	0.247	10.8 (2.5)	10.8 (2.9)	10.9 (2.7)	0.729
Min MAP	77.0 (10.3)	77.4 (15.0)	67.1 (9.1)	0.010*	7.1 (2.5)	7.0 (2.2)	7.2 (1.9)	0.88
HR	72.3 (13.8)	66.1 (9.3)	67.2 (11.7)	0.176	84.6 (12.3)	83.0 (12.3)	82.4 (8.0)	0.164
Min HR	61.9 (11.7)	57.8 (6.2)	55.5 (11.1)	0.108	75.6 (12.9)	74.7 (12.5)	74.1 (7.3)	0.217

BIS, Bispectral index; HR, Heart Rate; MAP, Mean Arterial Pressure; SD, Standard Deviation.

Table 4. Details of Sedation timings and comparison of different settings

Sedation timing	Procedure time	Sedation time	Sedation stop to discharge	Procedure stop to discharge
Mean (SD)	43.8 (55.7)	46.9 (55.6)	12.43 (4.43)	13 (4.70)
Median	25.00	26.00	12.00	13.00
Range	283 (4-287)	290 (0-290)	24 (3-27)	33 (1-34)

Clinics	Mean (SD)	P value	Mean (SD)	P value
	Sedation time		Recovery time	
Surgeon 1	16.7 (7)	0.001	12.4 (5.8)	0.306
Surgeon 2	38.17 (17.6)		11.88 (2.7)	
General	123.80 (84.3)		13.68 (4.1)	

SD, Standard Deviation.

The 10th percentile value determined that 90% of all patients were under sedation for 93 min or less. The average procedure time was 43.8 min with a standard deviation of 55.7 min. The average recovery time was 12.4 mins with a standard deviation of 4.4 min.

4. Amount of sedation drugs used

The results showed an average initial effect-site concentration (Ce) of 0.96 μg/ml and 1.0 ng/ml for propofol and remifentanil, respectively, which increased to 1.63 μg/ml and 1.52 ng/ml near the end of the sedation. While no statistically significant difference in the initial Ce of drugs in dental settings, a significant difference was observed in all other compared variables, and the total dose and concentration of drugs in the general clinic were lower than those outside the general clinic (Table 4 and 5).

DISCUSSION

Although previous studies have shown that procedural sedation in dentistry is safe, identifying and managing risks is critical to ensuring safe sedation in a non-hospital setting. An adequate depth of sedation is vital because deeper levels of sedation can cause respiratory depression, airway obstruction, and cardiovascular instability. In dentistry, the airway is shared with the dentist and the protective cough reflex might be impaired due to local anesthesia, therefore monitoring sedation depth and planning for adverse events management become particularly important [29,30]. Herein, the sedation charts of 101 patients were reviewed. The participating patients' ages ranged from 12 to 86 years, with a BMI of 14–38 and ASA categories of 1 and 2. A limitation of this study is that we did not examine patients in ASA categories 3 and 4; however, because most dental patients who

Table 5. Comparison of drugs used in different settings

Drugs		Mean (SD)				P value
		Surgery (N = 81)	General (N = 18)	Total	Range	
Propofol Ce (μg.ml $^{-1}$)	Initial	0.95 (0.15)	1.01 (0.14)	0.96 (0.15)	1.0 (0.5-1.5)	
	Min	0.95 (0.15)	0.64 (0.32)	0.89 (0.23)	.9 (0.2-1.1)	
	Max	1.83 (0.51)	1.18 (0.3)	1.70 (0.54)	2.3 (0.7-3)	
	Final	1.79 (0.53)	0.94 (0.37)	1.63 (0.60)	2.6 (0.4-3)	
Propofol infusion rate (mg/kg)/mins		0.12 (0.05)	0.05 (0.03)	0.11 (0.05)		0.001*
Total propofol (mg)		191.9	333.26	215.56		0.012
Remifentanil Ce (ng.ml $^{-1}$)	Initial	0.97 (0.1)	1.11 (0.27)	1.00 (0.16)	1.5 (0.5-2)	
	Min	0.97 (0.11)	0.69 (0.33)	0.92 (0.20)	1.2 (0.2-1.4)	
	Max	1.72 (0.49)	1.37 (0.35)	1.66 (0.49)	1.9 (1-2.9)	
	Final	1.64 (0.49)	1.03 (0.41)	1.53 (0.53)	2.4 (0.5-2.9)	
Remifentanil infusion rate(μg/kg)/mins		0.1 (0.04)	0.05 (0.03)	0.09 (0.04)		0.001*
Total propofol (μg)		171.4	357.67	202.91		0.004

Ce, Effect-cite concentration; N, number; SD, Standard Deviation.

received treatment in non-hospital settings were in categories 1 and 2, the results could be generalized [31]. In the general and oral surgery clinic, the participants received various dental procedures with different levels of stimulation, from oral surgeries to veneer preparation. Our results revealed that patients undergoing restorative treatment had lower minimum BIS and SpO2 averages. This might be due to the longer sedation duration and in turn the higher total dose of propofol in this group. Weisenberg et al. and Philips et al. reported that greater BIS changes from baseline and an increased risk of hypotensive episodes are related to higher propofol doses which are consistent with our findings [32,33].

The patients were sedated for 4 min to > 4 h depending on the procedure and their needs and received different concentrations of the drugs according to patient-to-patient differences and the amount of procedure stimulation.

Despite these differences, no adverse events were recorded in the reviewed sedation charts, demonstrating the flexibility of this technique in maintaining steady-state sedation for a wide range of procedures and sedation times. Furthermore, no significant difference was observed between the patient's vital signs and anxiety levels which supports the flexibility of the technique as well. These findings are consistent with those of the previous studies [13,19,34].

Ninety-five percent of the patients reported that this technique met their needs, and 99% were completely satisfied. The satisfaction rate reported in this study was higher than that reported by Dixon et al. [35] and Pourabbas et al. [36].

Another strength of short-acting drugs utilized by TCI is the rapid recovery time [19,37]. The results of this study showed that regardless of the duration of sedation, the patient's recovery time was approximately 12 min. The patients' average recovery time was comparable to that of our previous study, where we compared the recovery time of sedated patients with midazolam coupled with bolus fentanyl and TCI remifentanil. The recovery time in this study was slightly shorter than that in both groups (18 and 13 min, respectively, for the fentanyl and remifentanil groups) [38].

A commonly observed adverse effect of sedation with propofol is hypotension [39,40], and previous studies have shown dose dependency of propofol's hemodynamic effects [36]. Using a dual TCI pump with propofol and remifentanil, the dose required to obtain an adequate level of sedation was significantly reduced. The maximum propofol Ce in our study was 1.7 mg/ml, equal to the Ce reported by Wells et al. [20]. However, the reported remifentanil Ce of 1.65 ng/ml is less than the 1.86 ng/ml reported by them. The propofol Ce supports the findings of Cushion et al. [5], who reported a mean propofol Ce of 1.5 μg/ml to obtain an adequate depth of sedation for

dental procedures. Compared to our study, Berends et al. [23] reported an average maximum propofol Ce of 3.3 ± 1.09, which is almost twice as high as propofol Ce in our study. However, their study reported remifentanil at 0.99 ± 0.22, which is less than the results of our study. A higher propofol Ce may have contributed to the more frequent adverse events in that study, highlighting the importance of maintaining a proper balance between the concentrations of the two drugs.

A higher dose of drugs was administered in the general clinic because of longer procedures. However, the infusion rate (mg/kg/min for propofol and μg/kg/min for remifentanil) in the general clinic was 0.05 for both drugs, which is significantly lower than 0.12 and 0.1 for propofol and remifentanil administered in the surgery clinic, respectively. This may be due to the more intense surgical procedures, indicating that higher drug doses were required.

In conclusion, according to the results of this study, TCI pumps are safe and efficacious in administering propofol and remifentanil for moderate sedation in dentistry. All patients were maintained under moderate sedation, with few adverse events, the benefits of early discharge, and home readiness. Considering that the study population and settings are similar to those of Alberta, the results of this pilot study provided sufficient data for evaluating the potential of applying this technique in Alberta and provided valuable clinical research experience that can be used to conduct a more extensive study in Canada.

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Don Macalister: Data curation, Writing - review & editing
David Chrisp: Data curation, Writing - review & editing
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