Efficacy of continuous intravenous remimazolam versus midazolam in the extraction of impacted wisdom teeth: protocol of a randomised controlled trial

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ABSTRACT

Introduction Benzodiazepines such as midazolam are widely used to moderately sedate patients during impacted wisdom tooth extraction to reduce anxiety in outpatient surgery. This present protocol was designed to determine whether continuous intravenous remimazolam, a new ultrashort-acting benzodiazepine, produces superior postoperative recovery quality to that of midazolam in patients undergoing extraction of impacted wisdom teeth.

Methods and analysis This study is a multicentre randomised controlled trial conducted at Peking Union Medical College Hospital, Beijing Anzhen Hospital and Beijing Shijitan Hospital in China. Approximately 150 participants undergoing extraction of impacted mandibular wisdom teeth will be randomly allocated to two groups (remimazolam and midazolam). The participants will be administered standard interventions to ensure they achieve a sedation level of III on the Ramsay sedation scale during the treatment. Preoperative and anaesthesia management and surgical techniques will be standardised for all participants. The primary outcome is recovery time for complete alertness and the secondary outcomes are anterograde amnesia during and after surgery, and interruption during operation for poor compliance or safety concerns.

Ethics and dissemination This study has been approved by the Ethics Review Committee of Peking Union Medical College Hospital (approval number: ZS-3142), Beijing Anzhen Hospital (approval number: KS2022082) and Beijing Shijitan Hospital (approval number: 2023-4). Trial registration number NCT05350085.

INTRODUCTION

Impacted wisdom tooth extraction is a common practice in dentistry. Performing this type of surgery is associated with challenges, particularly pertaining to patient discomfort during the procedure. Despite the local anaesthesia, patients undergo local heel incision, flap turnover, bone removal, chisel as well as vibration of instruments, bleeding and odour in the mouth, which can all contribute to discomfort. Many patients experience dental anxiety (DA), a condition that refers to the anxiety, tension and fear surrounding dental treatment. DA can manifest as increased sensitivity, reduced tolerance and the avoidance or rejection of dental treatment.1 2 3

According to epidemiological surveys, the incidence rate of DA in outpatients ranges from 40% to 80%4 and leads to decreased satisfaction as well as continued deterioration of oral health in these patients.5 As such, severe DA is closely linked to poor dental health.6 In the past 10 years, dental sedation technology has rapidly developed, providing patients with a better treatment experience to reduce DA. Various conscious sedation strategies are available to reduce the anxiety of patients during dental care and surgery including oral,7 rectal,8 inhaled,9 intravenous sedation and general anaesthesia.10 Intravenous sedation is a commonly used technique in conscious sedation.11 Once venous access is established, administration is convenient, the onset of therapeutic effects is rapid and the degree of sedation is easily adjusted. Unlike many other outpatient operations, dental surgery is performed in the oral cavity and often requires irrigation with water. This
means that patients need to retain purposeful responses to verbal or tactile stimulation in order to reduce the risk of aspiration.

Propofol and midazolam\(^ {12} \) are effective intravenous sedatives commonly used for dental procedures, both have advantages and disadvantages that affect their clinical use. Propofol exhibits a rapid onset of action but can induce cardiorespiratory depression\(^ {13} \) and involuntary movements\(^ {14} \) as side effects. In contrast, midazolam has superior anxiolytic and anticonvulsant actions than propofol,\(^ {15,16} \) although it has a relatively prolonged onset of action and recovery time. Therefore, further research is required to find a new, effective and safe drug.

Remimazolam is a new type of ultrashort-acting benzodiazepine.\(^ {17,18} \) Remimazolam combined with opioid analgesics can be used for ambulatory sedation.\(^ {19} \) Phase III clinical studies of this agent have used remimazolam in colonoscopy,\(^ {20} \) fibrobronchoscopy\(^ {21} \) and for the induction and maintenance of general anaesthesia.\(^ {22,23} \) These studies show that when compared with other similar products, remimazolam exhibited a quick action onset, rapid metabolism and no accumulation. These observations indicate that remimazolam may have advantages over midazolam in ensuring optimal postoperative recovery in outpatient dental operations.

Based on these potential advantages, we designed a randomised controlled trial (RCT) to investigate the clinical efficacy of remimazolam. In addition, we aim to determine its possible superiority over midazolam in postoperative recovery quality, patient compliance and safety concerns under the same depth of sedation in patients undergoing extraction of impacted wisdom teeth.

**METHODS AND ANALYSIS**

**Study design**

This multicentre prospective RCT will last for 12 months and will be conducted at Peking Union Medical College Hospital, Beijing Anzhen Hospital and Beijing Shijitan Hospital. A total of 150 participants will randomly be assigned to one of the following two groups: trial or control and will be administered remimazolam or midazolam, respectively.

The trial schematic and time frame are shown in figures 1 and 2, respectively. The study will be monitored by an independent trial steering committee and data safety monitoring committee.

**Patient and public involvement**

Patients and/or the public were not involved in the design, or conduct, or reporting or dissemination plans of this research.

**Study population**

**Inclusion criteria**

Consenting patients will be eligible if they:

1. Have mandibular impacted wisdom teeth that need to be extracted.
2. Have a body mass index (BMI) between 18.5 and 30 kg/m\(^2\).
3. Are aged between 18 and 60 years.
4. Have American Society of Anesthesiology (ASA) classification grade of I–II.
5. Have Modified Dental Anxiety Scale (MDAS) score >15.
6. Volunteered to accept intravenous sedation.

![Study design and participant flow chart.](http://bmjopen.bmj.com/ BMJ Open: first published as 10.1136/bmjopen-2022-067908 on 25 April 2023. Downloaded from http://bmjopen.bmj.com/ on October 6, 2023 by guest. Protected by copyright.)
Exclusion criteria
Patients will be ineligible if they:
1. Are pregnant.
2. Experience respiratory infections, asthma attack or persistent state.
3. Have contraindications to anaesthesia or a previous abnormal surgical anaesthesia recovery history.
4. Have severe cardiopulmonary insufficiency.
5. Have preoperative blood pressure >160/100 mm Hg or diastolic blood pressure >100 mm Hg, or blood pressure <90/60 mm Hg.
6. Have a neuromuscular or mental disorder that renders them unable to communicate or cooperate effectively or sign informed consent.
7. Are suspected of abusing narcotic analgesics or sedatives.
8. Have a known allergy or contraindication to benzodiazepines.
9. Have participated in other drug trials within 6 months.

Randomisation and blinding
Patients who meet the inclusion criteria will sign informed consent before surgery, and then will be randomly assigned to one of two groups by a computer-generated random sequence. Block randomisation with random block sizes ranged from 4 to 8 will be used and randomisation will be stratified by trial centre. Random sequence will be held by an independent anaesthesiologist and the nurse will get the treatment allocation from the anaesthesiologist by telephone after the patient get into the operating room and before the surgery. According to allocation, patients will receive either 25 mg remimazolam or 15 mg midazolam diluted in a 50 mL syringe with normal saline. Participants, anaesthesiologists, surgeons and outcome assessors will be blinded to the group assignments. The syringes used in the trial will be visually identical to maintain blinding of participants and trial personnel. Blinding will be broken if it is necessary to know the intervention for emergency rescue situations.

Interventions
All participants will undergo a preliminary dental examination before treatment, in which X-ray films of the tooth to be extracted will be taken to evaluate the soft tissue and bone resistance. After signing the informed consent form, 75 participants will be randomly allocated to either the remimazolam (A) or midazolam (B) group. The baseline information for each participant will be recorded before surgery including age, gender, BMI, blood pressure, heart rate, pulse oximetry (SpO2) and MDAS score. All other preoperative procedures, anaesthesia management and surgical techniques will be
The anaesthesia scheme is as follows:

1. Initial injection rate: The first dose will be administered using a microinjection pump, at a rate of 100 mL/hour. The participant will be observed until they achieve Ramsay sedation grade III24 (table 1). This will now act as the maintenance dose and local anaesthesia will be started, followed by the dental surgery. (2) Maintenance injection rate: During this stage, the pump rate will be maintained at 10–30 mL/hour and the patients Ramsay sedation scale will be monitored every 5 min. The pump rate will be adjusted to maintain the patient at Ramsay sedation grade III and Houpt score ≥5. (3) Cessation: After the operation, the patient will be observed for 5 min and in the absence of active bleeding, the microinjection pump will be stopped.

The medication administration will be regarded as a failure, if the total amount of drug administered exceeds 50 mL, and the patient still fails to reach Ramsay sedation grade III, or Houpt score ≤4, which means treatment are difficult to perform. If treatment has not started yet, the alternative is local anaesthesia. If treatment are interrupted due to failure of sedation, operation will be stopped immediately and continued after general anaesthesia.

After drug discontinuation, the condition of the patient will be scored using the Modified Observer’s Assessment of Alertness/Sedation (MOAA/S) scale (table 2)25 each minute until the patient meets an MOAA/S score of 5, three consecutive times. The patient will be examined before leaving the hospital and specific adverse effects (AEs) will be noted. The recovery time, vital signs, AEs, operation duration and drug dose will also be recorded. Patient compliance during the operation will be evaluated using the Houpt behaviour scale26 and dentist satisfaction will be scored using a Likert scale.

To evaluate the extent and duration of anterograde amnesia, three cards with different images (including animals, fruits and vegetables) will be shown to patients during the operation and recovery period. They will be asked to recall the card contents immediately and approximately 5 min after (delayed) the immediate memory examination. The observation time points are after local anaesthesia, after tooth extraction, and 0, 15, 30 and 60 min after complete alertness. Failure to recall the contents of the cards will be regarded as anterograde amnesia.

After the operation, patients will be moved to the postanaesthesia care unit and subsequently leave hospital once they meet the discharge criteria. This includes receiving an Aldrete score27 of at least 9 out of 10. Investigators and outcome evaluators will receive specific training to ensure that the research and evaluation are conducted strictly according to the protocol design. The anaesthesia records, medical records and medical advice will be reviewed to confirm the interventions.

**Follow-up and withdrawal**

The study follow-up will be scheduled 1 day after treatment. Patients will be asked whether they can remember the manipulation performed during the procedure. The patient’s satisfaction rating will be scored using the Likert scale after treatment, through a telephone follow-up survey. For any patients who withdraw from the study, efforts will be made to complete the corresponding observation. The reason for the suspension will be documented in the case report form (CRF) and the original record. All participants withdrawn from the study will be managed in accordance with the standard procedures of the hospital.

**Outcomes**

**Primary outcome**

The primary outcome is to observe recovery time until complete alertness, which will be calculated from the cessation of sedative injection. Patients will be scored every minute using the MOAA/S scale, and the first minute with an MOAA/S score of 5, three consecutive times.

**Secondary outcomes**

The secondary outcomes include:

1. The anterograde amnesia during and after the operation. To determine this, three different cards will be shown to the patient, who will then be asked to recall the contents of each card. Each correct response is
recorded as 1 point and a score of more than 3 points will be considered as anterograde amnesia.

2. The interruption reasons during operation includes chokes, hypoxia, continuous movement that makes treatment difficult, or other situations requiring suspension of operation.

Statistical analysis

Sample size
This is an RCT with the main outcome being recovery time until complete alertness. The statistical method selected for the data analysis is the Z-test. Previous studies have reported a recovery time to complete alertness of 7.35±5.78 min in patients administered remimazolam and 15.84±11.57 min for midazolam (mean±SD). According to bilateral α=0.05, β=0.2, the required sample size of each group is 19 cases, and the sample size of each group is 21 cases according to the 10% shedding rate. In the actual study, 50 patients are to be included in each study centre, with 150 patients in total.

Statistical methods
Data management will include paper CRFs. The main outcome data will be analysed according to the intention-to-treat analysis principle, where the patients will be randomly divided into groups. The recovery time until complete vigilance and the onset of sedation will be analysed using the Student’s t-test of independent samples or Wilcoxon signed rank sum test. The number, category and severity of AEs in the two groups will be analysed using the χ² test or Fisher’s exact probability test to compare the incidence of AEs between the groups. The R V.4.0.2 software package will be used for statistical analysis. All statistical tests will be two sided and results with p values<0.05 will be considered statistically significant.

Adverse effects
The clinical symptoms and signs will be reviewed to determine if they are adverse drug effects, and all AEs will be determined as such by the test personnel. Serious AEs (SAEs) will be documented with a detailed description and recorded in a table within the summary report. The anaesthesiologist will be allowed to change the sedation and ventilation scheme at any time according to the requirements of the surgeon or if there is any concern about the safety of the patient.

AEs related to treatment, especially events such as decreased oxygen saturation and respiratory depression, will be recorded. Each SAE shall be recorded on the CRF and the study intervention shall be promptly unblinded for affected participants if it is urgently necessary. In the event of an SAE, all efforts shall be made to remedy the situation and necessary measures shall be actively instituted to avoid permanent damage. From the beginning of the patient’s trial participation to the development of any SAEs up to 24 hours after the operation, the tester must report the occurrence to the ethics committee within 24 hours.

Protocol amendments
The current protocol version is V.3.2, dated 1 April 2022. Any changes to the protocol during the trial that may affect the conduct, safety or the benefit to patients will require a formal protocol amendment.

DISCUSSION
The most significant advantage of a new type of ultrashort-acting benzodiazepine is the rapid recovery time. Both the terminal half-life and mean residence times for remimazolam were 20%–25% of that of midazolam. In addition, remimazolam is metabolised by tissue esterases to an inactive metabolite and thus, does not accumulate in the human body. Previous studies reported that remimazolam was effective and safe for moderate sedation in outpatient surgery. Most (>80%) remimazolam recipients successfully completed their endoscopy (≥97% of patients) within a predefined dosage regimen of remimazolam (≥84%), without requiring midazolam as a rescue sedative (≥90%). In bronchoscopy, the success rates were 80.6% in the remimazolam arm, 4.8% in the placebo arm (p<0.0001) and 32.9% in the midazolam arm. An exploratory analysis reported that remimazolam had a shorter onset of action and faster neuropsychiatric recovery than midazolam. In our study, we will compare the effects of remimazolam with those of a widely used similar drug, midazolam, in wisdom tooth extraction.

The initial dose will be constant, then the injection rate will be adjusted according to the Ramsay sedation score of the patient. Presently, there are no recognised guidelines for pumped dosage selection for remimazolam. A shallower depth of sedation and lower dose is required for impacted wisdom tooth extraction than for other outpatient surgeries or intensive care unit sedation because of the nature of dental irrigation. Initial titrating doses of midazolam have historically ranged from 2 to 10 mg when administered to normal, healthy (ASA 1) adult patients. This is based on continuing dental education programmes surrounding the use of intravenous remimazolam for moderate sedation at the University of Southern California School of Dentistry and Oregon Health Sciences University. Patients will be sedated within 4–8 min after the start of drug administration. Our research team has found that the total dose of intravenous midazolam was (9.58±3.76) mg to treat severe dental phobia, and mean infusion rate was (0.28±0.06) mg /kg/hour. The drug description recommends an induction dose of 7 mg for remimazolam. We considered previous research, the drug instructions used in this study, and practical effect to determine the ultimate dosing regimen. Consequently, after a 1 month pilot study, we selected an initial dosage of 50 mg/hour and 30 mg/hour for remimazolam and midazolam, respectively. The total amount of drug administered in the pilot study did not exceed the recommended dose.

Anterograde amnesia is a fascinating side effect of benzodiazepines and can be beneficial in suppressing the
patient’s memory of pain and other discomfort experienced during treatment. However, it can also suppress their memory of important details, such as medical orders and payments, which can be highly inconvenient for patients to forget. A previous study reported that half of the participants on midazolam were in a state of forgetfulness for 23.77 min, and 5% of the participants were still forgetful at 53.90 min. The ideal drug should prevent the patient from recalling the adverse experience during the treatment but this effect should not persist long after the drug is stopped. Therefore, we designed this study to evaluate the degree of anterograde amnesia during the operation, and its postoperative duration with both drugs. The evaluation method used involved post-traumatic amnesia evaluation. For the evaluation, common card types will be selected to ensure that each participant can correctly identify the card contents.

Respiratory depression will be the main concern of both remimazolam and midazolam, although previous studies showed its low liability for cardiovascular or respiratory depression. Moreover, dental treatment can also affect breathing, resulting in choking or intraoperative hypoxia. Continuous oxygenation is monitored. If $\text{SpO}_2$ is <93% and cannot be improved by oxygen inhalation or airway patency, the operation needs to be stopped until oxygenation improved. The benzodiazepine antagonist flumazenil can be used in case of adverse events.

The difficulty of wisdom teeth removal of all cases in different centres will be evaluated and determined by a single dentist, to ensure the surgical removal level is consistent to approximately the same degree of difficulty.

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Our study also has some limitations including being the first attempt to use remimazolam in dental surgery without previous literature support. The doses and timing of the intervention are based on preclinical experiments and clinical practice. Additionally, the available population is somewhat limited, as a single disease was investigated in this study. Ultimately, further studies extending the population to other dental operations would be necessary.

In conclusion, our study will compare the effect of remimazolam and midazolam in wisdom tooth extraction, to potentially prove the superiority of remimazolam to midazolam in recovery time, patient cooperation and anterograde amnesia effect. Based on current research, this study will provide strong evidential support for the application of remimazolam in dental operations and may provide a new choice of an intravenous sedation strategy in dentistry.

Contributors LP, LW, QJ and KW participated in the design and coordination of the study. LP, LW, ML, KW, QJ, XR, SC and YH collected references and developed the protocol. LP, LW and YZ performed the statistical analysis. LP, LW and QJ drafted the manuscript. All authors read and approved the final manuscript. LW and QJ contributed equally to the manuscript.

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