ISRCTN35903062 https://doi.org/10.1186/ISRCTN35903062

Remimazolam vs midazolam cognitive and motor recovery after intravenous conscious sedation for dental extractions

Submission date 10/06/2021	**Recruitment status** No longer recruiting	[X] Prospectively registered [_] Protocol [_] Statistical analysis plan [_] Results [_] Individual participant data [_] Record updated in last year
Registration date 09/12/2021	**Overall study status** Completed	
Last Edited 05/09/2022	**Condition category** Oral Health	

Plain English summary of protocol

Background and study aims

Over 12% of people in Britain are very anxious about dental work. Having teeth removed is often said to cause the most anxiety. Intravenous sedation is where a drug is injected into a patient's hand or arm. The drug stops them from feeling worried and helps them relax and feel better able to cope. About half a million sedations for dental treatment are carried out in England each year. Sedation is very safe, and people generally say that they have had a good experience. After sedation patients wait in a recovery area until they are safe to walk. They usually go home after about an hour, but the side effects of the drug can last until the next day. This can cause people to forget important things, like putting a cooker on, and to feel heavy and sleepy and risk bumping into things for the rest of the day. A new drug (remimazolam) is in development that has the same sedation effect and safety, but the recovery is much quicker. It is thought that the side effects from the new drug will have worn off by the time patients are ready to leave the hospital. This means patients might feel more alert going home and better able to look after themselves. The aim of this study is to find out whether remimazolam is better than the current drug that is used (midazolam) and allows patients to recover faster and feel better quicker after surgery.

Who can participate?

Patients aged between 18 and 59 years who are coming to Guy's Hospital to have their wisdom tooth extracted under sedation

What does the study involve?

Patients are randomly picked by a computer to be given the new or old drug. On the day of the appointment participants will be asked to follow all the normal sedation instructions. The sedation and dental treatment will be carried out in the normal way. The only extra things will be some questionnaires and some tests. This will add an extra 2 hours to the appointment time. Participants will only be discharged on the day of the procedure with an accompanying person. There are four research tests. In the learning test participants will be asked to listen to some words and repeat them back. This tests how well they can remember new information. In the reaction test participants will be asked to rest their fingers on a keypad and move their fingers

when lights come on above them. This tests how quick their reactions are. In the symbol test participants will be asked to draw small shapes that are linked to numbers. This tests how well they can process information. In the standing test participants will be asked to stand on a platform that measures how much they are swaying back and forth. This tests how stable they are to walk. These tests are designed to check different ways the brain and body are affected by the sedation. By testing people before and after the sedation the researchers can see how they recovered. They will then check the results of the new and existing drugs to see if people having the new drug recovered quicker.
The researchers plan to phone patients a few days after their appointment to check they were happy with the sedation. They will also check they did not have any side effects from the medication. The phone call will take about 20 minutes. Normal fasting instructions will be given and standard of care leaflets. Participants will be are asked to refrain from alcohol, using heavy machinery, making important decisions or taking non-prescription drugs for at least 24 hours after the procedure. Painkillers like paracetamol may be recommended by the doctor as per standard of care.

What are the possible benefits and risks of participating?
The patient will be asked to attend the hospital early on the day of the procedure for consent and will have two 30 minute episodes of memory and balance testing (one before procedure and one after procedure). This will add about 2 hours onto the normal treatment time but the patient is not required to wait in the Dental Institute between the first set of assessments and their procedure appointment. A member of the research team will be with the patient and can help with any questions during the testing. The tests were reviewed by the patient representative group and were not perceived to be burdensome.
The sedation and surgical tooth removal procedure will be carried out in the same way as patients who are not in the study. From published clinical trials and medication information available, the risks are the same as the standard of care and have been identified and mitigated by the use of monitoring by appropriately trained staff.
It is not anticipated that the patient will receive any direct benefit by participating in the trial. However, the patient will receive up to £60 reimbursement to cover reasonable expenses, including travel expenses, for themselves and their accompanying person.

Where is the study run from?
Guy’s Hospital (UK)

When is the study starting and how long is it expected to run for?
November 2020 to September 2023

Who is funding the study?
Paion AG (Germany)

Who is the main contact?
Dr Bryan Kerr
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Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number
2020-005121-89

IRAS number
1003587

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
CPMS 49437, IRAS 1003587

Study information

Scientific Title
A phase III randomised, triple-blind controlled superiority trial of remimazolam (CNS 7056), compared to midazolam, in adults having lower third molar wisdom tooth extraction under intravenous conscious sedation to assess cognitive and motor recovery at normal discharge times

Acronym
REMIDENT

Study objectives
To compare the cognitive recovery profile of a new sedative drug (remimazolam) to the current standard of care (midazolam). This may be a more appropriate sedative for dental extractions due to the pharmacokinetics and may increase patient safety when discharged and traveling home after sedation.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 28/09/2021, West of Scotland REC 1 (West of Scotland Research Ethics Service, Ward 11, Dykebar Hospital, Grahamston Road, Paisley, PA2 7DE, UK; +44 (0)141 314 0212; WosRec1@ggc.scot.nhs.uk), REC ref: 21/WS/0105

Study design
Interventional; Design type: Treatment, Drug, Other; Randomized

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
See additional files

Health condition(s) or problem(s) studied
Low risk mandibular third molar wisdom tooth extraction

Interventions
Participants will be randomised in a 1:1 ratio (remimazolam: midazolam). Randomisation will use permuted blocks of varying sizes and will be undertaken via a bespoke online randomisation service.

In the remimazolam arm, patients will be given an initial dose of 5 mg (2 ml) over 60 seconds, pausing for 90 seconds, followed by 2.5 mg (1 ml) over 30 seconds and waiting 30 seconds will be titrated to the response endpoint. Subsequent doses of 2.5 mg (1 ml) increments can be administered if required should the procedure take longer, or the patient recovers more quickly than expected, to maintain the sedation level. Top-up doses will be administered slowly, at least 2 minutes apart. Top-up doses will be limited to a maximum of 5 doses in a 15-minute window. Additionally, a maximum dose of 40 mg of remimazolam (16 ml) will be set.

In the midazolam arm, dosing of midazolam was based on local formulary and standard of care /local guidance. An initial dose of 2 mg (2 ml) over 60 seconds, pausing for 90 seconds, followed by 1 mg (1 ml) over 30 seconds and waiting 30 seconds will be titrated to the response endpoint. Subsequent doses of 1 mg (1 ml) increments can be administered if required should the procedure take longer, or the patient recovers more quickly than expected, to maintain the sedation level. Top-up doses will be administered slowly at least 2 minutes apart. Top-up doses will be limited to a maximum of 5 doses in a 15-minute window. Additionally, a maximum dose of 16 mg of midazolam (16 ml) will be set.

The patient will have the treatment on the day of their procedure only. Prior to their procedure, each patient will undergo memory and balance testing, which will be repeated again once the procedure is complete. They will be followed up with a phone call 3-10 days after their procedure.

Intervention Type
Drug

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
Remimazolam, midazolam

Primary outcome measure
Verbal learning measured using the Hopkins Verbal Learning Test Revised (HVLT(R)) at baseline and 60 min from last dose of Investigational Medicinal Product (IMP) vs midazolam (T60)

Secondary outcome measures

1. Recovery measured using the proportion of patients returning to within 1 standard error (SE) of pre-dose cognitive and motor testing, measured using HVLT(R), Digit Symbol Substitution Test (DSST), Multi-Operational Apparatus for Reaction Time (MOART) and sway scores at baseline and 60 min from last IMP dose (T60)
2. Cognitive operation measured using the Digit Symbol Substitution Test (DSST) at baseline and 60 min from last IMP dose (T60)
3. Sway measured using the scales for assessment and rating of ataxia (balance board) at baseline and T60
4. Reaction time measured using MOART device by choice reaction time (with Go/No Go) at baseline and last dose of IMP (T60)
5. The times to fully alert (first of three Modified Observer's Assessment of Alertness/Sedation (MOAA/S) scores of 5) after the end of the procedure (surgical “time out”) and after the last IMP dose (T60)
6. The times to ready for discharge after the end of the procedure (surgical “time out”) measured using Clinical Walk and orientation test
7. The overall co-operation score given by the surgical team (Dental Sedation Teacher Groups (DSTG) score) at end of the procedure
8. Occurrence of pain on injection at the application of study medication measured using the visual analogue score (VAS) at dosing
9. The procedure failure rate due to inadequate sedation at the maximum dose/top-up rate measured using the number of failures at the end of the trial
10. Comparative safety measures of adverse events measured using the number of adverse events at the end of the trial

Overall study start date
01/11/2020

Completion date
01/09/2023

Eligibility

Key inclusion criteria
Current participant inclusion criteria as of 11/05/2022:
1. Patients who are scheduled to have mandibular third molar removal with intravenous conscious sedation
2. Male and female patients, aged ≥18 to ≤59 years old
3. American Society of Anesthesiologists (ASA-PS) grade I or II
4. English as their first or main language for ≥5 years. The primary outcome measure (HVLT) is a cognitive test to remember English words and validated on this basis
5. A patient who has given informed written consent for inclusion to the study
6. Patients who are willing and able to comply with study requirements

Previous participant inclusion criteria:
1. Healthy adult male and female patients aged between 18 and 59 years old
2. Scheduled to have low risk mandibular third molar wisdom tooth extraction with intravenous conscious sedation

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
Planned Sample Size: 128; UK Sample Size: 128

Key exclusion criteria
Current participant exclusion criteria as of 11/05/2022:
1. Any surgical risk factor which, in the opinion of the study surgeon, can lead to increased procedure complexity (for example high risk of inferior alveolar nerve damage)
2. A known sensitivity to benzodiazepines or a medical condition such that these agents are contraindicated as per the SmPC, for example unstable myasthenia gravis, hepatic impairment, acute respiratory depression, and severe respiratory failure
3. Any neurological deficit where cognitive tests will be impaired (for example dementia)
4. A patient with known difficult airway/ mask ventilation or who has increased risk factors recorded by the clinical team at assessment
5. A patient who reports hypersensitive gag reflex
6. Body mass index >34.9 kg/m2 or weight <50kg or >130kg
7. Dental or needle phobia identified by a modified dental anxiety score ≥19 (MDAS questionnaire)
8. High Hospital Anxiety and Depression Score (HADS) >12
9. Chronic use of benzodiazepines or opioids for any indication
10. Use of medications known to interact with IMP or comparator as listed in the SmPC
11. All female patients with a positive urine pregnancy test within 8 hours before IMP administration. Female patients who are permanently sterile are not required to have a urine test. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.
12. Lactating female patients currently breastfeeding
13. Patients who self-report illicit drug use in the last 4 weeks
14. Patients who self-report alcohol abuse (AUDIT-C Scores > 7) or a history of abuse within the past 5 years
15. Patients who self-report a history of illicit drug abuse within the past 5 years or any history of benzodiazepine dependence
16. Inclusion in a study of an IMP in the previous 4 weeks or less than seven half-lives (whichever is the longer)
17. Hypersensitivity to the IMP or to any of the excipients
18. Patients who are unable to stand unassisted

Previous participant exclusion criteria:
Known sensitivity to benzodiazepines or a medical condition or concomitant medication such that these agents are cautioned or contraindicated

Date of first enrolment
09/03/2022

Date of final enrolment
01/02/2023

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
Guy's Hospital
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Sponsor information

Organisation
Guy's and St Thomas' NHS Foundation Trust

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Sponsor type
Hospital/treatment centre

Website
http://www.guysandstthomas.nhs.uk/Home.aspx

ROR
https://ror.org/00j161312

Funder(s)

Funder type
Industry

Funder Name
Paion AG

Results and Publications

Publication and dissemination plan
1. Protocol to be published online in due course
2. Planned publication in a high-impact peer-reviewed journal

Intention to publish date
01/10/2024

Individual participant data (IPD) sharing plan
The data-sharing plans for the current study are unknown and will be made available at a later date

IPD sharing plan summary
Data sharing statement to be made available at a later date

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Participant information sheet	version 1.2	30/06/2021	09/12/2021	No	Yes
HRA research summary			28/06/2023	No	No