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Effectiveness and safety of oral sedation in adult patients undergoing dental procedures: protocol for a systematic review

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ABSTRACT

Introduction The management of anxious patients undergoing dental procedures is still a challenge in clinical practice. Despite a wide variety of drugs for oral sedation in adult patients, there are relatively few systematic reviews that compare the effectiveness and safety of different drugs administered via this route. Thus, this study will evaluate the effectiveness and safety of oral sedation with benzodiazepines and other agents to patients undergoing dental surgical procedures.

Method/design We will conduct a systematic review and, if appropriate, a meta-analysis of randomised controlled clinical trials that will evaluate the use of conscious sedation administered orally to adult patients undergoing oral surgery. The search will be conducted using electronic databases, such as the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE (via Ovid), EMBASE (via Ovid), CINAHL (via Ovid), Lilacs (SciELO) and Capes database, without restriction of languages or date of publication. Primary outcomes include anxiety, sedation, treatment satisfaction, pain and adverse effects. Secondary outcomes include vital parameters (heart rate, respiratory rate and blood pressure) and patient cooperation during intervention. A team of reviewers will independently assess each citation for eligibility and in duplicates. For eligible studies, the same reviewers will perform data extraction, risk of bias assessment and determination of the overall quality of evidence using the Grading of Recommendations Assessment, Development and Evaluation classification system.

Ethics and dissemination The evidence gathered from this study should provide dental surgeons with knowledge on the effectiveness and safety of oral sedation in adults requiring dental surgical procedures. This in turn should contribute towards the decision-making process in dental practice, minimising the risks of anxiety and ineffective pain control in clinical procedures, as well as possible side effects. Ethics approval is not required in protocols for systematic reviews. The systematic review will be published in a peer-reviewed journal and presented at conferences.

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Strengths and limitations of this study

► Anxiety and risk of adverse effects with the use of sedatives are negative outcomes in dentistry that may interfere with preoperative, intraoperative and postoperative effects relating to surgical interventions in dental practice. Estimating the risk rate of such events in patients treated with oral sedation may contribute to the decision-making process regarding conscious sedation.
► This study will provide a summary on safety for the commonly used oral sedative drugs for conscious sedation in dentistry.
► The quality of the primary studies to be included in this review may be a limiting factor due to heterogeneity in study design and outcome measurements.

INTRODUCTION

Effective control of anxiety and pain plays a pivotal role on patient compliance and adherence to dental treatment. For behavioural management, the use of analgesia and conscious sedation are important strategies for treating patients who suffer from anxiety to dental treatment.[1]

Conscious sedation is an approach that uses one or more drugs to produce a state of central nervous system depression maintaining verbal contact with the patient throughout.[2] The sedation level must be such that the patient remains conscious and is capable of readily understanding and answering verbal commands or tactile stimulation.[3] Drug interventions to provide conscious sedation for dental treatment must have a wide enough safety margin so that loss of consciousness is unlikely to happen.[4] In addition, considering the different methods of sedation and patient profiles in dental

care, monitoring procedures and documentation have been recommended.[3 5 6]

Among the different types of sedation in dentistry, oral sedation is a relatively accessible means for dentists to address patient anxiety when chairside manner alone is insufficient.[6] Moreover, it involves the administration of a relatively large dose of oral sedatives in dental practice, which differs from the concept of premedication, which involves self-administration of a small dose of oral sedative to relieve anxiety.[3] As any other approach, oral sedation may present some limitations due to the pharmacokinetics relating to the oral route, such as delayed and variable onset of action.[6] Although it may help patients with mild to moderate levels of anxiety, this technique may not be effective in severely anxious patients.[7]

Oral sedation does not guarantee that a dental patient will achieve a state of anxiolysis or will not drift into deeper levels of sedation.[7] Since sedation is a continuum, it is not always possible to predict how an individual will respond. Therefore, practitioners intending to obtain a given level of sedation should also be able to rescue patients should they become overly sedated.[8] Indications for the use of conscious sedation as a patient management tool include a diagnosis of anxiety and dental phobia, prolonged or traumatic dental procedures, medical conditions potentially aggravated by stress and medical conditions that affect the capacity of the patient to cooperate, such as special needs.[9]

Benzodiazepines are the class of drugs most often used in dentistry to induce a state of anxiolysis[10] and are the drugs of choice for oral sedation in several countries,[3 6 7 11] although sublingual and intravenous administration are also available.[12 13] Historically, temazepam has been the drug of choice for oral sedation in dentistry in some countries, but its use has been largely replaced by midazolam.[3]

Although these drugs have a similar mechanism of action, they differ on pharmacokinetic characteristics, which in turn play an important role on selecting the best option to suit a patient's profile.[5] Among the different options for oral sedation in dentistry are midazolam, diazepam, triazolam and lorazepam as mainstream drugs, although alprazolam, temazepam and oxazepam have also been used.[6]

Despite a great variety of drugs used for conscious sedation in dentistry, there are only a few systematic reviews comparing their effectiveness and safety for oral sedation in adults. One systematic review evaluated the use of these drugs in adults but did not assess the risk of bias and the quality of the evidence of the outcomes found.[10] Another systematic review study on sedation methods in dentistry verified the effectiveness of benzodiazepines at children.[14] Hence, to fill this gap, we propose a systematic review to determine whether benzodiazepines and other drug interventions administered orally are effective and safe in controlling anxiety in adult patients undergoing dental surgical procedures.

METHODS AND ANALYSES

This systematic review will be conducted in accordance with the recommendations specified by the Cochrane Handbook for Intervention Reviews. Evaluation will be performed following the items from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.[15]

Eligibility criteria
The studies will be selected according to the following criteria.

Study designs
We will include only randomised controlled trial in that at least one arm should include the use of oral sedation with benzodiazepines or other drugs in adult patients and in the other arm placebo (same route of administration as the test sedative) or other treatment.

Participants
We will include studies that report adult outpatients, both sexes, requiring dental surgical procedures, such as simple exodontia, surgery for orthodontic purposes, removal of residual roots and third molars, dental implants and other dental surgical interventions.

Exclusion criteria
We will include studies including adults with respiratory diseases, contraindications to benzodiazepines, pregnant and/or breastfeeding women and those with a history of allergy will be excluded. In addition, studies combining administration of different drugs for oral sedation will also be excluded.

Outcomes
Studies should report at least one of the following outcomes: primary outcomes (pain, anxiety and adverse effects, for example, hypoxaemia and amnesia) and secondary outcomes (heart rate, respiratory rate, blood pressure and patient cooperation during the intervention).

Information sources
The search for studies will be performed using the following databases: Cochrane Central Register of Controlled Trials (CENTRAL), which includes Dentistry and Oral Health Group's Specialized Register, MEDLINE (via Ovid), EMBASE (via Ovid), CINAHL (via Ovid), Lilacs (SciELO) and Capes database, without restriction of languages or date of publication.

For review articles, one of the reviewers will analyse the reference list or citation in the text in order to verify and identify other possible eligible studies. Whenever necessary, main authors and/or pharmaceutical companies involved in the production of the drugs will be contacted for information on additional trials.

Search strategies
The search strategy will be conducted by reviewers individually based on keywords such as oral surgery,

benzodiazepines and other drugs combined. The search strategy in Ovid MEDLINE is available in online supplementary appendix 1 .

Study records
Data management
After performing the search strategies separately in each electronic database, the researchers will import the results from each search into an EndNote library. As the same article may be located in more than one database, duplicate entries will be identified and removed.

Study eligibility determination
Four reviewers (JdOA, CdCB, CCG and NKdA), working in pairs, will independently screen citations and abstracts based on the eligibility criteria. Full texts of all articles will be obtained in case either reviewer feels that they might be eligible. Two reviewers will independently assess the eligibility of each full-text article and resolve disagreements by consensus among the review team. In case of duplicate publications, the article with the most complete data will be used.

Kappa statistics will be used to measure agreement between the examiners. Values of kappa between 0.40 and 0.59 will be considered fair agreement, values between 0.60 and 0.80 good agreement and values equal to or higher than 0.75 excellent agreement.[16]

Data collection
Relevant data, from eligible studies, will be independently extracted by four reviewers in Excel program, using a standardised data extraction form. Extracted data will be summarised in tables and graphics. The discrepancies will be resolved by discussion and consensus among the review team.

Data items
The extracted data from each included study will include:
1. *article details*: year and journal of publication;
2. *study details*: setting, number of participants in each group, source population, lost to follow-up and/or reasons for non-participation (if applicable), type of benzodiazepines, type of dental procedure and participant characteristics (age, gender and clinical condition);
3. *methodological details*: measured outcomes, measure of risk of bias and measure of the body of evidence;
4. *quantitative measures*: data mean/SD or median/IQR for the outcomes evaluated;
5. *other details*: source of funding statement (present or absent), actual source of funding (present or absent) and conflict of interest statement (present or absent) and conflict of interest type (employee of company conducting study and others).

Data extraction
The reviewers will use a standardised and pretested form for data extraction. For articles published as abstracts only or articles lacking important information, an attempt

to obtain complete data on methods and results will be made by contacting the authors.

Two reviewers, in pairs and independently, will be calibrated based on data extraction from three articles, initially, and then, consensus will be reached. This procedure will continue until the reviewers are able to extract data in a standardised manner to minimise discrepancies.

Assessment of risk of bias in included studies
A modified version for the Cochrane collaboration approach will be used for assessing risk of bias.[17–19] Reviewers will independently evaluate the risk of bias for each randomised study according to the following criteria: adequate randomisation, allocation concealment blinding of the patient, healthcare professionals, outcome assessors, data collectors and data analysts; incomplete outcome data; selective outcome reporting and major baseline imbalance. Reviewers will attribute standard answers such as 'definitely yes', 'probably yes', 'probably no' and 'definitely no' for each domain, with 'definitely yes' and 'probably yes' denoting a low risk of bias and 'definitely no' and 'probably no' attributing a high risk of bias.[20] Reviewers will resolve disagreements by consensus, and one arbitrator (LCL) will settle unresolved disagreements.

Explaining heterogeneity of evidence
Possible complications for heterogeneity include drug types, doses (higher vs lower) with greater effect than expected at higher doses and treatment time (longer vs shorter) and doses with greater effect than expected with longer treatment time; heterogeneity will be assessed in terms of estimates of combined effect using the χ^2 test and I^2 statistic.[21] Heterogeneity will be categorised as until 25% (low heterogeneity), 50% (moderate heterogeneity) or 75% (high heterogeneity).[19]

Quality of the evidence analysis
The quality and strength of the body of evidence will be independently analysed (confidence in effect estimates) for each of the results via the Grading of Recommendations Assessment, Development and Evaluation (GRADE).[16 22] In the GRADE approach, randomised studies start with low evidence according to one or more of the five categories of limitation: risk of bias, inconsistency, indirectness, imprecision and reporting bias.

Data synthesis
Intervention drug, intervention group and each outcome of interest will be analysed. Confidence in the estimates for each group will be determined, and analysis for body of evidence will be performed on those with higher confidence. The hypothesis will be examined for which information will be documented on at least 10 studies for the independent variables or at least five studies for the independent categorical variables. Combined analysis will estimate the risks of negative outcomes such as anxiety and side effects of oral sedation.

Meta-analysis will be conducted using STATA (V.10.1) for random effect,[23] which is conservative with each study, and differences in the error calculation between studies will be used for the analysis. For the studies with dichotomous outcomes, relative risk will be calculated as well as 95% CIs.

For continuous data, the weighted mean difference (WMD) and their 95% CI as effect measurement will be used. Once the WMD is calculated, this value will be contextualised, taking into account, whenever available, the minimal important difference (MID); the smallest change in the measurement will be considered important for the patient.

If studies report the same construction, using different instruments of measurement, the standardised mean difference (SMD) will be calculated as sensitivity analysis. SMD expresses the effect of the intervention in units of SD, instead of initial measurement units, with the value of SMD depending on the size of the effect (the difference between the means) and the SD of the results (the inherent variability among the participants). Measurements of results that present MID will be used to convert SMD to an OR and difference of risk.[24]

In order to facilitate interpretation of effects of continuous outcome, MID will be replaced by SD (denominator) in the WMD equation,[25] whenever available for different scales. If an MID estimate is not available, a statistical approach will be used to provide an estimate of a proportion of patients who would benefit from the treatment in all studies.[26] Statistical approaches to enhance interpretation of results from continuous outcomes described herein will be included in the methods. Funnel plots will be created to explore possible biases of publication, when at least 10 studies are found.[27]

Combined estimates will be tested by Z statistics and heterogeneity by Q statistics between the studies analysed by the X^2 test. When heterogeneity is detected, a component of variance due to interstudy variability will incorporate the calculation of the CI for the estimate. Studies that do not include any of the above data will not be included in the grouped estimate; for such studies, bleeding rates will be summarised descriptively.

Approaches recently developed to deal with dichotomous[28] and continuous[29] outcomes will be performed. These approaches will be applied to results that meet the following criteria: significant effect in treatment is demonstrated and data loss is sufficient to potentially introduce clinically important bias. The threshold for loss of participant's data will be determined for each outcome.

If meta-analysis is not appropriate because of excessive heterogeneity of population, intervention, comparator, outcome or methodology, then summary charts will be developed, and a narrative synthesis will be provided.

Summarising evidence

Results will be presented in evidence profiles, as recommended by the work group GRADE.[30 31] Evidence profiles will provide succinct presentations of the quality of the evidence and magnitude of effects. An evidence profile will be built aided by software, GRADEpro (http://ims.cochrane.org/gradepro) in order to include the following seven elements: (1) a list of up to seven important results (desirable and undesirable), (2) a measure of typical load of such results (ie, control, group and estimated risk), (3) a measure of the difference between the risks with and without intervention, (4) the greatness regarding effect, (5) the number of participants and studies that approach these outcomes, as well as follow-up period, (6) an evaluation of the global confidence in the estimate of effect for each outcome and (7) comments, which will include MID, whenever available. In the GRADE approach, randomised trials begin as high-quality evidence but may be rated down by one or more of five categories of limitations: risk of bias, inconsistency, indirectness, imprecision and reporting bias.

DISCUSSION

This review will evaluate the available evidence regarding the efficacy and safety of oral sedation in adult patients undergoing dental surgical interventions, such as exodontia, dental implants, surgery for orthodontic purposes and removal of residual roots and third molars in order to provide estimates of evidence in a complete and consistent manner, using the GRADE approach.[32] The results of this systematic review will help dentists in the decision-making process in clinical practice for the best oral sedation choice for patients undergoing surgical procedures.

The information compiled regarding the use of conscious sedation by oral route in patients who will require ambulatory surgical intervention aims to provide professionals with reliable data on effectiveness and safety of pharmacological agents in such interventions, thus facilitating clinical decisions. This study may also identify areas of interest for future investigations.

Ethics and dissemination

Ethics approval is not required, as this is a protocol for a systematic review. The systematic review will be published in a peer-reviewed journal and presented at conferences. The evidence reported in this study will allow dentists to know about the effectiveness and safety of oral sedation. Updates of this study will be conducted in order to inform and guide clinical practice.

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