

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	EFFECTIVENESS AND SAFETY OF ORAL SEDATION IN ADULT PATIENTS UNDERGOING DENTAL PROCEDURES: A SYSTEMATIC REVIEW
AUTHORS	Motta, Rogério; Araújo, Jimmy; Bergamaschi, Cristiane; Lopes, Luciane; Guimaraes, Caio; de Andrade, Natalia Karol; Ramacciato, Juliana

VERSION 1 – REVIEW

REVIEWER	Paul Ashley UCL
REVIEW RETURNED	16-Aug-2020

GENERAL COMMENTS	<p>In general the English could do with some editing to improve it</p> <p>Title and introduction Appropriate. Justified study.</p> <p>Aim I thought this was confused. The hypothesis was safety (stated in the introduction). But the primary outcomes ranged from pain to anxiety. This paper needs a clearly defined aim in a PICO format. And there can only be one primary outcome - eg safety, or effectiveness. The remaining outcomes then become secondary outcomes or proxy measures for the primary outcome.</p> <p>Methods Patient cooperation is described as a secondary outcome. The majority of scales measuring sedation (one of the primary outcomes) measure patient behaviour or cooperation (eg Houpt).</p> <p>Which of the outcomes measured (except for the physiological ones) would allow you to assess safety?</p> <p>Presumably you included cross over trials - these are sometimes excluded in systematic reviews of sedation because outcomes are likely to be distorted by the design. Did you consider this? How might it have influenced your review if these papers had been excluded?</p> <p>The search strategy needs to a start date as well as the end date (March 2020)</p> <p>In the methods it states that a GRADE analysis was attempted but not completed as a meta-analysis was not possible. GRADE does</p>
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	<p>not require a meta-analysis to be carried out, I would suggest that you complete the GRADE process.</p> <p>Did you do any hand searching? If not - why not.</p> <p>Results You need to give the actual measurement scale used in each study in the table. So there are five studies measuring anxiety but I have no idea what the scale was without going through each of the narrative descriptions.</p> <p>What does the outcome of pain have to do with the efficacy or safety of sedation</p> <p>In general the results could be more usefully presented by type of drug.</p> <p>Adverse events are described in the results but there is nothing about them in the methods. What did you consider to be an adverse event?</p> <p>Discussion and conclusion The conclusion needs to be completely rewritten - given the inability to carry out meta-analysis or combine data it is inappropriate to conclude that any of the drugs should be recommended</p> <p>Overall the authors have done well to search, collect and extract data. But they need to consider what their outcomes are and re-present the review accordingly. Serious consideration as well should be given to excluding cross-over trials</p>
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REVIEWER	Janet H Southerland University of Texas Medical Branch - Galveston, USA
REVIEW RETURNED	19-Aug-2020

GENERAL COMMENTS	<p>The manuscript "Effectiveness and safety of oral sedation in adult patients undergoing dental procedures: a systematic review" provides a systemic review to evaluate the effectiveness and safety of oral sedation in patients undergoing dental procedures. The authors have focused the review on randomized clinical trials (RCTs) comparing oral use of benzodiazepines and other medications versus placebo for oral sedation in adults. The review protocol was published and registered at PROSPERO. The following outlined items represent significant weaknesses of the systematic review:</p> <ol style="list-style-type: none"> 1) Overall, the standard for written English language is not good making it very difficult to evaluate the results and quality of the review.. There are a significant number of grammatical and incomplete sentence structure errors 2) Throughout the text on numerous occasions, there are references that are made that state "Studies found" or "In the study", but there is not study clearly identified to reference these type statements 3) The order of tables and figures is not consistent with the presentation of methods and results
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VERSION 1 – AUTHOR RESPONSE

Reviewer: 1 (Name: Paul Ashley)

Please leave your comments for the authors below. In general the English could do with some editing to improve it. Title and introduction: Appropriate. Justified study.

6) Aim: I thought this was confused. The hypothesis was safety (stated in the introduction). But the primary outcomes ranged from pain to anxiety. This paper needs a clearly defined aim in a PICO format.

Our objective was to assess if oral sedation is effective and safe when performed on adult patients undergoing dental procedures. In this way, the "Introduction" has been corrected in order to improve the description of the hypothesis. We also inserted the PICO strategy in the item "Method".

7) And there can only be one primary outcome - eg safety, or effectiveness. The remaining outcomes then become secondary outcomes or proxy measures for the primary outcome.

We have followed the Cochrane handbook (you can check in Higgins JPT, Green S. Cochrane handbook for systematic reviews of interventions version 5.1.0: the Cochrane Collaboration. 2011) in that more than one outcome can be used. In this case of this systematic review, the effectiveness is too important as safety. We have performed adjustments to the outcomes as described below:

Primary outcomes

1) Effectiveness was measured by improvement in anxiety by using the Dental Anxiety Scale (DAS), Oral Surgery Confidence Questionnaire (OSCQ), and/or other scales for anxiety symptoms.

2) Safety was measured by the number of participants that reported side effects, number of adverse effects (or adverse drug reactions), and number of participants that dropped out due to side effects.

Secondary outcomes

1) Secondary outcomes of effectiveness were sedation and satisfaction with the treatment.

2) Secondary outcomes were heart rate, respiratory rate, blood pressure, and oxygen saturation.

7) Methods: Patient cooperation is described as a secondary outcome. The majority of scales measuring sedation (one of the primary outcomes) measure patient behaviour or cooperation (eg Houpt).

We agree with your recommendation and only the outcome sedation was maintained.

8) Which of the outcomes measured (except for the physiological ones) would allow you to assess safety? What does the outcome of pain have to do with the efficacy or safety of sedation?

We have considered "adverse effect" primary outcome of safety. We have described this information more detailed in the method, as previously mentioned. The pain outcome was removed as suggested.

9) Presumably you included cross over trials - these are sometimes excluded in systematic reviews of sedation because outcomes are likely to be distorted by the design. Did you consider this? How might it have influenced your review if these papers had been excluded?

We agree that there are disadvantages in using the RCT crossover as the carryover effect. However, the fact that the drugs were used in a single dose minimizes this effect. In Dentistry it is common to use this type of study design in many situations (including for oral sedation). Thus, we have inserted the wash out period information in table 2 in order to clarify this issue.

10) The search strategy needs to a start date as well as the end date (March 2020). Did you do any hand searching? If not - why not.

We have considered the studies from inception of the database to the date of 12 March, 2020. We have performed hand search analysing the reference list or citation of review articles and other systematic reviews to verify and identify other possible RCTs. Whenever necessary, main authors and/or pharmaceutical companies involved in the production of the drugs were contacted for information on additional trials.

11) In the methods it states that a GRADE analysis was attempted but not completed as a meta-analysis was not possible. GRADE does not require a meta-analysis to be carried out, I would suggest that you complete the GRADE process.

We based on previous studies that not justified the use of this tool when the meta-analysis was not performed. The GRADE tool is mainly used for the pooled data by outcome, to assess the quality of evidence. Hence, if it is not possible pooled the data in a meta-analysis, you may not be able to evaluate the quality of evidence, since you will not have much information other than the tables already present until the stage of qualitative synthesis. The evaluation of inconsistency, indirect evidence and publication bias seem to be impaired by the results found in clinical trials. Additionally, the included studies in this systematic review had methodological limitations and a small number of participants that limited our findings. However, we are available for any adjustments that the reviewer deems necessary. We have changed the information in the method in order to clarify this information.

12) Results: You need to give the actual measurement scale used in each study in the table. So there are five studies measuring anxiety, but I have no idea what the scale was without going through each of the narrative descriptions.

Thank you very much for this recommendation. We have inserted this information in table 2.

13) In general the results could be more usefully presented by type of drug. Overall the authors have done well to search, collect and extract data. But they need to consider what their outcomes are and re-present the review accordingly. Serious consideration as well should be given to excluding cross-over trials.

Thank you for this recommendation. We re-presented the results by type of drug and we understood that the outcomes of pain and cooperation with treatment should not be considered.

14) Adverse events are described in the results but there is nothing about them in the methods. What did you consider to be an adverse event?

This information was corrected. We have collected adverse effect data which is one of the adverse events related to the use of the medication.

Discussion and conclusion

15) The conclusion needs to be completely rewritten - given the inability to carry out meta-analysis or combine data it is inappropriate to conclude that any of the drugs should be recommended.

We have edited the conclusion as requested.

Dear Reviewer,

We would like to thank you very much for your interesting comments and for having considered our paper for publication. We have edited and corrected the paper according to your suggestions. We have corrected mistakes concerning the English Style. We also highlighted the changes within our manuscript using colored text.

Reviewer: 2

Janet H Southerland

16) Please leave your comments for the authors below the manuscript "Effectiveness and safety of oral sedation in adult patients undergoing dental procedures: a systematic review" provides a systemic review to evaluate the effectiveness and safety of oral sedation in patients undergoing dental procedures. The authors have focused the review on randomized clinical trials (RCTs)

comparing oral use of benzodiazepines and other medications versus placebo for oral sedation in adults. The review protocol was published and registered at PROSPERO. The following outlined items represent significant weaknesses of the systematic review:

1) Overall, the standard for written English language is not good making it very difficult to evaluate the results and quality of the review. There are a significant number of grammatical and incomplete sentence structure errors.

Sorry for this inconvenience. We have corrected mistakes concerning the English Spellings. After the final revision of the manuscript, a specialized service (www.editage.com) performed the English language editing.

2) Throughout the text on numerous occasions, there are references that are made that state "Studies found" or "In the study", but there is not study clearly identified to reference these type statements.

We have adapted the citations throughout of the text to improve the description of studies.

3) The order of tables and figures is not consistent with the presentation of methods and results.

We have edited the order of tables and figures as requested.

Dear Reviewer,

We would like to thank you very much for your interesting comments and for having considered our paper for publication. We have edited and corrected the paper according to your suggestions. We have corrected mistakes concerning the English Style. We also highlighted the changes within our manuscript using colored text.

VERSION 2 – REVIEW

REVIEWER	Janet H Southerland University of Texas Medical Branch
REVIEW RETURNED	22-Dec-2020
GENERAL COMMENTS	The manuscript is well written and organized. It has been properly registered and closely adheres to outlined standards for systematic reviews. The information is relevant and important to the to the profession.