

Peer Review File

Article information: <https://dx.doi.org/10.21037/joma-22-25>

Reviewer Comments

Title

Comment 1: This reflects the paper but does not identify the paper as a systematic review or scoping review (as appropriate), as per PRISMA checklists.

Response 1: Title has been changed accordingly

"The Analgesic Efficacy and Safety of Nonsteroidal Anti-inflammatory Agents (NSAIDs) in Patients Undergoing Oral & Maxillofacial Surgery– A Systematic Review"

Abstract

Comment 2: This is structured but does not provide all the information suggested by the 'PRISMA 2020 for Abstracts' checklist.

Response 2: The abstract has been edited accordingly to account for more information suggested by the PRISMA guidelines.

Comment 3: Background: L28 – this is probably a global problem rather than one solely limited to the US.

Response 3: The epidemic has been noted to be a worldwide problem.

Comment 4: Background: L29-31 The aim could be made more explicit e.g. by stating to what may be a suitable alternative.

Response 4: Treatment exclusively with NSAIDs is stated to be the suitable alternative

Comment 5: "Methods: Again, please see 'PRISMA 2020 for Abstracts' for guidance as to what information needs to be included in this section. No indication for the method of study selection, data extraction, risk of bias assessment or how the data were to be synthesized were included."

Response 5: More information on methods such as risk of bias assessment and data analysis have been included accordingly.

Comment 6: "Methods: Why were only placebo-controlled trials included if the review authors were trying to identify whether NSAIDs are a viable alternative to opioids? To assess this, head-to-head (H2H) trials would also be relevant and probably more relevant."

Response 6: The review has been adjusted to screen for H2H trials of NSAID vs opioid, instead of NSAID vs. placebo.

"The inclusion criteria specified for head-to-head randomized controlled trials (RCTs) comparing the efficacies of NSAIDs to opioids in patients undergoing OMFS."

Comment 7: Results: Inclusion of some data, to indicate the treatment efficacy of NSAIDs, would be helpful to the readers.

Response 7: Data from the meta-analysis have been included

"The meta-analysis showed no significant difference between the NSAID and opioid groups pertaining to postoperative pain control when analyzing VAS scores and rescue analgesic consumption. However, it was observed that comparison to primarily opioid-based treatment,

NSAID treatment was statistically significant in yielding more favorable outcomes for adverse effects including dizziness (RR = 1.26; 95% CI: (0.15, 0.15); I² = 0%), drowsiness/somnolence (RR = 2.11; 95% CI: (0.05, 4.18); I² = 0%), nausea (RR = 1.87; 95% CI: (0.39, 3.34); I² = 0%), and vomiting (RR = 1.64; 95% CI: (0.58, 2.71); I² = 0%), following OMFS.”

Comment 8: Conclusion: No data are provided to support the conclusion. For the second statement, H2H trials should have been considered.

Response 8: Data from newly conducted meta-analysis in the results section have been included to support conclusion, and H2H trials have been considered in the literature search.

Introduction

Comment 9: "Needs more references to support the statements made eg L52-53; L58-60; L76-78; otherwise it become an opinion statement. As opioid misuse is probably a global problem, the relevance of this paper to a global readership could be improved by considering countries other than US."

Response 9: New references have been added accordingly

References:

Gupta A, Bah M. NSAIDs in the Treatment of Postoperative Pain. *Curr Pain Headache Rep.* 2016;20(11):62.

Bailey E, Worthington HV, van Wijk A, Yates JM, Coulthard P, Afzal Z. Ibuprofen and/or paracetamol (acetaminophen) for pain relief after surgical removal of lower wisdom teeth. *Cochrane Database Syst Rev.* 2013(12):CD004624.

Comment 10: Although the risks of opioids are stated, the side effects of NSAIDs also need to be included to give a balanced view.

Response 10: Risks and side effects of NSAIDs have been provided “As with any drug, NSAIDs do come with their own risks. The use of NSAIDs can impact various physiological systems within the body, presenting an increased risk of serious adverse effects such as gastrointestinal bleeding or cardiovascular disease (3).”

Reference: Davis A, Robson J. The dangers of NSAIDs: look both ways. *Br J Gen Pract.* 2016;66(645):172-3.

Comment 11: "Reference to previous systematic reviews on pain relief following OMFS need to be made.

Response 11: The Bailey et al. systematic review has been referenced. Thank you for suggesting the source.

Comment 12: L52 suggest by perioperative rather than amongst

Response 12: Edited accordingly

Comment 13: L68 suggest analgesics rather than anesthetics

Response 13: Edited accordingly

Comment 14: "L81 Why was the PRISMA-ScR checklist used when there is no indication that this is a scoping review? If this is a scoping review, this needs to be made clear in the title. If this is a systematic review, which as written, it appears to be, this also needs to be made clear and the

appropriate guidelines and checklist needs to be used."

Response 14: Apologies for the ambiguity. The systematic review approach has been taken, and the title has been modified to reflect this. The PRISMA checklist for systematic review was used instead.

Comment 15: "L84 This is the first mention of 'scoping review' . Why was a scoping review undertaken when there are several other systematic reviews on pain relief in OMFS? I think this review would be better undertaken as a systematic review rather than scoping review and to include H2H trials of NSAIDs vs. opioids."

Response 15: Thank you for the suggestion. This review was modified and undertaken as a systematic review; and all references to scoping reviews have been removed. Additionally, the search criteria has been modified to search for H2H trials of NSAIDs vs opioids. The wording of this sentence has been changed to "a systematic review" .

Comment 16: The search terms may be too limited to identify all relevant trials. See Cochrane search in Bailey et al.2013, for guidance.

Response 16: New search strategy has been included.

"The following search strategy was utilized: (((("anti inflammatory agents non steroidal"[Pharmacological Action] OR "anti inflammatory agents, non steroidal"[MeSH Terms] OR ("anti inflammatory"[All Fields] AND "agents"[All Fields] AND "non steroidal"[All Fields]) OR "non-steroidal anti-inflammatory agents"[All Fields] OR "nsaid"[All Fields] OR "nsaids"[All Fields] OR "nsaid s"[All Fields] OR (("nonsteroid"[All Fields] OR "nonsteroidal"[All Fields] OR "nonsteroidals"[All Fields] OR "nonsteroids"[All Fields]) AND ("anti inflammatory agents"[Pharmacological Action] OR "anti inflammatory agents"[MeSH Terms] OR ("anti inflammatory"[All Fields] AND "agents"[All Fields]) OR "anti inflammatory agents"[All Fields] OR ("anti"[All Fields] AND "inflammatory"[All Fields] AND "drug"[All Fields]) OR "anti inflammatory drug"[All Fields]))) AND ("analgesics opioid"[Pharmacological Action] OR "analgesics, opioid"[MeSH Terms] OR ("analgesics"[All Fields] AND "opioid"[All Fields]) OR "opioid analgesics"[All Fields] OR "opioid"[All Fields] OR "opioids"[All Fields] OR "opioid s"[All Fields]) AND "OMFS"[All Fields]) OR (("mouth"[MeSH Terms] OR "mouth"[All Fields] OR "oral"[All Fields]) AND "maxillofacial"[All Fields])) AND ("pain"[MeSH Terms] OR "pain"[All Fields])) AND (clinicaltrial[Filter] OR randomizedcontrolledtrial[Filter])."

Comment 17: L88 this is a result and would be better placed in the Results section.

Response 17: This line has been moved to the results section

Comment 18: L90-91 why only English? What impact will this have on the generalisability of the review?

Response 18: This parameter has been removed to allow for a more inclusive selection criteria.

Comment 19: L91 why only placebo controlled when it is known that NSAIDs are effective for pain relief for patients undergoing OMSF. See Cochrane review.

Response 19: This search criteria has been modified to search opioid vs NSAID H2H trials, per a previous suggestion.

“A predetermined eligibility criteria for this literature search included (1) head-to-head RCTs concerning the efficacy of an NSAID to an opioid; (2) clinical trials assessing patient populations after undergoing OMF surgery. “

Comment 20: What was the primary and secondary outcomes for the review? These need to be stated.

Response 20: These have now been stated.

“The primary outcome of this study was assessments of numerical pain scores measured using the visual analogue scale (VAS). The secondary outcomes included (1) total rescue analgesic consumption and (2) adverse events”

Comment 21: L105 What does it mean by ‘inconclusive results’? Trials should not be excluded because their results were not significantly different. This would bias the results.

Response 21: Apologies for the ambiguous wording, it was not meant to indicate results that were not significantly different. This phrase has been changed to “ongoing clinical trials that had no results released at the time of the literature search” .

Comment 22: "L108 T1 Lidocaine is not a NSAID so why was this trial included in the review? It is a local aesthetic of the amide type. Also see Lyngstad et al which has a placebo arm from which data could be extracted."

Response 22: The lidocaine trial has been removed from the review

Comment 23: No data on the relative efficacy are presented.

Response 23: Data from meta-analysis have been included in the results section for efficacy, measured by VAS scores and rescue analgesic consumption.

Comment 24: No data synthesis has been undertaken.

Response 24: Meta-analysis was conducted to analyze data on VAS scores, adverse effects, and rescue analgesic consumption

Comment 25: This largely contains the results from the trials which would be better placed in the Results section.

Response 25: Tables for results have been created for results section, and outcomes from meta-analysis have also been included in results section.

Comment 26: It would be preferable to state which is the primary outcome and what are the secondary outcomes of interest.

Response 26: Stated in methods.

“The primary outcome of this study was assessments of numerical pain scores measured using the visual analogue scale (VAS). The secondary outcomes included (1) total rescue analgesic consumption and (2) adverse events”

Comment 27: "L244 This is a significant limitation and consideration should be given to consider a review of NSAIDs versus placebo or an opioid drug. This would address the aims of this study with the background of the problems surrounding opioid abuse."

Response 27: Review now assesses H2H trials for NSAID vs opioid drug

Comment 28: L248-250 This review only considered placebo-controlled trials so how can the authors make this comment when they didn't search for H2H comparisons of NSAIDs versus opioids.

Response 28: H2H trials have been searched in the new review. Comment has been removed.

Comment 29: "L258-260 The authors can't conclude that "NSAIDs serve as an optimal therapy... ." As they have not compared to other analgesics. It appears to be better than a placebo. Optimal implies the 'best or most favourable' option."

Response 29: Thank you for the clarification. "Optimal" wording has been removed.

Comment 30: L262-263 Again, the authors haven't looked at this so this statement can't be made from the evidence presented.

Response 30: Statement has been removed

Comment 31: Again, on a simple search in PubMed "pain AND molar AND opioid AND ibuprofen", I have found RCTs comparing NSAIDs with opioids in OMFS.

Response 31: Such trials have now been included in review

Table and Figure

Comment 32: T1 This is confusing in that the study name (Col1) is given as the drug name rather than the first author name.

Response 32: The first author's last name has been included in the first column to identify each study.

Comment 33: See above – lidocaine is not a NSAID so inclusion of this trial is inappropriate.

Response 33: Study has been removed.

Comment 34: I'm surprised no ibuprofen trials were found. See above.

Response 34: The search criteria has been modified. A number of ibuprofen trials were found in the initial search; however, they did not satisfy all requirements stated in the inclusion criteria and were thus excluded from the review.

Comment 35: F1 this is important. I'm surprised so few records were identified. In Bailey et al, 1500+ records were found initially and 590 following removal of duplicates, for a search of ibuprofen vs. paracetamol RCTs for third molar removal.

Response 35: A new review search criteria has been implemented with 1,616 records initially identified. The figure has been modified accordingly.

Summary

Comment 36: This review appears to be a superficial review of the literature and I am still confused as to whether this is a systematic review or scoping review. The current paper doesn't really fulfill the criteria for either. There are several omissions from the reporting for either type of review and the inclusion of one of the RCTs is wrong in that lidocaine is an anesthetic and not a NSAID.

Response 36: Thank you for reviewing this manuscript. The review has been clarified to be a systematic review. The lidocaine trial has been removed.

Editorial Comments:

1. PRISMA-ScR Reporting Checklist

Comment: Please kindly fill out the PRISMA-ScR Reporting Checklist (https://cdn.amegroups.com/static/public/12s_PRISMA-ScR-Fillable-Checklist.pdf). The relevant page/line and section/paragraph number in the manuscript should be stated for each item in the checklist. A statement "We present the following article in accordance with the PRISMA-ScR reporting checklist" should be included at the end of the "Introduction".

Response: Seeing as this manuscript has taken on the form of a systematic review now, the PRISMA checklist has been attached for reference.

2. Title

Comment: We suggest the authors clearly identify this manuscript as a scoping review, i.e. "The Analgesic Efficacy of Nonsteroidal Anti-inflammatory Agents (NSAIDs) in Patients Undergoing Oral & Maxillofacial Surgery: A Scoping Review".

Response: Title has been modified to reflect a systematic review

"The Analgesic Efficacy and Safety of Nonsteroidal Anti-inflammatory Agents (NSAIDs) in Patients Undergoing Oral & Maxillofacial Surgery– A Systematic Review"

3. Abstract

Comment: Please briefly describe the search strategy, including eligibility criteria, sources of evidence, the process of data extraction in the Abstract-Methods. We also suggest the authors clarify regarding the databases instead of vaguely stating "various databases" on page 2, line 32.

Response: The methods section has been modified to state the following-

"A search of all relevant literature spanning various databases including PubMed, The Cochrane Library, and www.clinicaltrials.gov was conducted for all relevant publications dating up to 01/05/2023, in pursuit of records outlining the use of NSAIDs and opioids in OMFS. The inclusion criteria specified for head-to-head randomized controlled trials (RCTs) comparing the efficacies of NSAIDs to opioids in patients undergoing OMFS. Non-RCT studies were excluded if they did not primarily compare the efficacies of a specific NSAID and opioid, used external drugs other than

NSAIDs and opioids, or had no results released at the time of the literature search. Risk of bias was assessed using the Cochrane Collaboration's Risk of Bias tool. A systematic review and meta-analysis were performed to analyze the data using the SPSS software.”

4. Introduction

Comment: (1) P. 3, L.62-65: Please cite related references for the sentence “Opioids pose several significant risks...and eventual addiction” .

Response:

Reference- Benyamin R, Trescot AM, Datta S, Buenaventura R, Adlaka R, Sehgal N, et al. Opioid complications and side effects. Pain Physician. 2008;11(2 Suppl):S105-20.

Comment: (2) P. 4, L.71-73: We suggest the authors consider citing the source reference not the reference 3 for the “opioid crisis to be a public health emergency” . The reference 3 was published in 2019 which was inconsistent with the date “2017” in the manuscript.

Response: A new reference has been added that was first published in 2017

Reference: Skolnick P. The Opioid Epidemic: Crisis and Solutions. Annu Rev Pharmacol Toxicol. 2018;58:143-59. Salmond S, Allread V. A Population Health Approach to America's Opioid Epidemic. Orthop Nurs. 2019;38(2):95-108.

Comment: (3) P. 4, L.77-79: Don't also forget to cite references for the sentence “Various RCTs and ongoing clinical trials have...addiction and misuse” .

Response: Source has been added:

Bailey E, Worthington HV, van Wijk A, Yates JM, Coulthard P, Afzal Z. Ibuprofen and/or paracetamol (acetaminophen) for pain relief after surgical removal of lower wisdom teeth. Cochrane Database Syst Rev. 2013(12):CD004624.

5. Materials & Methods

Comment: (1) P. 4, L.87: Please specify the clear search timeframe. Whether it was from origin until 07/01/2022?

Response: Time frame has been added

“A search of all relevant literature spanning various databases including PubMed, The Cochrane Library, and www.clinicaltrials.gov was conducted for all relevant publications dating up to 01/05/2023”

Comment: (2) Search Strategy: we suggest the authors present the full electronic search strategy for at least 1 database, including any limits used, such that it could be repeated.

Response: New search strategy has been included.

Comment: (3) Data Extraction: we suggest the authors also describe the process for developing the charting form. For example, calibrated forms, or forms that have been tested by the team before their use.

Response: Seeing as this paper is no longer a scoping review and has taken on the form of a systematic review, unsure if charting form is necessary?

6. Results

Comment: We suggest the authors use the the first author name not the drug name in the Table 1. Please also mark the corresponding reference numbers of the included articles (e.g. Costa et al., (5)).

Response: The table has been modified accordingly.