Oral Microbiome Response to Powered vs Manual Toothbrush: Protocol for a Systematic Review & Meta-Analysis

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Protocol

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Abstract

Background: Subclinical changes in response to different types of toothbrushes represent a challenging knowledge gap in the context of self-administered oral hygiene regimes; therefore, this systematic review will be the first to evaluate the oral microbiome response to powered versus manual toothbrushes.

Methods: We will conduct a systematic review using the Cochrane Handbook's guidelines and will adhere to a standardized reporting format: Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). A comprehensive search strategy will be conducted in the following databases for published studies: Ovid MEDLINE(R), EMBASE, Cochrane Library, Web of Science, Scopus, ProQuest Central, ProQuest Dissertations Theses Global, Bibliographia Medica Cechoslovaca, and Dentistry Oral Sciences Source. Following a two-level screening process, data including the full reference, objectives, target population, description of the intervention and control intervention, outcome measures, design, length of the post-intervention follow-up period, and the study results will be extracted, synthesized, and reported. Risk of bias and quality of the studies will also be assessed.

Discussion: No primary data collection will be undertaken; therefore, no formal ethical assessment is required. The results of this systematic review and meta-analysis will be published in a peer-reviewed journal.

Registration: The protocol has been registered with the PROSPERO International Prospective Register of Systematic Reviews (CRD42020153557) since April 28th, 2020.

Background

1. **Rationale**

Toothbrushing is the most widely accepted personal oral hygiene practice worldwide. It principally aims to lower the burden of oral microorganisms that might be responsible for oral diseases and conditions like dental caries, periodontal diseases, and halitosis.(1) The latest update of Cochrane review comparing powered and manual toothbrushing revealed substantial superiority of powered toothbrushes in plaque removal and gingival inflammation reduction; however, the clinical importance of these findings remains unclear in terms of cost-effectiveness, reliability and side effects.(2) This advantage of powered toothbrushing disappears in case of adequately instructed and motivated patients and in case of orthodontic patients.(3–5)

The safety of powered toothbrushes has been evaluated as a part of few efficacy investigations and it was rarely reported as a primary outcome of interest; therefore reviewers suggested that powered toothbrushes could be as safe as their manual counterparts.(6) These studies seem to overlook a frequent and sometimes a life-threatening consequence of powered toothbrushing; the brushing-induced bacteremia is more significantly associated with powered toothbrushing than with manual toothbrushing.(7–9) Another criticism for the previously published systematic reviews of toothbrushes is that they

exclusively utilized clinical parameters to evaluate the performance of powered and manual toothbrushes. The reliability of gingival and plaque indices is significantly limited due to its dependency on inter-rater and intra-rater agreements.(10–13) An evaluating study showed that Löe-Silness gingival index has the lowest intraclass correlation 0.25 among the most used dental indices; however, this was the most used index in individual clinical studies and systematic reviews.(2,14) Periodontal indices are designed to measure the disease progress by evaluating its clinical manifestations like bleeding, colour and texture changes, and attachment loss; this is a true limitation for their usability in a research setting because their efficacy in disease prognosis or prevention is empirically questionable.(13,15)

The oral microbiome is a complex and dynamic ecosystem that determines the balance between oral health and disease.(16) A healthy state of the oral cavity can be described by having an equilibrium of the oral species with each other and with their host, which can be disturbed by alterations of the oral environment or systemic health leading to pathogenic changes.(17) Therefore, the study of the oral microbiome as a part of the disease process is justified. (13,15)

To the best of our knowledge, this is the first systematic review to evaluate the oral microbial changes in response to powered versus manual toothbrushing.

2. **Objectives**

The aim of this systematic review is to evaluate the effectiveness of powered and manual toothbrushes in terms of their mediating capacity for the oral microbiome. This review is trying to answer the following questions:

2.1. Is there a significant difference between powered and manual toothbrushing in terms of oral microbiome response?

2.2. Are the microbiological changes significantly correlated with clinical changes in response to powered and manual toothbrushing?

2.3. If the answer of the 1st question is Yes; Which toothbrushing modality is more effective in reducing pathogenic microorganisms?

2.4. If the answer of the 1st question is Yes; What are the most sensitive oral species to powered toothbrushing and to manual toothbrushing?

2.5. If the answer of the 2nd question is Yes; What is the most diagnostic lab testing protocol that identifies microbiological changes in correlation to clinical changes?

Methods & Analysis

1. **Eligibility Criteria**

This systematic review will be developed according to published guidelines(18) and reported according to the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA).(19) (Appendix 1)

Eligibility of papers for inclusion in the review will be assessed inclusion and exclusion criteria applied to each of the following domains: study designs, types of participants, types of interventions and comparison conditions, and the outcome measures assessed. Inclusion and exclusion criteria within each of these domains are described in turn below.

- Study Designs

In accordance with the objective of providing an overview of the current evidence for oral microbiome response to different types of powered and manual toothbrushes, the following designs will be included – parallel-arm randomized controlled trials (RCTs), cluster randomized controlled trials, cross-over randomized controlled trials; non-randomized controlled trials; case-series and cross-sectional studies. In-vitro studies, observational studies, literature reviews and editorials will be excluded.

- Types of Participants

The studies of adults and adolescents who are professionally instructed to use toothbrushes as a part of their daily routine will be included. Healthy volunteers, hospitalized patients, pregnant patients, orthodontic patients, periodontitis patients and patients on maintenance therapy will be included in this review. Frail and disabled patients who are unable to perform their personal hygiene instructions independently will be excluded.

- Types of Interventions

The intervention of interest is powered toothbrushing. All generations of powered toothbrushes will be included in this review – side to side action, counter oscillation, rotation oscillation, circular, ultrasonic and sonic toothbrushes. Powered toothbrushes that have more than one action, referred to as “multi-dimensional toothbrushes” will be included.(2) Studies using powered toothbrushes without specifying the mode of its action or generation will be included. Trials instituting combined interventions like brushing combined with the use of antibiotic mouth rinse or toothpaste will be included, with estimating the effect of these additional interventions as a confounding variable. Studies with a follow-up period less than 28 days will be excluded.

- Comparison Conditions

Given the broad perspective of the intervention of interest, all types of manual toothbrushes will be relevant for inclusion as control groups. Therapeutic and traditional alternatives of toothbrushes like toothette and miswak will be excluded. As previous reviews comparing powered and manual toothbrushes considered the analysis of filament arrangement, orientation, size, shape and flexibility, brush head size and shape along with presence or absence and characteristics of a timer difficult to define across time and brush types, these factors will not be assessed in this current review.(2)

- Types of Outcome Measures

The **primary outcome** measures employed to evaluate the effectiveness of powered versus manual toothbrushes in terms of the oral microbiome will be included. Microbiological samples harvested from the following sites will be included:

1. **a**. sub-gingival plaque
2. **b**. supra-gingival plaque
3. **c**. oral rinse (salivary)
4. **d**. oral mucosa (buccal or labial)
5. **e**. tongue (dorsal or lateral)

All studies using molecular methods for identifying and quantifying oral microbiota species will be included.

The **secondary outcome** measures employed to evaluate the effectiveness of powered versus manual toothbrushes in terms of clinical parameters will be included.

The following periodontal indices used for evaluating oral health will be included:

1. **a**. Plaque Index (Quigley Hein Turesky, Silness and Loe, Visible Plaque Index Ainamo Bay, Ortho Modification of Silness and Loe, Navy Plaque Index mod Rustogi, and O'Leary Index)
2. **b**. Gingival Index (Loe Silness, Lobene Gingival Index, Bleeding on Probing, Papillary Bleeding Index, and Bleeding on Marginal Probing)
3. **c**. Periodontal Index (Rusell's Periodontal Index, Community Periodontal Index of Treatment Needs)

2. **Information Sources**

An initial limited search of MEDLINE and EMBASE will be undertaken followed by the analysis of the text words contained in the title and abstract, and of the index terms used to describe the article.

A second search using all identified keywords and index terms will then be undertaken across all included databases.

Thirdly, the reference list of all identified reports and articles will be searched for additional studies.

Studies published in all possible languages, if they have a title and an abstract in English will be considered for inclusion in this review. Studies published without any time restriction will also be considered for inclusion in this review.

The databases to be searched include:

Ovid MEDLINE(R), EMBASE, Cochrane Library, Web of Science, Scopus, ProQuest Central, ProQuest Dissertations & Theses Global, Bibliographia medica Cechoslovaca, Dentistry & Oral Sciences Source.

The search for unpublished studies will include:

Open Grey, Current Controlled Trials (ISRCTN registry), MedNar, ClinicalTrials.gov., International Clinical Trials Registry Platform of the World Health Organisation.

3. **Search Strategy**

Consistent with the methods detailed in Cochrane Guidelines for systematic reviews the search strategy will be conducted as follows:(18)

- Abstract, title, keywords of the identified database will be searched.

- Both randomized and non-randomized clinical trials will be sought. No study design, date, or language limits will be imposed on the search.

- Reference lists of identified publications will be manually searched to identify any additional publications.

- These searches will be re-run just before final analyses and further studies retrieved for inclusion.

- An example of the search strategy for MEDLINE is attached to this protocol. (Table 1)

4. **Study Records**

- Data Management

Literature search results will be uploaded to reference management software (Endnote X8) and duplicate citations will be removed electronically.

- Selection Process

Once duplicate entries are removed, RIAD A and CHUCHMOVA V will develop and test screening questions and forms for level 1 and 2 assessments based on the inclusion and exclusion criteria. Both reviewers will classify the entries independently according to the eligibility criteria. Disagreements will be resolved by discussion between the two reviewers or (when unable to be resolved) third author KLUGAR M adjudication. Reasons for excluding studies from Screening Level 2 will be recorded.

- Screening Level 1:

Titles and/or abstracts of retrieved entries will be checked against general inclusion/exclusion criteria of studies designs (in-vitro studies, observational studies, non-comparative studies, literature reviews, editorials and case reports), types of participants (frail and dependent patients), types of interventions

(follow-up period less than 28 days), and comparison conditions (therapeutic and traditional toothbrushes alternatives).

Each entry will be classified as one of the following options; a) eligible-for-inclusion, b) eligible-for-exclusion, c) unclear.

- Screening Level 2:

The full text of eligible-for-inclusion and unclear entries will be retrieved for extensive review. If necessary, reviewers will seek additional information from study authors to resolve any concerns about eligibility.

- Data Collection Process

The Cochrane template of RCTs Data Extraction Forms (EF) will be used.(20) In order to optimize the parameters of EF, piloting of data extraction will be performed by two reviewers independently on five pilot articles which will be randomly chosen from the full list of included entries.

5. **Data Items**

In addition to the standard parameters of Cochrane EF, the following variables will be recorded:

- Intervention Group(s)

- Powered toothbrush mode of action

- Powered toothbrush brand/model

- Adjunct oral hygiene practices/methods

- Advised period of brushing

- If professional advice/training was delivered to patients

- If patients underwent conventional periodontal therapy before or during the study

- Control Group(s)

- Manual toothbrush brand/model

- Adjunct oral hygiene practices/methods

- Advised period of brushing

- If professional advice/training was delivered to patients

- If patients underwent conventional periodontal therapy before or during the study

- Exclusion Criteria

- Antibiotic prophylaxis

- Smoking or other risk behaviours

When multiple reports of the same study are identified like related journal articles and conference proceedings which are then published, data from each report will be extracted separately and then combined across multiple EFs.

6. **Outcomes and Prioritization**

- The primary outcomes will be changes in oral microbiome after using powered and manual toothbrushes. These may be measured as a total count of microbial species at different time points or as a percentage of change of microbial counts in relation to powered or manual toothbrushing.

- The secondary outcomes will be changes in clinical parameters after using powered and manual toothbrushes. These may be measured as a mean of measured parameters at different time points or as a percentage of change of measurements in relation to powered or manual toothbrushing.

- The estimate of effect which will be used is the mean difference (MD) and corresponding 95% confidence intervals (CI). Whenever possible, the different clinical indices of secondary outcomes that measure the same concept will be incorporated, as long they have a high correlation between each other. If it is not possible to combine the results from different indices, the effects will be expressed as standardized values, which have no units, before combining. The standardized mean difference (SMD) will be therefore calculated along with the appropriate 95% CI and will be used as the effect measure for each meta-analysis where results will be available for more than one index.

- Other secondary outcomes may include cost-effectiveness, safety, and reliability of powered versus manual toothbrushing. This will be decided according to the availability of evidence.

7. **Risk of Bias in Individual Studies**

The critical appraisal of individual studies will be guided by an experienced methodologist, KLUGAR M. To facilitate this process, the revised version of Risk of Bias Assessment Tool (RoB 2) will be used.(21)

This tool uses signalling questions in order to critically appraise the following methodological domains:

- Domain 1: Risk of bias arising from the randomization process

- Domain 2: Risk of bias due to deviations from the intended interventions

- Domain 3: Risk of bias due to missing outcome data

- Domain 4: Risk of bias in the measurement of the outcome

- Domain 5: Risk of bias in the selection of the reported result

The overall risk of bias After receiving proper training and calibration of their skills, RIAD A and CHUCHMOVA V will assess each included study according to each risk of bias domain independently. Disagreements will be resolved through discussion between the two reviewers or, when unable to be resolved, KLUGAR M will be consulted. All studies regardless of their risk of bias will be included in final data synthesis. Influence of bias on the results will be explored by sensitivity analysis.

8. **Data Synthesis**

- Narrative synthesis using “summary of findings” (SOF) tables will explore the findings within and between each included study as they pertain to the powered toothbrushing impact on the oral microbiome, the correlation between microbial and clinical outcomes and lab protocols used.

- Data from cross-over trials will be included with that of similar parallel-group trials, using the techniques described by Elbourne and colleagues.(22) This will be done using the generic inverse variance method within RevMan.(18)

- For heterogeneity assessment, an inspection of a graphical display of the estimated treatment effects from the trials along with their 95% CI and by Cochrane’s test for heterogeneity will be undertaken before each meta-analysis as described in the Cochrane Handbook for Systematic Reviews of Interventions.(18)

The heterogeneity will also be quantified using the I2 statistic, using guidance for interpretation from the Cochrane Handbook for Systematic Reviews of Interventions:(18)

0% to 40%: might not be important;

30% to 60%: may represent moderate heterogeneity;

50% to 90%: may represent substantial heterogeneity;

75% to 100%: considerable heterogeneity.

- An overall assessment of the robustness of the evidence will be ascertained using weightings from the quality appraisals; the strength of evidence for each main outcome variable will be synthesized and presented as key recommendations for policy and practice and to inform future inquiry.

9. **Meta-Bias(es)**

To evaluate reporting bias, the revised version of Risk of Bias Assessment Tool (RoB 2) will be thoroughly used.

An important part of this tool mechanism is to document all the available source that is used to complete the assessment including – journal article(s), trial protocol, statistical analysis plan (SAP), non-commercial trial registry record (e.g. ClinicalTrials.gov record), company-owned trial registry record (e.g.

GSK Clinical Study Register record), grey literature (e.g. unpublished thesis), conference abstract(s) about the trial, regulatory document (e.g. Clinical Study Report, Drug Approval Package), research ethics application, grant database summary (e.g. NIH RePORTER or Research Councils UK Gateway to Research). The second and fifth domains of RoB 2 will enable us to detect if there's any selective reporting bias, especially in case of deviation from the protocol.

10. **Confidence in Cumulative Evidence**

The certainty of the evidence for all outcomes will be evaluated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group methodology. SOF table for this review outcomes will be created using GRADEpro GDT sw.

#	search	results
1	toothbrush*.af	8704
2	"tooth brush*".af	1548
3	1 OR 2	9364
4	powered.af	14727
5	power.af	242275
6	electric.af	255435
7	sonic.af	7568
8	ultrasonic.af	47093
9	"ultra sonic".af	80
10	rotation.af	82561
11	rotating.af	15232
12	oscillating.af	6046
13	oscillation.af	15878
14	4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13	15878
15	microbiota.af	35808
16	microbiome.af	23552
17	microbial.af	382595
18	microbiological.af	58750
19	microflora.af	13876
20	flora.af	31400
21	microorganism?.af	88184
22	micro-organism?.af	9290
23	bacteria.af	438739
24	bacterium.af	64201
25	bacterial.af	1102786
26	microbe?.af	44395
27	15 OR 16 OR 17 18 OR 19 OR 20 OR 21 OR 22 OR 23 OR 24 OR 25 OR 26	1525896
28	3 AND 14 AND 27	103

Search was conducted on 14th November. 2019 at 13:00 am (CET) in All fields.

Table 1
Ovid MEDLINE(R) search strategy

Abbreviations

EF Extraction Forms

GRADE Grading of Recommendations Assessment, Development and Evaluation

PRISMA Preferred Reporting Items for Systematic Reviews and Meta-Analyses

RISMA-P Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols

RoB Risk of bias

ROBINS-I Risk of Bias in Non-Randomized Studies of Interventions

Declarations

Ethical Approval and Consent to Participate

No primary data collection will be undertaken; therefore, no formal ethical assessment is required.

Consent for Publication

We plan to present the findings of this systematic review for peer-review in an appropriate journal. We also intend to present our results to clinicians and researchers at appropriate conferences.

Availability of Supporting Data

The datasets generated during the current study are available in the Open Science Framework repository, [https://osf.io/5xg9c/]

Competing Interests

The authors declare no conflict of interest is involved.

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Authors’ Contributions

RIAD A is the guarantor of the review protocol and wrote the draft protocol for the systematic review. KLUGAR M, KLUGAROVA J and POKORNA A contributed to the design of the whole method section of the protocol. CHUCHMOVA V contributed to the development of the selection criteria. SLEZAKOVA S contributed to the data extraction criteria. KRSEK M contributed to the conception and design of the study. All authors read, provided feedback, and approved the final manuscript.

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