SYSTEMATIC REVIEW

Effectiveness of triple antibiotic paste as an intra-canal medication for the root canal treatment of non-vital teeth with apical periodontitis: A systematic review [version 1; peer review: 1 approved with reservations]

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Abstract

Background: This is a systematic review to assess and provide a pooled effect estimate, if possible, for the effects of triple antibiotic paste as an intra-canal medication for root canal treatment of mature permanent non-vital teeth with apical periodontitis. This review will assess post-operative pain, flare-up incidence, and clinical and radiographic healing.

Methods: Nine electronic databases (Pubmed, CENTRAL, VHL, Scopus, EBSCOhost, Web of Science, Trip, OpenGrey, Proquest) were searched along with two major clinical trial registries. Conference proceedings, reference lists and citations of the included studies were also searched. A total of 537 records were identified and 392 were obtained after duplicate removal. Six records were identified after screening and three studies were included after full text eligibility assessment.

Results: Three comparators were reported in the included studies: calcium hydroxide paste, 2% chlorhexidine gel and ledermix paste. There was no statistically significant difference between triple antibiotic paste and calcium hydroxide regarding postoperative pain, and clinical and radiographic healing of periapical lesions. There was no difference between triple antibiotic paste and chlorhexidine regarding flare-up incidence. However, triple antibiotic paste reduced the level of post-operative pain more than ledermix, which was statistically significant.

Conclusions: The evidence is still insufficient surrounding the use of triple antibiotic paste; therefore more clinical investigations with high levels of evidence and rigorous methodologies are needed.

Keywords

Root canal therapy, postoperative pain, nonvital tooth
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Introduction
Pulpal tissue infection initiates inflammation of periapical tissues and results in apical periodontitis. Root canal treatment aims to prevent or manage apical periodontitis by decreasing the intra-canal microbial load. The anatomy of the root canal system makes it almost impossible to completely eliminate the bacteria using conventional mechanical and chemical techniques, even with the highest technical standards. Therefore, an effective intra-canal medication in the root canal is required to kill remaining bacteria, thereby reducing postoperative pain and inducing periapical healing. Calcium hydroxide has been considered the gold standard for optimally disinfecting root canals; however, it has been reported that Enterococcus faecalis the dominant bacteria in resistant endodontic infections, is resistant to calcium hydroxide. Recently, triple antibiotic paste (a mixture of ciprofloxacin, metronidazole and minocycline) has been used as an intra-canal medication for root canal disinfection. It had been shown that triple antibiotic paste could kill any remaining bacteria in the root canal system.

To the best of our knowledge, the effectiveness of triple antibiotic paste as an intra-canal medication in the treatment of non-vital permanent teeth with apical periodontitis hasn’t yet been subjected to systematic review. Thus, the purpose of this study is to systematically review and provide a pooled effect estimate, if possible, for the effects of triple antibiotic paste as an intra-canal medication for root canal treatment of mature permanent non-vital teeth with apical periodontitis. This review will assess post-operative pain, flare-up incidence, and clinical and radiographic healing.

Methods
This systematic review was reported according to PRISMA Statement. Supplementary File 1 contains the completed PRISMA checklist. The protocol was registered in PROSPERO database, registration number: CRD42018106518.

Eligibility criteria
Population: adult patients who had non-vital permanent mature teeth with apical periodontitis or previously root canal-treated teeth with apical periodontitis, undergoing root canal treatment in multiple visits. Primary teeth, immature, vital teeth and single visit root canal treatment were excluded.

Intervention: triple antibiotic paste, which is a mixture of ciprofloxacin, metronidazole and minocycline.

Comparators: placebo, no intra-canal medication or any other intra-canal medication other than the intervention.

Outcome measures: primary outcomes were post-operative pain and flare-up incidence after the first visit as defined by the trial authors. Secondary outcome was clinical and radiographic healing as defined by the trial authors with at least one year follow-up.

Study designs: randomized and quasi randomized controlled clinical trials were included. Non-randomized clinical trials, observational, in vitro or animal studies were excluded.

Information sources
The following electronic databases were searched: CENTRAL, Medline via Pubmed, Virtual Health Library, Trip, Scopus, Web of Science, EBSCOhost, OpenGrey, ProQuest thesis and dissertation. Ongoing clinical trial registries were searched: ICTRP and ClinicalTrials.gov. The search was conducted until 5/7/2018. Other sources included searching reference lists of included studies and relevant systematic reviews, citation searching of included studies done in Google Scholar and searching conference proceedings of International Association of Dental Research (IADR), European Society of Endodontology (ESE) and American Association of Endodontists (AAE).

Search strategy was conducted using free text terms and controlled terms (MeSH) regarding the population and intervention. A sensitivity and precision filter maximizing randomized clinical trials was used in PubMed to help identify randomized clinical trials as recommended by Cochrane handbook. The full search strategy for CENTRAL database is shown in Table 1.

Study selection
After searching the electronic sources 534 records were identified, and an additional three records were identified through searching other sources. After duplicate removal by Endnote X7 reference manager software, 392 records were identified. Two independent reviewers (EAH, AMI) screened the search results by title and abstract then by full text assessment to determine included studies.

Data collection process
A data extraction sheet was written according to the main data extraction items recommended by the Cochrane handbook.

Data items
The following items were extracted from each included study: methods - study design, setting and country; participants - selection criteria, tooth type, tooth condition, diagnostic criteria, gender/age, number randomized/analyzed and unit of randomization/analysis; interventions - groups, cleaning and shaping technique, irrigation method, intra-canal medication placement technique and period; outcomes - outcome domain, outcome measurement, time points and the outcome assessor.

Risk of bias
To assess the risk of bias in the included randomized clinical trials, the revised RoB 2.0 domain-based tool was used to assess the risk of bias in the included randomized clinical trials. Studies were judged to be of “low risk”, “some concerns of risk” or “high risk” based on these domains: bias arising from the randomization process, bias due to deviation from intended interventions, bias due to missing outcome data, bias in measurement of the outcome and bias in selection of the reported results. The individually randomized, parallel group trials template of the RoB 2.0 tool was used on the outcome level for each study.
Summary measures and data synthesis
Single tooth or a patient with a single tooth was chosen as a unit of analysis. For dichotomous outcome, risk ratio and its 95% CI was used as a measure for the effect size. For the continuous outcome, mean difference and its 95% CI was used as a measure for the effect size. Meta-analysis was not possible due to studies assessing different outcomes and could not be combined. A qualitative synthesis was done instead.

Results
Study selection
After screening 392 records by title and abstract; 386 records were irrelevant. Six records were identified for full text eligibility assessment: one study was excluded due to using another combination of antibiotics (metronidazole, ciprofloxacin and clindamycin); two studies were awaiting assessment due to unavailable full text and no separate results for non-vital teeth (the authors of these previous two studies were contacted to obtain the missing data with no response). Therefore, three studies were included in this systematic review (Figure 1).

Study characteristics
Characteristics of the included studies are presented in Table 2. All the included studies were randomized parallel multi-arm clinical trials conducted in a single center. The settings of the included studies were done in university or dental college hospitals. There were two studies in India and one study in Turkey. A total of 171 patients with 174 teeth were enrolled in the three included studies and 167 teeth were analyzed. All types of teeth were included, either single or multiple rooted teeth.

The intervention of interest was a combination of three antibiotics (metronidazole, ciprofloxacin and minocycline) mixed with inert vehicles to form a paste. In the included studies, three comparators were reported - either calcium hydroxide paste, 2% chlorhexidine gel or ledermix paste.

JOHNS et al. 2014 evaluated clinical and radiographic healing of periapical lesions in which treatment success was based on either strict criteria (absence of clinical signs and symptoms with complete radiographic healing) or loose criteria (absence of clinical signs and symptoms with complete healing or reduction of lesion size). UVAN et al. 2018 evaluated postoperative pain after root canal retreatment. SINAL et al. 2017 evaluated incidence of interappointment flare up in diabetic patients in which flare-up incidence was defined as score 4 and 5 of the verbal rating scale.

Risk of bias assessment
Risk of bias summary is presented in Table 3. Two studies had overall high risk of bias due to high risk of bias in domains regarding bias in selection of the reported results and bias in the measurement of the outcome. One study reported the results of flare-up incidence with no time points, while the other study reported only the results of clinical and radiographic healing for one time point and did not mention any data about the blinding of the outcome assessors.

Results of individual studies
It was not possible to combine the results of the studies in a meta-analysis, due to different outcomes being assessed with different time points and one study was reported in each outcome. A narrative synthesis was done for each study separately.

Triple antibiotic paste VS calcium hydroxide. Regarding postoperative pain, UVAN et al. 2018 found that at six hours, the mean and standard deviation values for pain intensity were 24.44 ± 3.13 in the triple antibiotic paste group and were 19.77 ± 3.18 for calcium hydroxide (mean difference = 4.67, 95% CI 2.72-6.63). At 12 hours, the mean and standard deviation values for pain intensity were 24.44 ± 3.13 in the triple antibiotic paste group and were 28.38 ± 3.59 for calcium hydroxide.
At 24 hours, the mean and standard deviation values for pain intensity were 44.95 ± 3.51 in the triple antibiotic paste group and were 36.92 ± 3.56 for calcium hydroxide (mean difference = 8.04, 95% CI 5.85-10.23). At 48 hours, the mean and standard deviation values for pain intensity were 36.82 ± 3.14 in the triple antibiotic paste group and were 38.75 ± 3.19 for calcium hydroxide (mean difference = -1.93, 95% CI -3.89-0.03) after first visit of treatment.

Calcium hydroxide decreased the level of post-operative pain more than triple antibiotic paste in a statistically significant way at 6, 12 and 24 hours. There was no statistically significant difference at 48 hours.

Regarding flare-up incidence, Sinhal et al. 2017\textsuperscript{18} reported that 40% of patients in calcium hydroxide group experienced interappointment flare-up, with no flare-up seen in triple antibiotic paste group. However, the presented data in this study was insufficient to calculate the effect size and its 95% confidence intervals.\textsuperscript{19} Regarding clinical and radiographic healing, Johns et al. 2014\textsuperscript{17} presented data only at 18 months follow-up. Based on the strict criteria of success, 13 out of 20 participants were healed in the triple antibiotic paste group and 7 out of 20 participants were healed in calcium hydroxide group (RR 1.86, 95% CI 0.94-3.66). Based on the loose criteria of success, 19 out of 20 participants were healed in triple antibiotic paste group and 17 out of 20 participants were healed in calcium hydroxide group (RR 1.12, 95% CI 0.91-1.38). There was no statistically significant difference between the two groups at 18 months follow-up based on either of the criteria of success.

Triple antibiotic paste VS 2% chlorhexidine gel. Only flare-up incidence was evaluated by Sinhal et al. 2017\textsuperscript{18}, who reported no flare-up incidence in either chlorhexidine or triple antibiotic paste groups. However, the presented data in this study was insufficient to calculate the effect size and its 95% confidence intervals.

Triple antibiotic paste VS ledermix paste. Regarding post-operative pain, Uyan et al. 2018\textsuperscript{19} found that at six hours, the mean and standard deviation values for pain intensity were...
Table 2. Characteristics of the included studies.

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Study design</th>
<th>Participants</th>
<th>Age (years)</th>
<th>Number of patients</th>
<th>Groups</th>
<th>Cleaning/shaping</th>
<th>Period of ICM placement</th>
<th>Outcome domain</th>
<th>Tool of measurement</th>
<th>Time points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Johns et al. 2014</td>
<td>RCT</td>
<td>Patients who had periapical lesions in the maxillary anterior region</td>
<td>15–30</td>
<td>60</td>
<td>Ca(OH)$_2$, TAP, PAD</td>
<td>Step back with K files and 1% NaOCL solution</td>
<td>Not mentioned</td>
<td>Treatment success and failure</td>
<td>Clinical and radiographic assessment</td>
<td>3,6,12,18 months</td>
</tr>
<tr>
<td>Sinhal et al. 2017</td>
<td>RCT</td>
<td>Diabetic patients with primary endodontic lesion</td>
<td>≥ 20</td>
<td>36</td>
<td>Ca(OH)$_2$, TAP, CHX</td>
<td>Crown down technique and 2.5% NaOCL solution</td>
<td>2 weeks</td>
<td>Incidence of inter-appointment flare-up</td>
<td>VRS</td>
<td>1,2,3,7,14 days</td>
</tr>
<tr>
<td>Uyan et al. 2018</td>
<td>RCT</td>
<td>Failed asymptomatic root-canal-treated permanent maxillary and mandibular multi-rooted teeth with a periapical lesion 2–5 mm</td>
<td>18–45</td>
<td>75 patients (78 teeth), single visit</td>
<td>Ledermix, TAP, Ca(OH)$_2$</td>
<td>Protaper retreatment kit with no solvents, 2.5% NaOCL solution</td>
<td>1 week</td>
<td>Post-operative pain intensity</td>
<td>Heft parker VAS 0–170 mm</td>
<td>6,12,24,48 hours</td>
</tr>
</tbody>
</table>

RCT, randomized clinical trial; Ca (OH)$_2$, calcium hydroxide paste; TAP, triple antibiotic paste; PAD, Photo activated disinfection; CHX, chlorhexidine; ICM, intra-canal medication; VRS, verbal rating scale; VAS, visual analogue scale.

24.44 ± 3.13 for triple antibiotic paste and were 54.89 ± 3.31 for ledermix (mean difference = -30.45, 95% CI -32.47 to -28.43). At 12 hours, the mean and standard deviation values for pain intensity were 40.15 ± 3.54 in the triple antibiotic paste group and were 64.27 ± 3.74 for ledermix (mean difference = -24.12, 95% CI -26.41 to -21.83). At 24 hours, the mean and standard deviation values for pain intensity were 44.95 ± 3.51 in the triple antibiotic paste group and were 61.77 ± 3.71 for ledermix (MD -16.82, 95% CI -19.09 to -14.55). At 48 hours, the mean and standard deviation values for pain intensity were 36.82 ± 3.14 in the triple antibiotic paste group and were 44.32 ± 3.32 for ledermix (mean difference = -7.50, 95% CI -9.53 to -5.47) after first visit of treatment. Triple antibiotic paste reduced the level of post-operative pain more than ledermix in a statistically significant way at all time points. Regarding flare-up incidence, Uyan et al. 2018 reported no flare-up incidence with either triple antibiotic paste or ledermix groups.

Discussion
Use of antibiotics agents had been suggested by various authors for the eradication of bacteria associated with persistent endodontic infections. Due to side effects of systemic application,
and ineffectiveness in necrotic teeth, local application of
antibiotics would be more effective in endodontics. Research
showed that a combination of metronidazole, ciprofloxacin
and minocycline could destroy any bacteria in the infected root
canal dentin and periapical lesions. The purpose of this system-
atic review was to assess the effectiveness of triple antibiotic
paste as an intra-canal medication for endodontic treatment of
non-vital teeth with apical periodontitis in terms of post-operative
pain, flare-up incidence, clinical and radiographic healing.

The search strategy in this systematic review was comprehen-
sive to identify all published and unpublished articles. Seven
electronic databases were searched along with two clinical trial
registries. Also, grey literature, conference proceedings, back-
ward and forward searches were included in the search strategy
to identify all relevant articles. Risk of bias was assessed
using the revised RoB 2.0 tool, which had some advantages
over the originally developed tool in the Cochrane handbook. The RoB 2.0 tool assessed risk of bias on outcome level for
each study and provided templates for different study designs at
which the overall risk of bias assessment was easier to reach.

Regarding post-operative pain, the evidence could be regarded
as insufficient since only one study provided data for this
outcome. Also, this study suffered from some limitations such as:
adding new patients to replace the ones that were lost to follow-up, excluding patients from the analysis after treatment
and unclear unit of randomization and analysis, since the
number of teeth exceeded the number of patients with no
mention if they were randomized an equal number of times.
Therefore, this study had a unit of analysis issue.

Regarding flare-up incidence, the evidence could be regarded
as insufficient since only one study that had high risk of bias
reported data for this outcome, which was insufficient to
calculate the effect size and its 95% confidence intervals.

Regarding clinical and radiographic healing, the evidence
could be regarded as insufficient since it was provided by one
study that had high risk of bias.

One of the limitations of this review is the low numbers of
studies that were identified despite the comprehensive search
strategy conducted. Also, there were two studies awaiting
assessment, which, if they were available, might have
changed the results of this review. Most of the studies suffered
from high risk of bias so that the results of the included studies
should be interpreted with caution.

It could be concluded that, the evidence of effectiveness
of triple antibiotic paste is insufficient regarding post-operative
pain, flare-up incidence, and clinical and radiographic healing.
The number of randomized clinical studies assessing triple
antibiotic paste effectiveness as an intra-canal medication is
few. Consequently, we recommend conducting clearly reported,
well designed, high quality, large randomized clinical trials to
assess the effectiveness of triple antibiotic paste as an intra-
canal medication in endodontic treatment of non-vital teeth with
apical periodontitis or failed cases concerning relevant patient
outcomes.

Data availability
All data underlying the results are available as part of the article
and no additional source data are required.

Grant information
The author(s) declared that no grants were involved in supporting
this work.

Supplementary material
Supplementary File 1: PRISMA checklist. HYPERLINK
Click here to access the data

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Introduction:
1. No comments.

Methods:
1. The authors have to mention if the data was extracted in duplicate or not. If so, who were those authors? If not, why was it not considered? Same applies to risk of bias assessment.

2. "Risk of bias" could be abbreviated as "RoB" when it is used as a term for the first time in the text as the expanded word for the abbreviation RoB, which is mostly stated in the text as a tool, is not found.

3. Risk of bias table should have quotes or relevant statements from the article to justify the risk judgement.

4. It is not clear what measures were adopted to address any disagreement among the authors while following methodology such as data extraction and risk of bias assessment.

5. It is not clear why the randomized clinical trial (RCT) filter was not used in the search strategy.

6. As there were no restrictions in the language, the authors could have searched in Asian and Latin American databases.

7. The search dates for each database are not clear.
8. It is good practice to grade the quality of evidence.

**Discussion:**

Suggested grammatical corrections:

1. Page no. 7, Paragraph no. 1, Sentence line no. 12:
   
   - **Stated as:** post-operative pain, flare-up incidence, clinical and radiographic healing.
   - **Suggested correction:** post-operative pain, flare-up incidence, and clinical and radiographic healing.

2. Page no. 7, Paragraph no. 6, Sentence line no. 4:
   
   - **Stated as:** assessment\textsuperscript{15,16}, which, if they were available, might have…
   - **Suggested correction:** assessment\textsuperscript{15,16}, which if were available, might have…

3. Page no. 7, Paragraph no. 7, Sentence line no. 4-6:
   
   - **Stated as:** The number of randomized clinical studies assessing triple antibiotic paste effectiveness as an intra-canal medication is few.
   - **Suggested correction:** The number of randomized clinical studies assessing triple antibiotic paste effectiveness as an intra-canal medication is less.

**Note:**

Since the answer is "Partly" to the 2nd evaluation criteria in the peer review form i.e. “Are sufficient details of the methods and analysis provided to allow replication by others?”, the following suggestions are recommended to the authors:

1. Need for data extraction and risk of bias assessment in duplicate.

2. Provide quotes or relevant statements from the article to justify the risk judgement in the risk of bias table.

3. State clearly measures adopted to address any disagreement among the authors during data extraction and risk of bias assessment.

4. Use randomized clinical trial (RCT) filter in the search strategy.

5. Further search for articles in Asian and Latin American databases.

6. State the search dates for each database.

7. Specify the grade of the quality of evidence.

**Are the rationale for, and objectives of, the Systematic Review clearly stated?**

Yes

**Are sufficient details of the methods and analysis provided to allow replication by others?**

Partly
Is the statistical analysis and its interpretation appropriate?
Yes

Are the conclusions drawn adequately supported by the results presented in the review?
Yes

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:**
- Dr A. R. Vivekananda Pai: Restorative dental materials, Restorative & Esthetic dentistry, and Endodontics.
- Dr Sumanth Kumbargere Nagraj: Evidence Based Health Care.

**We confirm that we have read this submission and believe that we have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however we have significant reservations, as outlined above.**

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