



Systematic Review

Antimicrobial efficacy of triple antibiotic paste in teeth with primary endodontic infection: A systematic review

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ABSTRACT

Objectives: This systematic review aims to assess the antimicrobial efficacy of triple antibiotic paste (TAP) as an intracanal medicament for root canal treatment of permanent or primary teeth with primary endodontic infection, as compared to other intracanal medicaments.

Material and Methods: Three electronic databases, namely PubMed, CENTRAL, and Google Scholar, were searched for articles published in the English language till December 2019. Two hundred eighty-three studies were obtained for screening from an electronic database and one from the reference list of an article. After screening 234 records by title and abstract, 226 were excluded, and eight were selected for full-text eligibility assessment. Finally four studies were included in the systematic review.

Results: Due to variations in the methods of outcome measurement and its evaluation at different time points, it was impossible to present the results as a meta-analysis. Thus, a narrative synthesis was performed for TAP compared to comparators used. The overall quality of included studies suggested a moderate risk of bias. Three comparators were reported in the included studies: Calcium hydroxide (CH) with 2% chlorhexidine (CHX), CH alone, and *Ocimum sanctum*. The antimicrobial efficacy of TAP was significantly better than plain CH and *O. sanctum*, whereas results did not differ significantly between TAP and CH plus 2% CHX.

Conclusion: There is a lack of sufficiently high-quality clinical studies regarding the use of TAP. More clinical trials are recommended comparing the antimicrobial efficacy of TAP and other intracanal medicaments under standard protocols to establish a strong clinical evidence.

Keywords: Calcium hydroxide, Intracanal medicament, Triple antibiotic paste

INTRODUCTION

Effective decontamination of the infected root canals is essential for achieving predictable treatment outcomes in teeth with apical periodontitis.^[1] Although disinfection is primarily achieved by chemo-mechanical procedures, the role of intracanal medicaments cannot be ignored, especially in cases of refractory lesions.^[2] Evidence suggests that many bacteria remain in the dentinal tubules of the infected root canals even after chemo-mechanical procedures.^[3] Calcium hydroxide (CH) has been the gold standard as an intracanal medicament for many years and is also used with additives such as povidone-iodine and 2% CHX. However, few studies have found bacteria in the canals even after 1 week of placement of CH. Sathorn *et al.* (2007), in a recent systematic review, concluded that CH had limited effectiveness in eliminating

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bacteria from human root canal when assessed by culture techniques.^[4]

More recently, the field of endodontics has seen a paradigm shift from repair towards regeneration, especially in immature necrotic teeth. Apexogenesis and thickening of intraradicular dentin are now achievable with the advent of procedures such as revascularization and the use of biological scaffolds such as platelet-rich plasma and platelet-rich fibrin.^[5] Asepsis plays a crucial role in regenerative endodontics. Hoshino's triple antibiotic paste (TAP), a mixture of three antibiotics, ciprofloxacin, metronidazole, and minocycline has been proved to be most effective for this.^[6] This paste is also useful in lesion sterilization and repair procedures to achieve periradicular healing by non-surgical means.^[7]

Since its introduction by Hoshino *et al.* in 1996, many *in vitro* studies have proved its worth as an effective root canal disinfectant.^[8,9] Various authors have used different models such as infecting the extracted teeth with oral microflora, teeth with *Enterococcus faecalis* biofilm grown in the roots, and animal models for studying and evaluating the antimicrobial potential of TAP.^[10-12] Surprisingly, there have been very few human clinical trials for the same.

Keeping in view the increasing number of clinical cases where this mixture is used and the fact that *in vitro* studies are performed under a controlled environment, which may differ from clinical situations, it is imperative to base the evidence on human clinical trials. Thus, this systematic review was taken up to study the various human clinical trials which have tested the antimicrobial efficacy of TAP; and to answer the question "is the antimicrobial efficacy of TAP better than the other intracanal medicaments when used clinically inside root canals of teeth with primary root canal infection."

MATERIAL AND METHODS

This systematic review was reported according to Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines (<http://www.prisma-statement.org>). The protocol was registered in the PROSPERO database, registration number CRD 42018083806.

Focused PICO question

The following review question was developed based on the population (P), intervention (I), comparison (C), and outcome (O) framework for conducting a systematic review of existing literature: Does TAP used as an intracanal medicament, compared with no/any other intracanal medicament, result in reduced bacterial colonies in the root canal system of patients undergoing endodontic treatment for primary root canal infection?

Eligibility and inclusion criteria

Population

Systemically healthy patients having teeth with primary endodontic infection due to caries or trauma, for which they had not received any endodontic treatment or antibiotics in the last 3 months. Both primary and permanent teeth were included in the study.

Intervention

TAP, a combination of ciprofloxacin, metronidazole, and either minocycline or tetracycline.

Comparators

No intracanal medicament or any intracanal medicament other than the intervention.

Outcomes

Change in bacterial colonies present with root canal infection, before and after treating with TAP.

Study designs

Randomized control trials and quasi-randomized trials on human volunteers.

Exclusion criteria

Case reports, animal studies, cell culture, and laboratory studies or studies not in the English language were excluded from the study. Studies where TAP was used as an irrigant and not as an intracanal medicament were excluded from the study.

Literature search strategy

The search strategy included electronic databases and a reference list of articles in the English language only, published until December 2019. We searched Medline through PubMed, CENTRAL, and Google scholar. A search was completed using medical subject headings terms and other relevant free-text terms about population and intervention. Keywords used for the search were "TAP," "antimicrobial efficacy," "root canal infection," "disinfection," and "intracanal medicament" using Boolean operators (AND, OR). A filter to help recognize clinical trials was applied in an advanced search tool in PubMed. Tables 1 and 2 show the search strategy for PubMed and CENTRAL, respectively.

Table 1: Search strategy in PubMed (Medline).

Search	Query	Items found
#1	Search triple antibiotic paste OR TAP OR tri-biotic paste OR tri paste	46341
#2	Search Intracanal medicament	321
#3	Search root canal infection	2760
#4	Search antimicrobial efficacy	102343
#5	Search (((triple antibiotic paste OR TAP OR tri-biotic paste OR tri paste)) AND Intracanal medicament) AND root canal infection) AND antimicrobial efficacy	5

TAP: Triple antibiotic paste

Table 2: Search strategy in CENTRAL.

ID	Search	Number of hits
#1	TAP	2516
#2	TAP	86
#3	Tri biotic paste	1
#4	#1 OR #2 OR #3	2583
#5	Intracanal medicament	76
#6	#4 AND #5	11
#7	Antimicrobial OR disinfection	12186
#8	#7 AND #6	5

TAP: Triple antibiotic paste

Study selection and inclusion

Two reviewers (RB and PP) evaluated independently the titles and abstracts of retrieved publications related to antimicrobial efficacy and disinfection quality of TAP in patients with necrotic teeth. Only the title and abstract of the articles found in the databases were read in the preliminary search. The full text of the articles was then reviewed to evaluate the inclusion criteria and confirm eligibility. In case of a disagreement between the two reviewers, a third examiner was consulted to reach a consensus.

Data extraction

A data extraction sheet was prepared based on the following study features: Methods: Study design, setting, and country; participants: Selection criteria, tooth number, gender/age, number analyzed/randomized; intervention: groups, cleaning, and shaping technique, intracanal medicament used, intracanal medicament placement technique and period, and bacterial sampling; outcomes: Bacterial sampling before and after intracanal medicament, method of bacterial load measurement, and time points.

Risk of bias

The risk of bias was assessed in the included studies using the RoB.2 tool.^[13] Studies were judged to be “low risk,”

“some concerns,” or “high risk” based on the following domains:

- Bias arising from randomization or allocation concealment
- Bias due to deviation from intended interventions
- Bias due to missing outcome data
- Bias in measuring the outcome
- Bias in reporting the results

RESULTS

Study selection

Two hundred eighty-three studies were obtained for screening from an electronic database and one from the reference list of an article. After screening 234 records by title and abstract, 226 were excluded, and eight were selected for full-text eligibility assessment. From these, two studies were excluded as they used TAP as an irrigant and not intracanal medicament,^[14,15] one excluded because it used a different combination of TAP,^[16] and one study was excluded as it was an animal study.^[12] Finally, four studies were included for this systematic review [Figure 1].

Study characteristics

Table 3 shows the characteristics of the eligible studies. All studies were published between 2005 and 2018. These were randomized or quasi-randomized controlled parallel multi-arm clinical trials conducted in a single center. The settings of the study were universities and dental colleges based in the USA, India, and Brazil and involved 151 participants in the age group of 4–71 years with a history of necrotic pulp as a result of caries or trauma. All studies included all types of teeth were, single or multi-rooted, but only a single canal was used for intervention.

Three of the studies used a mixture of ciprofloxacin, metronidazole, and minocycline in a ratio of 1:1:1, and one study did not mention the constituents. However, it was assumed to be the same as it is the most commonly used combination. One out of these four studies used it as a solution rather than a paste form. The comparators used were 2% CHX, CH or a combination of CHX and CH, and *Ocimum sanctum*.

In three of the studies, Arruda *et al.*,^[17] Ahirwar *et al.*,^[18] and Dutta *et al.*,^[19] sampling was done at three-time points, namely, S1: Just after access opening and before chemo-mechanical preparation; S2: After chemo-mechanical preparation; and S3: after a certain period of intracanal medicament placement. In one study by Nagata *et al.*,^[20] sampling was done at five points of time S1: Just after access opening and before chemo-mechanical preparation, S2: after irrigating with NaOCl, S3: after irrigation with CHX S4: after

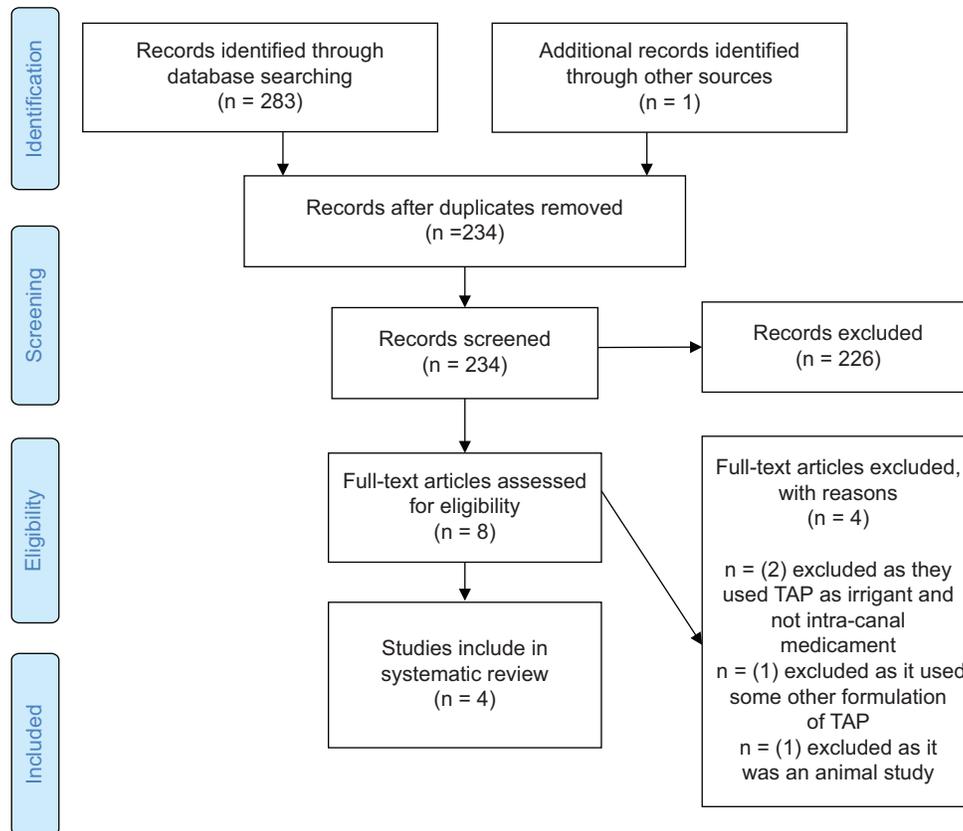


Figure 1: PRISMA flow chart showing identification and selection process of articles included.

intracanal medicament, and S5 after final irrigation with EDTA. Two studies (Arruda *et al.* and Nagata *et al.*) utilized quantitative real-time polymerase chain reaction (qRT-PCR). The other two studies (Ahirwar *et al.* and Dutta *et al.*) used blood agar plate methods for microbiological culture and to measure colony-forming units before and after medication. One study, Dutta *et al.* precisely measured colony-forming units for *E. faecalis* only, while all other studies did a polymicrobial count.

Risk of bias assessment

Table 4 shows the risk of bias assessment for the present review. One study (Dutta *et al.*) was assigned “high” overall risk due to “some concerns” in risk of bias in randomization (randomization and allocation concealment methodology not described) and measurement of outcomes (it did not specify the composition of TAP used as well as a proper method of asepsis during sample collection not described). One (Ahirwar *et al.*) had “some concerns” overall due to “some concerns” in risk of bias in randomization (randomization and allocation concealment methodology not described) and measurement of outcomes (as a proper method of asepsis during sample collection not described).

The other two studies (Arruda *et al.* and Nagata *et al.*) were judged to have a “low” overall risk. The overall quality of included studies was a moderate risk of bias.

Results of individual studies

Due to variations in the methods of outcome measurement, the difference in units of measurement of outcomes, and evaluation at different time points, it was not possible to present the results as a meta-analysis. Thus, a narrative synthesis was performed for TAP compared to comparators used.

TAP and CH with CHX

In the study by Arruda *et al.*, there was a percentage reduction of 99.98% (IRR 0.0002, CI [0.0004–0.0010]) from S1 (pre-instrumentation) to S3 (post-medicament) and a percentage reduction of 96.7% (0.033 [0.004–0.30]) between S2 (post-instrumentation) and S3 in the TAP group. In the CHX plus CH group, there was a percentage reduction of 99% (IRR 0.001, CI [0.0005–0.002]) from S1 to S3 and a percentage reduction of only 39.4% (IRR 0.606 [0.27–1.34]) between S2 and S3. Comparing the presence/absence of bacteria in S2 and S3, the significantly

greater number of canals were negative for bacteria in the antibiotic group than CH plus CHX group ($P = 0.04$). According to the results of Nagata *et al.*, there was no significant reduction ($P = 0.95$) between initial sample S1 and after intracanal medicament was placed S4 in the TAP group compared to CHX plus CH. Likewise, Dutta *et al.* concluded no significant difference in bacterial counts (*E. faecalis*) between the TAP group and CH plus CHX group ($P = 0.74$).

TAP and CH

Dutta *et al.* stated a highly significant difference ($P = 0.00$) in the reduction in bacterial counts for TAP and CH groups.

TAP and *O. sanctum*

Ahirwar *et al.* concluded that there was a significantly higher reduction for TAP for anaerobic culture than the Basil group. At the same time, the difference was not significant for aerobic cultures.

DISCUSSION

This study focused on the effect of TAP on bacterial counts in primary root canal infections. Studies done in infected root canals of both primary and permanent teeth were considered as the microbiota of both mature and immature teeth are pretty similar.^[20,21] Studies where a combination of ciprofloxacin, metronidazole, and either tetracycline or

Table 3: Study characteristics of the included studies.

Study ID	Study Design	Participants	Age	Number of patients	ICM used	Irrigant used	Sampling	Period of placement of ICM	Outcome measurement
Arruda <i>et al.</i> , 2018, Brazil	RCT	Patients with carious necrotic teeth	13–71 years	48	TAP CH CHX	2.5% NaOCl	S1: Before instrumentation S2: After cleaning/shaping S3: After ICM	7–10 days	Culture independent molecular microbiological assay (qPCR)
Ahirwar <i>et al.</i> , 2018, India	RCT	Patients with necrotic teeth	4–9 years	40	TAP <i>Ocimum sanctum</i>	Saline	S1: Before instrumentation S2: After cleaning/shaping S3: After ICM	3 days	CFU counts by microbiological culture
Dutta <i>et al.</i> , 2017, India	RCT	Patients with carious necrotic teeth	4–6 years	48	TAP TAP+CHX CH CH+CHX	2.5% NaOCl	S1: Before instrumentation S2: After cleaning/shaping S3: Post ICM	7 days	CFU counts by microbiological culture
Nagata <i>et al.</i> , 2014, Brazil	RCT	Patients with a history of dental trauma resulting in pulp necrosis	7–17 years	15	TAP CH+CHX	5% NaOCl	S1: Before instrumentation S2: After cleaning/shaping S3: After NaOCl S4: After ICM S5: After EDTA	21 days	CFU counts by microbiological culture

TAP: Triple antibiotic paste, CH: Calcium hydroxide, CHX: Chlorhexidine, ICM=Intracanal Medicament, CFU: Colony forming units

Table 4: Risk of bias summary.

Study ID	Bias arising from randomization	Bias due to deviation from intended results	Bias due to missing data	Bias in measurement of outcome	Bias in selection of reported results	Overall bias
Arruda <i>et al.</i> , 2018	Low	Low	Low	Low	Low	Low
Ahirwar <i>et al.</i> , 2018	Some concerns	Low	Low	Some concerns	Low	Some concerns
Dutta <i>et al.</i> , 2017	Some concerns	Low	Low	Some concerns	Low	High risk
Nagata <i>et al.</i> , 2014	Some concerns	Low	Low	Low	Low	Low

minocycline in a ratio of 1:1:1 was used were considered. Minocycline is a semi-synthetic derivative of tetracycline with a similar antibiotic spectrum but has resulted in tooth discoloration.^[22] To overcome this drawback, recently, few studies have substituted minocycline with cefaclor, amoxicillin, or doxycycline.^[23]

Due to variations in the methods of outcome measurement and its evaluation at different points of time, it was not possible to present the results as a meta-analysis. Thus, a narrative synthesis was performed for TAP compared to comparators used. The overall quality of included studies suggested a moderate risk of bias.

Although many *in vitro* and *ex vivo* studies have been conducted and proved the antimicrobial efficacy of TAP over other intracanal medicaments in reducing bacterial flora in infected tooth canals, few clinical trials have been conducted for the same.^[8,24,25] The clinical studies included in the current review do reiterate the higher efficacy of TAP as an intracanal medicament, but still they were not without limitations. Concentration in which TAP can be used effectively as an intracanal medicament is also essential. It is found to be cytotoxic against stem cells and apical papilla cells at higher concentrations;^[11] however, none of the included studies except Arruda *et al.* has discussed this fact. Arruda *et al.* concluded that TAP, when used in a concentration of 1 mg/ml, can also be as effective and less cytotoxic as compared to a higher concentration of 1 g/ml traditionally used. Interestingly, in an *in vitro* study by Mehta *et al.*,^[26] where they compared antimicrobial efficacy of TAP and CH, a minimum optical density against *E. faecalis* could be achieved at a concentration as low as 1.25 µg/ml. Moreover, with these included studies though it was clear that TAP has a higher antimicrobial activity than its comparators, it could not be concluded that what is the optimum duration for its intracanal placement, as all the studies used a different time-period of 7–10 days (Arruda *et al.*), 21 days (Nagata *et al.*), 3 days (Ahrwar *et al.*), and 7 days (Dutta *et al.*). In an *ex vivo* study by Ghabraei *et al.*,^[27] it was found that TAP requires a minimum time of 7 days as intracanal dressing. However, they had tested it specifically against *E. faecalis* only.

Method of bacterial quantification may also affect the outcome assessment. In the included studies, only in the one by Arruda *et al.*, the reduction of total bacterial levels was evaluated using a culture-independent molecular microbiology assay qPCR. In the other three studies, the colony-forming units cultured on sheep blood agar plates were counted for evaluating the reduction in bacterial colonies after intracanal medication. Kotsilkov *et al.*^[28] compared the culture method and RT-PCR for detection of periodontitis causing bacteria in deep periodontal pockets. In their study, the RT-PCR exhibited a higher sensitivity when compared to the microbiological culture method for detecting periodontal pathogens. This may

be because cultivation methods can identify a lesser amount of bacteria because of the problem in keeping the pathogenic bacteria viable, which is essential for standard cultivation. A low sample size (range: 15–48) in all the included studies is also a reason for concern.

CONCLUSION

The results of the present systematic review suggest that there is not enough evidence to suggest a better antimicrobial efficacy of TAP over other intracanal medicaments in clinical studies as there very few randomized clinical studies have assessed antimicrobial efficacy of TAP. Moreover, although several *in vitro* studies suggest so, there is a need to conduct well reported, correctly designed, high quality, and randomized clinical trials with a large sample size to assess the antimicrobial efficacy of TAP clinically as an intracanal medication in non-vital teeth with apical periodontitis.

Declaration of patient consent

Patient's consent not required as there are no patients in this study.

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Conflicts of interest

There are no conflicts of interest.

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