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, 1 approved with reservations]

Ehab Abdel Hamid , Saied Abdel Aziz , Hany Samy Sadek, Ahmed Mohamed Ibrahim

Department of Endodontics, Faculty of Oral and Dental Medicine, Cairo University, Cairo, 11553, Egypt

V1 First published: 11 Oct 2018, 7:1627
<https://doi.org/10.12688/f1000research.16423.1>
 Latest published: 11 Oct 2018, 7:1627
<https://doi.org/10.12688/f1000research.16423.1>

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.

Open Peer Review

Approval Status

	1	2
version 1		
11 Oct 2018	view	view

1. A. R. Vivekananda Pai , Melaka-Manipal Medical College (Manipal Academy of Higher Education [MAHE]), Malacca City, Malaysia
 Sumanth Kumbargere Nagraj, Melaka-Manipal Medical College (Manipal Academy of Higher Education [MAHE]), Malacca City, Malaysia
2. Vivek Aggarwal , Jamia Millia Islamia, New Delhi, India

Any reports and responses or comments on the article can be found at the end of the article.

Keywords

Root canal therapy, postoperative pain, nonvital tooth

Corresponding author: Ehab Abdel Hamid (ehab.hussein@dentistry.cu.edu.eg)

Author roles: Abdel Hamid E: Writing – Review & Editing; Abdel Aziz S: Supervision; Sadek HS: Supervision; Ibrahim AM: Writing – Original Draft Preparation

Competing interests: No competing interests were disclosed.

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

Copyright: © 2018 Abdel Hamid E *et al.* This is an open access article distributed under the terms of the [Creative Commons Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

How to cite this article: Abdel Hamid E, Abdel Aziz S, Sadek HS and Ibrahim AM. **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, 1 approved with reservations]** F1000Research 2018, 7:1627 <https://doi.org/10.12688/f1000research.16423.1>

First published: 11 Oct 2018, 7:1627 <https://doi.org/10.12688/f1000research.16423.1>

Introduction

Pulpal tissue infection initiates inflammation of periapical tissues and results in apical periodontitis¹. Root canal treatment aims to prevent or manage apical periodontitis by decreasing the intra-canal microbial load². 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 standards³. Therefore, an effective intra-canal medication in the root canal is required to kill any remaining bacteria⁴, thereby reducing postoperative pain and inducing periapical healing⁵. Calcium hydroxide has been considered the gold standard for optimally disinfecting root canals; however, it had been reported that *Enterococcus faecalis* the dominant bacteria in resistant endodontic infections, is resistant to calcium hydroxide⁶. Recently, triple antibiotic paste (a mixture of ciprofloxacin, metronidazole and minocycline) has been used as an intra-canal medication for root canal disinfection⁷. It had been shown that triple antibiotic paste could kill any remaining bacteria in the root canal system⁸.

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 Statement⁹. [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.

Other: there were no restrictions on language, timing or settings.

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^{10,11}, 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 handbook¹². 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 handbook¹².

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 used¹³ 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.

Table 1. Full search strategy used for CENTRAL database.

ID	Search	Number of hits
#1	triple antibiotic paste	57
#2	tri antibiotic paste	12
#3	tri-antibiotic paste	1
#4	triantibiotic paste	1
#5	TAP	1786
#6	antibiotic paste	153
#7	antibiotic mix	124
#8	{or #1-#7}	2042
#9	MeSH descriptor: [Root Canal Therapy] explode all trees	1051
#10	endodontic	1178
#11	endodontic therapy	569
#12	endodontic treatment	701
#13	endodontic filling	311
#14	endodontically treated teeth	228
#15	root canal therapy	926
#16	root canal treatment	909
#17	root canal filling	671
#18	{or #9-#17}	2225
#19	intracanal medication	60
#20	intra-canal medication	7
#21	root canal medication	138
#22	intra-canal medicament	1
#23	intracanal medicament	43
#24	root canal medicament	61
#25	intra-canal dressing	4
#26	intracanal dressing	42
#27	root canal dressing	75
#28	intracanal disinfectant	4
#29	intra-canal disinfectant	0
#30	root canal disinfectant	0
#31	{or #19-#30}	242
#32	#8 and #31 and #18	19

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 study¹⁴ was excluded due to using another combination of antibiotics (metronidazole, ciprofloxacin and

clindamycin); two studies were awaiting assessment due to unavailable full text¹⁵ and no separate results for non-vital teeth¹⁶ (the authors of these previous two studies were contacted to obtain the missing data with no response). Therefore, three studies¹⁷⁻¹⁹ 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^{17,18} in India and one study in Turkey¹⁹. 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.* 2014¹⁷ 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). UYAN *et al.* 2018¹⁹ evaluated postoperative pain after root canal retreatment. SINHAL *et al.* 2017¹⁸ 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^{17,18} 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 study¹⁸ reported the results of flare-up incidence with no time points, while the other study¹⁷ 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 post-operative pain, UYAN *et al.* 2018¹⁹ 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 40.15 ± 3.54 in the triple antibiotic paste group and were 28.38 ± 3.59 for calcium hydroxide

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

(mean difference = 11.77, 95% CI 9.56-13.98). 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.* 2017¹⁸ 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. UYAN *et al.* 2018¹⁹ reported no flare-up incidence with either calcium hydroxide or triple antibiotic paste groups.

Regarding clinical and radiographic healing, JOHNS *et al.* 2014¹⁷ 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.* 2017¹⁸, 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.* 2018¹⁹ found that at six hours, the mean and standard deviation values for pain intensity were

Table 2. Characteristics of the included studies.

Study ID	Study design	Participants	Age (years)	Number of patients	Groups	Cleaning/shaping	Period of ICM placement	Outcome domain	Tool of measurement	Time points
JOHNS <i>et al.</i> 2014 ¹²	RCT	Patients who had periapical lesions in the maxillary anterior region	15–30	60	Ca(OH) ₂ TAP PAD	Step back with K files and 1% NaOCL solution	Not mentioned	Treatment success and failure	Clinical and radiographic assessment	3,6,12,18 months
SINHAL <i>et al.</i> 2017 ¹⁵	RCT	Diabetic patients with primary endodontic lesion	≥ 20	36	Ca(OH) ₂ TAP CHX	Crown down technique and 2.5% NaOCL solution	2 weeks	Incidence of inter-appointment flare-up	VRS	1,2,3,7,14 days
UYAN <i>et al.</i> 2018 ¹⁶	RCT	Failed asymptomatic root-canal-treated permanent maxillary and mandibular multi-rooted teeth with a periapical lesion 2–5 mm	18–45	75 patients (78 teeth), single visit	Ledermix TAP Ca(OH) ₂	Protaper retreatment kit with no solvents, 2.5% NaOCL solution	1 week	Post-operative pain intensity	Heft parker VAS 0–170 mm	6, 12, 24, 48 hours

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.

Table 3. Risk of bias summary.

Study ID	Bias arising from randomization	Bias due to deviation from intended interventions	Bias due to missing data	Bias in measurement of the outcome	Bias in the selection of reported results	Overall bias
Post-operative pain						
UYAN <i>et al.</i> 2018 ¹⁶	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Flare up incidence						
UYAN <i>et al.</i> 2018 ¹⁶	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
SINHAL <i>et al.</i> 2017 ¹⁵	Some concerns	Low risk	Some concerns	Low risk	High risk	High risk
Radiographic healing						
JOHNS <i>et al.</i> 2014 ¹²	Low risk	Low risk	Low risk	High risk	High risk	High risk

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.* 2018¹⁹ 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 infections²⁰. Due to side effects of systemic application,

and ineffectiveness in necrotic teeth, local application of antibiotics would be more effective in endodontics²¹. Research showed that a combination of metronidazole, ciprofloxacin and minocycline could destroy any bacteria in the infected root canal dentin and periapical lesions⁸. The purpose of this systematic 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 comprehensive to identify all published and unpublished articles. Seven electronic databases were searched along with two clinical trial registries. Also, grey literature, conference proceedings, backward 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 tool¹³, which had some advantages over the originally developed tool in the Cochrane handbook¹². 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 study¹⁹ 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 issue²².

Regarding flare-up incidence, the evidence could be regarded as insufficient since only one study¹⁸ 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 study¹⁷ 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^{15,16}, 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](#)

References

1. Sundqvist G: **Bacteriologic studies of necrotic dental pulps [PhD thesis].** Umeå, Sweden: University of Umeå; 1976.
[Reference Source](#)
2. Möller A, Fabricius L, Dahlén G, *et al.*: **Influence on periapical tissues of indigenous oral bacteria and necrotic pulp tissue in monkeys.** *Scand J Dent Res.* 1981; 89(6): 475–84.
[PubMed Abstract](#) | [Publisher Full Text](#)
3. Gursøyr H, Özçakır-Tomruk C, Tanalp J, *et al.*: **Photodynamic therapy in dentistry: a literature review.** *Clin Oral Invest.* 2013; 17(4): 1113–25.
[PubMed Abstract](#) | [Publisher Full Text](#)
4. Spångberg LSW, Haapasalo M: **Rationale and efficacy of root canal medicaments and root filling materials with emphasis on treatment outcome.** *Endod Topics.* 2002; 2(1): 35–58.
[Publisher Full Text](#)
5. Calışkan MK: **Prognosis of large cyst-like periapical lesions following nonsurgical root canal treatment: a clinical review.** *Int Endod J.* 2004; 37(6): 408–16.
[PubMed Abstract](#) | [Publisher Full Text](#)
6. Siqueira JF Jr, Lopes HP: **Mechanisms of antimicrobial activity of calcium hydroxide: a critical review.** *Int Endod J.* 1999; 32(5): 361–369.
[PubMed Abstract](#) | [Publisher Full Text](#)

7. Sato T, Hoshino E, Uematsu H, *et al.*: ***In vitro* antimicrobial susceptibility to combinations of drugs on bacteria from carious and endodontic lesions of human deciduous teeth.** *Oral Microbiol Immunol.* 1993; 8(3): 172–6.
[PubMed Abstract](#) | [Publisher Full Text](#)
8. Sato I, Ando-Kurihara N, Kota K, *et al.*: **Sterilization of infected root-canal dentine by topical application of a mixture of ciprofloxacin, metronidazole and minocycline *in situ*.** *Int Endod J.* 1996; 29(2): 118–24.
[PubMed Abstract](#) | [Publisher Full Text](#)
9. Liberati A, Altman DG, Tetzlaff J, *et al.*: **The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration.** *PLoS Med.* 2009; 6(7): e1000100.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
10. Anjaneyulu K, Nivedhitha MS: **Influence of calcium hydroxide on the post-treatment pain in Endodontics: A systematic review.** *J Conserv Dent.* 2014; 17(3): 200–7.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
11. Sanu N, Sindhu R: **Comparative evaluation of postoperative pain with different intracanal medicaments? A Systematic Review.** *AJPTR.* 2016; 6(5): 34–61.
[Reference Source](#)
12. Higgins JPT, Green S: **Cochrane Handbook for Systematic Reviews of Interventions version 5.1.0 [updated March 2011].** *The Cochrane Collaboration*, 2011.
[Reference Source](#)
13. Higgins JPT, Sterne JAC, Savović J, *et al.*: **A revised tool for assessing risk of bias in randomized trials.** In: CHANDLER J, MCKENZIE J, BOUTRON I, WELCH V (editors). *Cochrane Methods. Cochrane Database of Systematic Reviews*, 2016.
14. Prasad LK, Tanwar BS, Kumar KN: **Comparison of calcium hydroxide and triple antibiotic paste as intracanal medicament in emergency pain reduction: *in vivo* study.** *Int J Oral Care Res.* 2016; 4(4): 244–6.
[Publisher Full Text](#)
15. Sanu N, Sindhu R: **Comparative evaluation of inter appointment pain with calcium hydroxide and triple antibiotic paste as intracanal medicaments in patients with apical periodontitis: A randomized controlled clinical trial.** *J Dent Res.* 2016; 95: 0272.
[Reference Source](#)
16. Pai S, Vivekananda Pai AR, Thomas MS, *et al.*: **Effect of calcium hydroxide and triple antibiotic paste as intracanal medicaments on the incidence of inter-appointment flare-up in diabetic patients: An *in vivo* study.** *J Conserv Dent.* 2014; 17(3): 208–11.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
17. Johns DA, Varughese JM, Thomas K, *et al.*: **Clinical and radiographical evaluation of the healing of large periapical lesions using triple antibiotic paste, photo activated disinfection and calcium hydroxide when used as root canal disinfectant.** *J Clin Exp Dent.* 2014; 6(3): e230–6.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
18. Sinhal TM, Shah RRP, Shah N, *et al.*: **Comparative evaluation of 2% chlorhexidine gel and triple antibiotic paste with calcium hydroxide paste on incidence of interappointment flare-up in diabetic patients: A randomized double-blinded clinical study.** *Endodontology.* 2017; 29(2): 136–41.
[Publisher Full Text](#)
19. Uyan HM, Olcay K, Özcan M: **Comparative evaluation of postoperative pain intensity after single-visit and multiple-visit retreatment cases: a prospective randomized clinical trial.** *Brazilian Dent Sci.* 2018; 21(1): 26–36.
[Publisher Full Text](#)
20. Abbott PV: **Medicaments: aids to success in endodontics. Part 2. Clinical recommendations.** *Aust Dent J.* 1990; 35(6): 491–496.
[PubMed Abstract](#) | [Publisher Full Text](#)
21. Mohammadi Z, Abbott PV: **On the local applications of antibiotics and antibiotic-based agents in endodontics and dental traumatology.** *Int Endod J.* 2009; 42(7): 555–67.
[PubMed Abstract](#) | [Publisher Full Text](#)
22. Fergusson D, Aron SD, Guyatt G, *et al.*: **Post-randomisation exclusions: the intention to treat principle and excluding patients from analysis.** *BMJ.* 2002; 325(7365): 652–4.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)

Open Peer Review

Current Peer Review Status: ? ✓

Version 1

Reviewer Report 29 July 2021

<https://doi.org/10.5256/f1000research.17944.r90674>

© 2021 Aggarwal V. This is an open access peer review report distributed under the terms of the [Creative Commons Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Vivek Aggarwal

Department of Conservative Dentistry and Endodontics, Faculty of Dentistry, Jamia Millia Islamia, New Delhi, Delhi, India

The authors have presented a systematic review evaluating the efficacy of triple antibiotic paste (vs other medications) in patients with apical periodontitis. The study has been initially published on 11-Oct-2018. This is an invited review (invitation by the Editorial Team, F1000Research, and dated 28-Jul 2021) of this paper. Triple antibiotic pastes are commonly used in regenerative endodontics. However, potential discoloration has led to the use of double antibiotic paste. Since the review is performed 3 years after the publication of the study, I shall limit my comments to the methodology and the reliability of the data.

The systematic review (SR) and meta-analysis are considered the highest evidence for treatment planning. The SRs require a 'priori' design/protocol to be prospectively registered at databases such as PROSPERO. This manuscript has been registered at PROSPERO on 28-Aug-2018 and subsequently revised on 31-Oct-2018. The protocol matches with the reported data and there has been no selective reporting.

Introduction: A rationale for the study is required. The introduction should be expanded to include a suitable background for this study.

For an accurate SR analysis, a good PICO question should be developed. The current review states 'primary outcomes were post-operative pain and flare-up incidence after the first visit as defined by the trial authors. The secondary outcome was clinical and radiographic healing as defined by the trial authors with at least one-year follow-up'. Out of three included studies, Johns *et al.* did not evaluate the post-operative pain (i.e. the primary outcome), and rest other two studies did not evaluate the secondary outcome.

Considering the limitations of the data, the authors have accurately decided to perform a narrative review. It would be better to report the 95% confidence intervals for all the data. Raw data, if required, can be requested from the individual authors.

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

Partly

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

Yes

Is the statistical analysis and its interpretation appropriate?

Not applicable

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

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: There are limited studies on this topic. The authors have included all the studies and presented a narrative review.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Reviewer Report 23 May 2019

<https://doi.org/10.5256/f1000research.17944.r45204>

© 2019 Pai A et al. This is an open access peer review report distributed under the terms of the [Creative Commons Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

A. R. Vivekananda Pai

Department of Conservative Dentistry and Endodontics, Faculty of Dentistry, Melaka-Manipal Medical College (Manipal Academy of Higher Education [MAHE]), Malacca City, Malaysia

Sumanth Kumbargere Nagraj

Department of Oral Medicine and Oral Radiology, Faculty of Dentistry, Melaka-Manipal Medical College (Manipal Academy of Higher Education [MAHE]), Malacca City, Malaysia

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^{15,16}, which, if they were available, might have...
 - Suggested correction: assessment^{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.

The benefits of publishing with F1000Research:

- Your article is published within days, with no editorial bias
- You can publish traditional articles, null/negative results, case reports, data notes and more
- The peer review process is transparent and collaborative
- Your article is indexed in PubMed after passing peer review
- Dedicated customer support at every stage

For pre-submission enquiries, contact research@f1000.com

F1000Research