Postoperative pain of patients with necrotic teeth with apical periodontitis following single visit endodontic treatment versus multiple visit endodontic treatment using triple antibiotic paste: a randomized clinical trial [version 1; peer review: 1 approved, 1 approved with reservations]

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Abstract
Background: A randomized clinical trial was conducted to compare the postoperative pain following endodontic treatment of necrotic teeth with apical periodontitis. Treatments were performed in multiple visits with application of triple antibiotic paste interappointment dressing or single visit without interappointment dressing.

Methods: In total 44 participants were assigned randomly into two groups. Group A: multiple visit endodontic treatment with triple antibiotic paste interappointment dressing; group B: single visit endodontic treatment without interappointment dressing. Postoperative pain of participants was assessed after 24, 48, 72 hours and one week using numerical rating scale.

Results: No statistically significant difference was found in postoperative pain after 24, 48, 72 hours and one week between the two groups.

Conclusion: Triple antibiotic paste as an interappointment dressing in multiple visits endodontic treatment was not proved to reduce the postoperative pain compared to a single visit in patients with necrotic teeth with apical periodontitis who did not have an interappointment dressing.

Trial registration: clinicaltrials.gov, NCT02947763. Date: 28th October 2016.

Keywords
Apical periodontitis, multiple visits, triple antibiotic paste, interappointment dressing

Open Peer Review
Invited Reviewers
1
2

version 1
published
26 Jul 2019

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2 Reham Hassan, Minia University, Minya, Egypt

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

Apical periodontitis (AP) arises primarily by continuous bacterial irritation from the root canals. AP significantly reduces the endodontic success rate. Therefore, treatment of AP should aim to completely eliminate the underlying root canal infection, either by chemomechanical preparation or placement of an interappointment dressing.

Recent systematic reviews found that multiple visits with calcium hydroxide did not improve postoperative pain and flare-up and radiographic healing compared to single visit endodontic treatment without interappointment dressing. Consequently, the search for a better antimicrobial alternative is required. Previously, triple antibiotic paste (TAP) has been shown to effectively reduce the bacterial load in necrotic teeth.

The aim of the present study was to compare the postoperative pain following endodontic treatment, of necrotic teeth having apical periodontitis, either performed in single visit or in multiple visits with application of triple antibiotic paste interappointment dressing.

**Methods**

**Trial design**

The study was registered on clinicaltrials.gov and the registration number is NCT02947763.

The protocol was approved by the Committee of Ethics, Faculty of Dentistry, Cairo University, Egypt (approval no 16562). Participants were asked to sign a printed informed consent that explained the study aim, alternative treatments to endodontic treatment, and the investigator’s instructions.

The trial design of this study was a parallel, randomized, clinical design with allocation ratio 1:1. This article follows the CONSORT 2010 statement and a copy of the CONSORT checklist can be found in the Data availability section.

The study began in November 2016 and was completed in February 2018.

**Sample size calculation**

Prior data indicated that standard deviation of pain score was 20.3. If the true difference in the intervention and control is 20.6, we should study 16 in each group to be able to reject the null hypothesis that the population means of the intervention and control groups are equal with probability (power) 0.8. The Type I error probability associated with this test of this null hypothesis was 0.05. The size of the sample was increased to 22 per group to correct for non-parametric usage and to substitute for any drop-out.

**Randomization**

At this step, the participants were divided randomly into two groups with a table of random numbers from 1 to 44 generated by SMA using a freely available computer program with n=22/group. The allocation table was kept with an investigator not involved with participant enrollment (SIG). Numbers from 1 to 44 were written on 44 pieces of paper folded eight-times. Each paper was placed separately in a closed opaque envelope. Each participant was asked to pick one of the envelopes and the participant was assigned to the groups based on the number in the envelope.
Group A: multiple (two) visit endodontic treatment with triple antibiotic paste interappointment dressing; group B: single visit endodontic treatment without interappointment dressing.

For group A, triple antibiotic paste (ciprofloxacin, metronidazole, and doxycycline mixed with saline) was prepared and 1 mL of the mixed paste was placed into the canals with a 20-gauge needle of sterile plastic syringe. A sterile cotton pellet was placed, and glass ionomer was placed (Riva Self Cure, Australia). Preparation of the triple antibiotic paste followed the protocol of a previous study13, using ciprofloxacin 250 mg tablets (EPICO, Egypt), metronidazole 500 mg tablets (Aventis, Egypt) and doxycycline 100 mg capsules (Pfizer, Egypt). The powder content of doxycycline capsule was placed in a sterile mortar. In the same mortar, a tablet of metronidazole and a tablet of ciprofloxacin were crushed and all are mixed with saline to a creamy paste. A second appointment was scheduled after at least 7 days. Under rubber dam isolation, the interappointment dressing was removed by H-files and 2.6% sodium hypochlorite and 17% EDTA irrigation followed by saline final wash. Then, obturation was performed using cold lateral condensation technique with resin sealer (ADSEAL, META, Korea). After obturation, glass ionomer was placed to seal the access cavity till final restoration.

For group B, no interappointment dressing was applied and endodontic treatment was ended in the same visit without placement of interappointment dressing. Obturation and sealing of access cavity were performed as in group A.

Outcomes

Primary outcomes. Postoperative pain at 24, 48, 72 hours and one week after instrumentation (first visit of Group A and the single visit of Group B); recorded by the participants using NRS in a pain diary.

Secondary outcomes. Incidence of analgesic intake and number of tablets consumed in case of presence of moderate or severe postoperative pain. Participants were instructed to take one tablet of Ibuprofen 400 mg (NOVARITIS, Canada) every 6 hours and to report the number of tablets consumed.

Blinding

The operator was blinded until the end of instrumentation until she saw the number of the envelope, then the operator either administered the interappointment dressing in group A or ended the endodontic treatment in a single visit (group B). Blinding of the operator to the end of treatment was difficult as there was only a single operator (SA). The participant did not know whether endodontic treatment was done in multiple or single visit; as another appointment was given to all participants whether to complete the endodontic treatment in Group A or for follow-up in Group B. The data analyst was blinded to the group assignment.

Statistical analysis

All the data was collected and tabulated. Statistical analysis was performed by Microsoft Office 2013 (Excel) and statistical package SPSS version 22. The significance level was set at p-value ≤ 0.05. Non-parametric data was summarized as minimum, maximum and median. Chi-squared test was used to compare the incidence of studied parameters and Mann-Whitney test for analysis of severity of pain.

Results

After enrollment of 78 patients, only 44 participants were included (Figure 1). The age, gender, and preoperative pain did not differ significantly between the two groups; all participants in the two groups had preoperative no-to-mild pain (Table 1).

The data of the postoperative pain are shown in Table 2. There was no statistically significant difference between the two tested groups, either in the intensity nor the incidence of different pain categories. In both groups, there was a significant decrease in the incidence of pain at different follow-up periods (p < 0.05; Table 3).

There was no statistically significant difference between the two tested groups regarding the incidence of analgesic intake and number of analgesics tablets taken by the participants (p > 0.05; Table 4).

Discussion

Presence of AP decreases the endodontic success rate, regarding postoperative pain and radiographic healing, by about 10%–15%. Maximum removal of the bacteria and irritants causing AP is essential to achieve better prognosis. Placement of inter-appointment dressing has been previously recommended to completely disinfect the root canal system.

TAP has been found to remain active for 30 days and shows better antibacterial efficacy than calcium hydroxide in previous in-vitro studies. TAP has been used clinically in case reports and series to treat cases with large periapical lesions, when the use of calcium hydroxide cannot eliminate the symptoms. Moreover, previous randomized clinical trials found that TAP is better than calcium hydroxide, as an intracanal medicament, both clinically and radiographically.

In the present study, the intensity and the incidence at different pain categories did not differ statistically to a significant level (age, gender and preoperative pain were similarly distributed among both groups). This finding is in accordance to the results of previous studies comparing single visit versus multiple visits with calcium hydroxide. During a previous literature search, the authors found no similar studies comparing single visit versus multiple visits with TAP.

In our study, the median postoperative pain of multiple visits group (with TAP) at all follow-up periods was 0 and the incidence of moderate and severe pain ranged from 18.2% to 0%.
Table 1. Demographic data and preoperative pain of the two groups.

<table>
<thead>
<tr>
<th></th>
<th>Group A* (n=22)</th>
<th>Group B* (n=22)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) mean ± SD</td>
<td>31.27±13.5</td>
<td>37.9±10.3</td>
<td>0.07</td>
</tr>
<tr>
<td>Gender [n (%)]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>18 (81.8%)</td>
<td>17 (77.2%)</td>
<td>0.7</td>
</tr>
<tr>
<td>Men</td>
<td>4 (18.2%)</td>
<td>5 (22.8%)</td>
<td></td>
</tr>
<tr>
<td>Preoperative pain (NRS)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>0</td>
<td>0</td>
<td>0.165</td>
</tr>
<tr>
<td>Range</td>
<td>0–3</td>
<td>0–3</td>
<td></td>
</tr>
<tr>
<td>Preoperative pain incidence [n (%)]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No pain</td>
<td>18 (81.4%)</td>
<td>14 (63.6%)</td>
<td>0.175</td>
</tr>
<tr>
<td>Mild</td>
<td>4 (18.6%)</td>
<td>8 (36.4%)</td>
<td></td>
</tr>
</tbody>
</table>

*Multiple visits group; + Single visit group; NRS = numerical rating scale; SD = standard deviation.

Figure 1. Consort 2010 flow diagram of the study design.
Table 2. Incidence and intensity of postoperative pain of the two groups.

<table>
<thead>
<tr>
<th>Pain</th>
<th>Group A* (n=22)</th>
<th>Group B* (n=22)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>After 24 hours</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intensity (NRS)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>0</td>
<td>0</td>
<td>0.878</td>
</tr>
<tr>
<td>Range</td>
<td>0–9</td>
<td>0–10</td>
<td></td>
</tr>
<tr>
<td>Incidence [n (%)]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No pain</td>
<td>15 (68.2%)</td>
<td>14 (63.6%)</td>
<td>0.228</td>
</tr>
<tr>
<td>Mild</td>
<td>3 (13.6%)</td>
<td>5 (22.7%)</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>0 (0%)</td>
<td>2 (9.1%)</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>4 (18.2%)</td>
<td>1 (4.5%)</td>
<td></td>
</tr>
<tr>
<td>After 48 hours</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intensity (NRS)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>0</td>
<td>0</td>
<td>0.452</td>
</tr>
<tr>
<td>Range</td>
<td>0–8</td>
<td>0–7</td>
<td></td>
</tr>
<tr>
<td>Incidence [n (%)]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No pain</td>
<td>16 (72.7%)</td>
<td>18 (81.8%)</td>
<td>0.773</td>
</tr>
<tr>
<td>Mild</td>
<td>2 (9.1%)</td>
<td>2 (9.1%)</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>3 (13.6%)</td>
<td>1 (4.5%)</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>1 (4.5%)</td>
<td>1 (4.5%)</td>
<td></td>
</tr>
<tr>
<td>After 72 hours</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intensity (NRS)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>0</td>
<td>0</td>
<td>0.962</td>
</tr>
<tr>
<td>Range</td>
<td>0–4</td>
<td>0–3</td>
<td></td>
</tr>
<tr>
<td>Incidence [n (%)]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No pain</td>
<td>20 (90.9%)</td>
<td>20 (90.9%)</td>
<td>0.513</td>
</tr>
<tr>
<td>Mild</td>
<td>1 (4.5%)</td>
<td>2 (9.1%)</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>1 (4.5%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>After one week</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intensity (NRS)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Range</td>
<td>0–0</td>
<td>0–0</td>
<td></td>
</tr>
<tr>
<td>Incidence [n (%)]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No pain</td>
<td>22 (100%)</td>
<td>22 (100%)</td>
<td>1</td>
</tr>
<tr>
<td>Mild</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
</tbody>
</table>

*Multiple visits group; * Single visit group. NRS = numerical rating score.

Table 3. Incidence of pain at different time intervals for each group.

<table>
<thead>
<tr>
<th></th>
<th>Preoperative</th>
<th>24hrs</th>
<th>48hrs</th>
<th>72hrs</th>
<th>1 week</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A* n</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>%</td>
<td>4 (18.18)</td>
<td>7 (31.8)</td>
<td>6 (27.2)</td>
<td>2 (9.1)</td>
<td>0 (0)</td>
<td>0.032</td>
</tr>
<tr>
<td>Group B* n</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>%</td>
<td>8 (36.3)</td>
<td>8 (36.3)</td>
<td>4 (18.18)</td>
<td>2 (9.1)</td>
<td>0 (0)</td>
<td>0.005</td>
</tr>
</tbody>
</table>

* Multiple visits group; * Single visit group.

These results are comparable to the results of previous studies. Pai et al.35 found no interappointment flare-up in the group treated with TAP after 1, 2, 3, 7, and 14 days (in diabetic patients). Prasad et al.33 found that the mean of postoperative pain after one week was 0.86, while Bilgi et al.42 found that the mean of postoperative pain after 24 and 48 hours was 0.08.

In the present study, nearly 95% of the participants were asymptomatic after 72 hours postoperatively. Previous studies found that severe postoperative pain is reduced to a mild pain during this period of time43,44.

Within the conditions of this study, it could be concluded that postoperative pain was similar after performing endodontic treatment in multiple visits with triple antibiotic paste interappointment dressing or in a single visit.

Data availability
Underlying data

Reporting guidelines
Figshare: CONSORT checklist, https://doi.org/10.6084/m9.figshare.8797592.v1

Data are available under the terms of the Creative Commons Zero “No rights reserved” data waiver (CC0 1.0 Public domain dedication).

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


Open Peer Review

Current Peer Review Status: ☑

Version 1

Reviewer Report 13 August 2019

https://doi.org/10.5256/f1000research.21880.r51777

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Reham Hassan
Faculty of Dentistry, Minia University, Minya, Egypt

The current manuscript links between intra-canal medication, number of visits and the post-operative pain after endodontic treatment. While the results were insignificant, the antibiotic paste presents some disadvantages, like discoloration which was not reported.

Overall, the study was well written and designed. Additionally, it fits in a Randomized Control Trial, which increases the significance of the research.

- **Introduction**: Which was well-written and covers the relevant theoretical data of literature.

- **Aim of the study**: Here the authors stated the objectives and goals of the study in an appropriate manner.

- **In the Methods**: The authors gave a detailed description of the employed Allocation concealment and sequence generation was described adequately. The concentration of the creamy antibiotic paste prepared was not mentioned.

- The discussion section fails to explain the results.

---

**Is the work clearly and accurately presented and does it cite the current literature?**

Partly

**Is the study design appropriate and is the work technically sound?**

Yes

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

Yes

**If applicable, is the statistical analysis and its interpretation appropriate?**

Yes
Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
Yes

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

**Reviewer Expertise:** Endodontics

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.

Alireza Adl
Department of Endodontics, Biomaterials Research Center, School of Dentistry, Shiraz University of Medical Sciences (SUMS), Shiraz, Iran

This article is aimed at comparing the postoperative pain following single or two-visit endodontic treatment of necrotic teeth with apical periodontitis. The subject has been previously investigated when calcium hydroxide was used as the intracanal medicament. The point of this article is using triple antibiotic paste as the inter-appointment medicament. The authors have shown that there is no difference between two groups of patients regarding post-operative pain. Although the subject is interesting, there are a few issues that need to be clarified:

1. The introduction is very short. I believe the authors should explain more about the post-operative pain following endodontic treatment, its mechanisms and incidence. Moreover they also should explain why and how triple antibiotic paste might be effective in reducing the post-operative pain.

2. In this study, only necrotic teeth with periapical lesions were included. These teeth are prone to flare up (a combination of pain and swelling). I am interested to know why the authors evaluated only pain and not swelling.

3. Normally in this kind of study only teeth with a single canal are included. However, in the methods part of this article, it is not clear what types of teeth were selected; single-rooted or multiple-rooted or both types?

**Is the work clearly and accurately presented and does it cite the current literature?**
Partly
Is the study design appropriate and is the work technically sound?
Partly

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

If applicable, is the statistical analysis and its interpretation appropriate?
I cannot comment. A qualified statistician is required.

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
Yes

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

**Reviewer Expertise:** Endodontics

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, however I have significant reservations, as outlined above.

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