Original Article

Effect of apical foraminal enlargement on postoperative pain and inflammatory markers in asymtomatic single-rooted mandibular teeth with apical periodontitis - An *in vivo* randomized controlled trial

Pooja Gandhe, Swathi Aravelli, Sivaram Penigalapati, Swetha Kasam, Nimeshika Ramachandruni, Sindhura Alam

Department of Conservative Dentistry and Endodontics, Malla Reddy Dental College for Women, Hyderabad, Telangana, India

Abstract

Aim of the Study: This study aims to assess the effect of apical foraminal enlargement on inflammatory markers and pain in patients with asymptomatic single-rooted mandibular teeth with apical periodontitis.

Materials and Methods: The study included 60 patients based on inclusion and exclusion criteria. Before beginning root canal treatment (RCT), a blood sample was obtained from the antecubital fossa to evaluate the inflammatory markers, C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR). Access opening was done and initial irrigation was done. Working length (WL) was determined with an electronic apex locator and verified with a radiograph. In the control group, the determined WL was maintained, while in the experimental group, the WL was set till the apical foramen. Biomechanical preparation was done in both groups till F2 or F3 based on the initial apical file, followed by final irrigation and obturation based on the master apical file size. Patients were given a Visual Analog Scale to record pain sensations at 24, 48, and 72 h postoperative. After 72 h, patients were recalled for follow-up appointments, and blood was taken from the antecubital fossa again to evaluate inflammatory markers.

Statistical Analysis: The resultant findings for the reduction in inflammatory markers before and after RCT with or without foraminal enlargement were statistically analyzed using the Student's *t*-test. The pain was statistically examined with one-way "analysis of variance" and Tukey's *post hoc* test for inter-group comparison of pain. The level of significance was set at $P < 0.05$. The statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) Version 23 for Windows (SPSS Inc., Chicago, IL, USA). As pain in the control groups is zero before and after RCT, statistical analysis is not required as the overall pain score is zero.

Results: The *P* values of the CRP and ESR of the control group were 0.02 and 0.03, respectively, which indicates it is significant whereas the *P* values of the ESR and CRP of the experimental group were 0.0002 and 0.0008 which indicates it is highly significant. Results indicate that the experimental group is more effective compared to the control group in reducing inflammatory markers. Pain in the control group after RCT was zero at the end of 24, 48, and 72 h. In the experimental group, where RCT was done with apical foraminal enlargement, mild pain was present at the end of 24 h which gradually decreased at the end of 48 h and no pain was reported at the end of 72 h.

Address for correspondence:
Dr. Swathi Aravelli,
Department of Conservative Dentistry and Endodontics,
Malla Reddy Dental College for Women, Suraram, Hyderabad,
Telangana, India.
E-mail: drswathi.endo@gmail.com

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Conclusion: Reduction in inflammatory markers was more effective in RCT with apical enlargement than without apical enlargement. RCT with apical enlargement caused mild pain in the patients immediately after treatment which gradually decreased over time.

Keywords: Apical periodontitis; C-reactive protein; electronic apex locator; erythrocyte sedimentation rate; foraminal enlargement

INTRODUCTION

A microbial infection in the tooth's root canal system causes a condition known as apical periodontitis (AP), which is an inflammatory condition of the periapical tissues. AP frequently follows irreversible pulpal tissue inflammation and subsequent necrosis.[1]

AP can be acute (highly virulent bacteria) and chronic (low-virulence bacteria).[2]

A widespread rise in systemic inflammatory mediators such as C-reactive proteins (CRP), interleukins (IL)-1, 6, 8, erythrocyte sedimentation rate (ESR), and immunoglobulins (IgA, IgG, IgM) levels may be linked to low-grade systemic inflammation caused by AP.[3]

The correlation between apical lesions of endodontic origin, the systemic inflammatory load, and cardiovascular risk as measured by CRP suggests a functional relationship for cardiovascular disorders (CVD) in young adults.[4]

The high prevalence of periapical radiolucency results in an inflammatory burden. Pulpal necrosis and AP are two conditions that affect the periapical tissues and the root canal system.

Certain investigations indicate that bacteria can live outside the root canal close to the apical foramen and attach to the cementum at the root apex to form a biofilm.

In Wang *et al*.'s study,[5] molecular studies have shown the existence of bacterial biofilms in both the apical region of the root canal system and the apical lesion. Therefore, enlarging the apical foramen is acceptable.

Therefore, intentional enlargement of apical foramen is necessary to reduce the microbial load, inflammation, and inflammatory markers when the infection develops beyond the range of apical constriction.

Aim of the study

The study aims to evaluate pain perception and reduction in inflammatory markers with or without apical foramen enlargement.

MATERIALS AND METHODS

The procedure in this study followed the recent version of the Declaration of Helsinki. The Institutional Ethical Review Board and the Scientific Review Committee gave their approval to this study protocol (Ethical Clearance Number: MRDCW/IEC/AP/37/2023). This article is reported in accordance with CONSORT guidelines [Figure 1].

All patients participating in this study were explained about the study and provided both verbal and written informed consent.

Sample size calculation

A pilot study of five patients from the target group was performed to examine the required sample size for the current study.

$$N = (Z_{1-\alpha/2}\,\sigma/e)^2$$

- N is the sample size needed
- $Z_{1-2\alpha}$ is the Z-score corresponding to the upper $(1-\alpha/2)^{th}$ percentile of the standard normal distribution. This is used to determine the confidence level
- σ is the standard deviation of the population
- e is the margin of error, which is the maximum expected difference between the sample mean and the population mean.

$$= [(1.96)(1.06)/0.41]^2$$
$$= (2.0776/0.41)^2$$
$$=4.3164/0.1681$$
$$=25.6$$

The necessary sample size was calculated to be 50. Sixty patients were enrolled (to account for dropouts), ranging in age from 20 to 40 years. Thirty patients were enrolled in the control group and thirty patients were enrolled in the experimental group. Patients having a body mass index (BMI) (weight divided by height in square meters) of <30 kg/m^2 and no history of systemic disorders (e.g., diabetes, dyslipidemia, or hypertension) were eligible for the study. Patients with a single tooth diagnosed with asymptomatic AP, no response to pulp sensitivity tests, as well as a "periapical index" (PAI) score $>$ three were considered.

Exclusion criteria were patients with multiple decays, oral ulcers, Patients with acute/chronic systemic disease, recent hospitalization within 2 years, infection, inflammatory diseases such as systemic lupus erythematosus, rheumatoid arthritis, vasculitis, tissue injury or necrosis that cause damage to tissues, such as burns or trauma, autoimmune diseases, chronic kidney disease, pregnancy, female

patients during menstruation, moderate-to-severe marginal periodontal illness, use of antibiotics/corticosteroids within 3 months and use of drugs that impact bone metabolism. Such drugs include immune suppressants, oral contraceptives, bisphosphonates, selective serotonin uptake inhibitors, or hormone replacement therapy. This study excluded previously root-filled teeth to ensure participant uniformity.

Every potential source of postoperative pain was avoided in this investigation. Acute exacerbation of a chronic periapical lesion, cysts, periapical abscess, and teeth with vital or necrotic pulp exhibiting symptoms of AP were not taken into consideration.[6]

Medical and dental histories were noted. All patients underwent oral prophylaxis to eradicate marginal gingivitis. The Löe and Silness index (Löe 1967) employed parameters to assess gingival health, including firm gingival tissue, no bleeding, and no apparent erythema when probed.

Preoperative serum CRP and ESR levels were assessed seven days following oral prophylaxis to allow the gingival inflammation time to subside.

CRP was evaluated using the RHELAX-CRP kit (Tulip Diagnostics) following a quantitative method. In this method, serial dilutions of the test specimen (serum) were done using isotonic saline in the ratio of 1:2, 1:4, 1:8, 1:16, 1:32, 1:64, and so on. Six distinct reaction circles on the slide included in the kit were pipetted with each dilution of the test specimen (serum). Subsequently, a single droplet of RHELAX-CRP latex reagent was added to the material under test on the slide. The test specimen and the latex reagent were evenly combined over the whole circle with a mixing stick from the kit. A macroscopically observed agglutination was then seen after gently rocking the slide back and forth for 2 min.

The following formula was used to calculate CRP concentrations:

$$\text{CRP (mg/dl)} = S \times D$$

Here, S indicates the sensitivity of the reagent namely 0.6 mg/dl.

D represents the highest dilution of serum indicating agglutination.

ESR was tested following the Westergren method, in which a Westergren tube made of glass was used, with an internal diameter of 2.5 mm and a length of 190 mm. The standardized tube was placed in an upright position. In this method, the distance (in millimeters) was measured at which red blood cells in anticoagulated whole blood fall to the bottom of the tube over 1 h due to the effect of gravity.

After the evaluation of preoperative CRP and ESR of the control and experimental groups, root canal treatment (RCT) was initiated.

Root canal treatment

Under a dental dam isolation, an access cavity was done after local anesthesia using 2% lidocaine with 1:80,000 epinephrine (LIGNOX® 2% A, Indoco remedies Ltd., India). Using a DG 16 probe (Dentsply Sirona, USA), root canal orifices were examined. An electronic apex locator ("Root ZX; J. Morita, Tokyo, Japan") was used to assess the working length (WL) after which it was confirmed with a radiograph. In the control group, the determined WL was maintained, while in the experimental group, the WL was set till the apical foramen. A mechanical glide path was generated on the maintained WL using a size 15 K-file (Mani Inc., Utsunomiya, Japan). Biomechanical preparation was done in both groups with rotary Nickel-Titanium files (Pro-Taper Gold, Dentsply Sirona, USA) till F2 or F3 based on the initial apical file, followed by irrigation with 5 ml of 5.25% NaOCl (Prime® Dental Products Pvt. Ltd., India) with 30-gauge side vented needle ("Top Endo, NMD, 166 Mumbai, India"). A size 10 K file was used to maintain canal patency in between each rotary file. After drying the canals, obturation was done based on the master apical file size using gutta-percha coated with AH Plus sealer (AH Plus® Dentsply Sirona, USA). Composite resin (3M ESPE Filtek™ X250 XT with Adper™ single bond universal Adhesive, USA) was used to restore the access cavity.

Patients may have postoperative discomfort after endodontic therapy, which can vary from 3% to 58%.[7,8]

The patients were instructed to take 400 mg of ibuprofen every 6 h if had unbearable pain. The patients who required medication for pain control will be excluded from the study. No patients required medication as there was mild pain hence no patients were excluded after the procedure.

Visual Analog Scale was employed in this study to assess pain scores. At 24, 48, and 72 h after treatment, the patients were given the Visual Analog Scale sheet to record their pain levels, and data were collected over the phone at each interval. This helped to prevent any recollection bias and allowed for the real-time tracking of pain scores.[9]

The patients were recalled 72 h following the RCT, and blood was drawn from the antecubital fossa and tested for CRP and ESR values once again.

Statistical analysis

The resultant findings for the reduction in inflammatory markers before and after RCT with or without foraminal

enlargement were statistically analyzed using the Student's *t*-test. Pain was statistically examined with one-way "analysis of variance" and Tukey's *post hoc* test for inter-group comparison of pain. As pain in the control groups is zero before and after RCT, statistical analysis is not required as the overall pain score is zero. The level of significance was set at $P < 0.05$. The statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) V.23 for Windows (SPSS Inc., Chicago, IL, USA).

RESULTS

Table 1 shows CRP, ESR of the control group and Table 2 shows CRP, ESR of the experimental group. Table 3 shows the pain analysis of the experimental group and Table 4 shows inter-group comparison of pain. The mean CRP value of the control group before the RCT was 1.70 ± 0.5 mg/l and after the RCT was 1.67 ± 0.5 mg/l. The mean ESR value of the control group before the RCT was 20.41 ± 0.5 mm/h and after the RCT was 20.36 ± 0.5 mm/h. The mean difference between CRP and ESR before and after RCT was 0.03 mg/l and 0.05 mm/h, respectively.

The mean CRP value of the experimental group before and after the RCT was 1.92±0.5 mg/l and 1.15±0.5 mg/l respectively. The mean ESR value of the experimental group before the RCT was 21.67 ± 0.5 mm/h and after the RCT was 14.13 ± 0.5 mm/h. The mean difference between CRP and ESR before and after RCT was 0.76 mg/l and 7.54 mm/h, respectively.

The *P* values of CRP and ESR of the control group were 0.02 and 0.03, respectively, which indicates it is significant whereas the *P* values of CRP and ESR of the experimental were 0.0008 and 0.0002 which indicates it is highly significant. Results indicate that the experimental group is more effective compared to the control group in reducing inflammatory markers.

Pain in the control group and experimental group before RCT was zero as the patients included in the study were asymptomatic. Pain in the control group after RCT was also zero at the end of 24, 48, and 72 h. In the experimental group, where RCT was done with foraminal enlargement, mild pain was present at the end of 24 h which gradually decreased at the end of 48 h and no pain was reported at the end of 72 h.

Table 1: Evaluation of C-reactive protein, erythrocyte sedimentation rate values of the control groups

Control	Mean	Number of samples	SD	SEM	*t*	*P*
CRP						
Before treatment	1.7040	30	0.44172	0.08065	3.341	0.02
After treatment	1.6770	30	0.44392	0.08105		
ESR						
Before treatment	20.4153	30	2.52357	0.46074	4.203	0.03
After treatment	20.3687	30	2.52888	0.46171		

CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, SD: Standard deviation, SEM: Standard error of mean

DISCUSSION

The localized inflammation of the periapical tissues resulting from pulp disease is known as AP.[10] It can result from the progression of dental caries, trauma, or dental procedures.[11] AP is mostly caused by an infected pulp. Inflammation is the host's defensive response to pathogenic microorganisms, which leads to the eventual loss of periradicular tissues. Negative vascular effects in the body have been related to a delayed onset of chronic low-grade oral infection as well as inflammation.[12] Periapical lesions and periodontal disease are prevalent chronic infection diseases that cause persistent inflammatory reactions. Several analyses have linked oral bacteria to atherothrombotic plaques and vascular biopsies.[13] Studies on chronic periodontal disease provide the majority of data associating dental conditions with elevated inflammatory markers serum levels. Periodontal disease can cause IL-6 and CRP to spread throughout the body, thereby impacting the endothelium and cardiac smooth muscles.[14] The biological processes relating to systemic conditions and chronic periodontal disease are similar to those linking chronic AP and overall health.

Studies indicate that RCT failures are often caused by bacteria in the apical root canal system or outside the foramen.[15,16] Bacteria can create a biofilm by entering the root canal through an apical foramen and adhering to the cementum around the root apex, according to research.[17] A prolonged infection results from the special characteristics of biofilm microorganisms, which make them resistant to phagocytic cells and treatments.[18] Even after routine root canal treatment for periapical periodontitis with extraradicular

Table 2: Evaluation of C-reactive protein, erythrocyte sedimentation rate values of the experimental groups

Experimental	Mean	Number of samples	SD	SEM	*t*	*P*
CRP						
Before treatment	1.9163	30	0.42923	0.07837	9.465	0.0008
After treatment	1.1560	30	0.27436	0.05009		
ESR						
Before treatment	21.6717	30	1.84954	0.33768	8.914	0.0002
After treatment	14.1367	30	4.81510	0.879111		

CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, SD: Standard deviation, SEM: Standard error of mean

Table 3: Evaluation of pain in the experimental groups

	Number of samples	Mean±SD	*F*	*P*
Before treatment	30	0.0000±0.00000	107.5	0.002
24 h	30	3.1000±1.12495		
48 h	30	1.3333±0.88409		
72 h	30	0.2333±0.43018		

SD: Standard deviation

Table 4: Inter-group comparison of pain

Groups	Significant
Before treatment (h)	
24	0.000
48	0.000
72	1.000

infection, a lesion may not heal if the causative agents have advanced beyond the reach of therapeutic techniques.[19] Hence, when the infection spreads beyond the boundaries of apical constriction, intentional enlargement of the apical foramen is required to lower the microbial load, inflammation, and inflammatory markers.

A widespread rise in systemic inflammatory mediators such as CRP, IL-1, IL-2, and IL-6, as well as immunoglobulin (IgM, IgG, and IgA) levels, may be linked to low-grade systemic inflammation caused by AP.[3] In acute inflammatory conditions, both CRP and ESR tend to rise rapidly. CRP typically rises more quickly and to a greater extent than ESR in response to acute inflammation. ESR tends to be a slower and less dynamic marker, taking longer to peak and decline compared to CRP. In some chronic inflammatory conditions, CRP levels may remain consistently elevated while ESR levels fluctuate less predictably.[20]

In 2002, The American Heart Association Panel and The Centre for Disease Control and Prevention suggested that serum levels of CRP be evaluated as a measure of systemic inflammation that eventually results in CVD. Therefore, serum CRP measurement may be useful in determining a person's CVD risk status.[21]

Overall, while both CRP and ESR can indicate the presence of inflammation, they are not interchangeable, and their interpretation often depends on the clinical context. In many cases, health-care providers may use both tests together to assess the degree and progression of inflammation in a patient.[20]

RCT decreased serum levels of CRP in systemically healthy people with AP.[21]

In the present study, we examined CRP and ESR since they can help with clinical monitoring and diagnosis algorithms for a range of inflammatory and infectious diseases.[22]

To the best of our knowledge, there are no studies that assessed the effect of foraminal enlargement on postoperative pain and inflammatory markers mainly CRP and ESR in asymptomatic single-rooted mandibular teeth.

To avoid confounders, systemically healthy people aged 20–40 years with a BMI <30 kg/m^2 and no history of systemic disorders (e.g., diabetes, dyslipidemia, or hypertension), patients with a single tooth diagnosed with chronic AP, no response to pulp sensitivity tests, and a PAI score > three were considered.

Patients with conditions that increase the inflammatory markers were excluded.[22]

CRP and ESR levels evaluated before the RCT were high in both control and experimental groups which indicates inflammatory conditions in the patients.

Posttreatment CRP and ESR levels were evaluated only once after 3 days, not on days one and two following ethical considerations. Inflammatory markers may take different periods to reach normal levels after treating the underlying cause. To standardize the period, posttreatment evaluation of all the cases was done at the end of 3 days.

In the current research, the mean CR*P* value of the control group before the RCT was 1.70 ± 0.5 mg/l, and after the RCT was 1.67 ± 0.5 mg/l. The mean ESR value of the control group before the RCT was 20.41 ± 0.5 mm/h and after the RCT was 20.36 ± 0.5 mm/h. The mean difference between CRP and ESR before and after RCT was 0.03 mg/l and 0.05 mm/h, respectively. There is a significant variation in the mean value before and after RCT in the control group.

The mean CR*P* value of the experimental group before the RCT was 1.91 ± 0.5 mg/l and after the RCT was 1.15 ± 0.5 mg/l. The mean ESR value of the experimental group before the RCT was 21.67 ± 0.5 mm/h and after the RCT was 14.13 ± 0.5 mm/h. The mean difference between CRP and ESR before and after RCT was 0.76 mg/l and 7.54 mm/h, respectively. The difference in mean values of experimental groups before and after RCT is highly significant when compared to control groups.

The pain was evaluated at intervals of 24, 48, and 72 h as foraminal enlargement causes the pain. If had unbearable pain patients were asked to take the prescribed medication. The patients who required medication for pain control were excluded from the study. Pain was evaluated at three intervals.

The current study is in accordance with the previous research that there is not a significant association between the cases where apical enlargement was done and postoperative

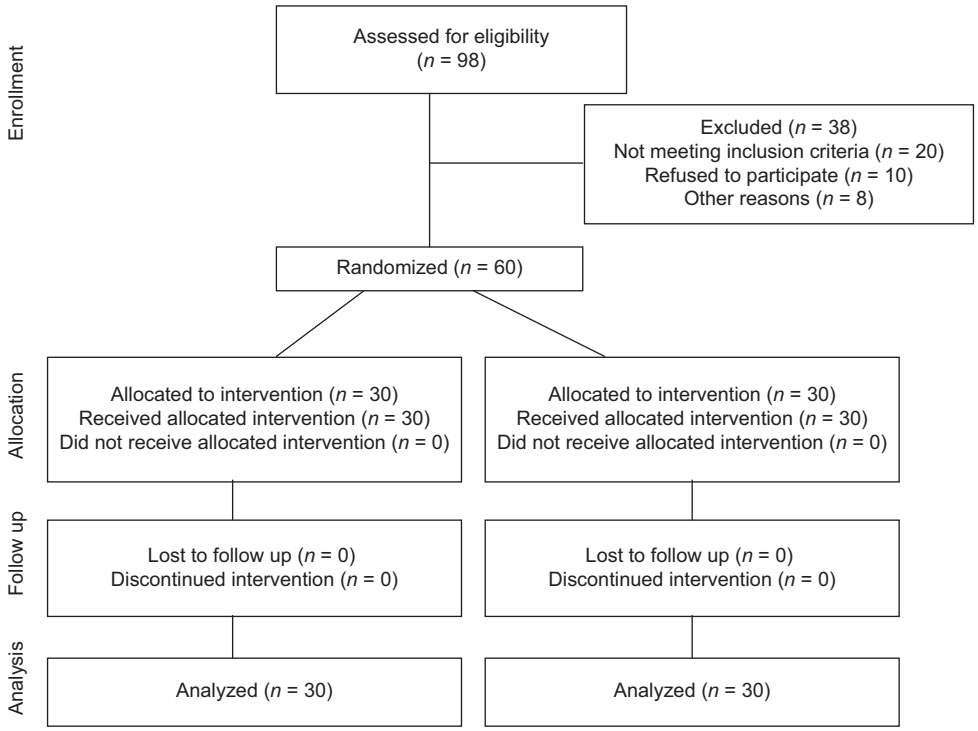

Figure 1: The CONSORT diagram showing the flow of participants through each stage of a randomized trial

pain. Patients treated with apical enlargement reported lower levels of pain perception overall.[23]

Foraminal enlargement increased the sense of pain within the first 24 h after treatment, however, the overall incidence of pain was considered low, irrespective of the WL.[24]

The fact that each patient has a distinct pain threshold is a significant research drawback. In certain individuals, the placement of rubber dams and anxiety may intensify their postoperative discomfort.[25]

CONCLUSION

RCT decreased serum CRP and ESR levels in systemically healthy individuals with AP with or without apical enlargement. However, reduction in inflammatory markers was more effective in RCT with apical enlargement than RCT without apical enlargement. RCT with apical enlargement caused mild pain in the patients immediately after treatment which gradually decreased over time.

Clinical significance

By enlarging the apical foramen, the clinician can more effectively remove infected or necrotic tissue, bacteria, and debris from the root canal system. This can lead to better disinfection of the canal, which is essential for the success of RCT. Foraminal enlargement also reduces the risk of reinfection by removing the biofilm in the extraradicular area.

Overall, foraminal enlargement can contribute to the success of RCT by improving the cleaning and also reducing the chance of reinfection, with mild postoperative pain for only a limited period which are crucial factors in the long-term success of endodontic therapy.

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Conflicts of interest

There are no conflicts of interest.

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