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A Novel Combination of Resolvin D2 and Calcium Hydroxide as an Intracanal Medicament

Research Article

Rukhsaar Akbar Gulzar[1], Hima Sandeep[2*]

[1] Post Graduate Student, Department of Conservative Dentistry and Endodontics, Saveetha Dental College and Hospitals, Saveetha Institute of Medical and Technical Sciences, Saveetha University, Chennai, India.
[2] Senior Lecturer, Department of Conservative Dentistry and Endodontics, Saveetha Dental College and Hospitals, Saveetha Institute of Medical and Technical Sciences, Saveetha University, Chennai, India.

Abstract

Introduction and Aim: Resolvins are lipid mediators that are released during the resolution phase of inflammation and regulate tissue repair. Previous literature has identified the antimicrobial potential of RvD2. The present study aimed at identifying the minimum inhibitory concentration of RvD2 against E faecalis and determining if the combination of RvD2 and calcium hydroxide has any synergistic antimicrobial effect.
Materials and Method: The antimicrobial efficacy was evaluated using the agar diffusion test by determining the zone of inhibition. MIC was defined as the minimum concentration of extract that caused 80% inhibition in growth of test microorganism. For statistical analysis of data, multiple comparisons were performed using one-way analysis of variance (ANOVA) followed by the LSD test for post hoc analysis. Statistical significance was accepted at a level of $P<0.05$.
Results: The zone of inhibition observed around the disc impregnated with RvD2 (10.8 ± 0.9 mm) was smaller as compared to calcium hydroxide (11.4 ± 0.54mm). However this difference was statistically significant. The maximum zone of inhibition was seen around the disc impregnated with a combination of RvD2 and calcium hydroxide (15.4 ± 0.98mm) which was highly significant. The MIC value of RvD2 was 1.5 µg/ml and the MBC value was 2.0 µg/ml.
Conclusion: Resolvin D2 has shown comparable antimicrobial activity to that of calcium hydroxide against E faecalis. The combination of RvD2 and calcium hydroxide has a significant synergistic antimicrobial effect.

Keywords: Apical Periodontitis; Calcium Hydroxide; E Faecalis; Intracanal Medicament; Resolvin.

Introduction

The ethics of reasonable endodontic therapy are focused on prevention, minimization and elimination of infection which are not easy tasks within the condition of a root canal system. In conditions of periradicular diseases and pulp necrosis, the need for intracanal medicament becomes highly relevant [1]. Over the years considerable research has been done to understand the colonization and composition of microflora in the root canal system. There are microflora differences seen in primary infections of the root canal and in reinfection [2]. Microorganisms in the root canals are found in planktonic form and as well as biofilms. Biofilm is a complex structure composed of microcolonies in a matrix of polysaccharide and poses a challenge during disinfection of the canal [3, 4]. The management of apical periodontitis is highly complex due to the presence of biofilms, colonies in the dentinal tubules as well as the complexity of the anatomy which warrants the use of an intracanal medicament which is usually placed in the canal for a minimum of 7 days after the complete shaping and irrigation is performed. The medicament eliminates residual microorganisms present in the areas that are not easily accessible to the rotary files and irrigant and helps in resolution of the periapical inflammation.

An endodontic infection is a polymicrobial disease, hence when the use of a single medicament does not suffice, one might consider using a combination of two drugs or using them in succession till the desired disinfection is achieved. An efficacious medicament is one that has good prolonged antibacterial effect, is

***Corresponding Author**:
Dr Hima Sandeep,
Senior Lecturer, Department of Conservative Dentistry and Endodontics, Saveetha Dental College and Hospitals, Saveetha Institute of Medical and Technical Sciences, Saveetha University, Chennai, India.
E-mail: himas.sdc@saveetha.com

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not irritant to the periapical tissue and induces healing [1].

Resolvins are lipid mediators that are released during the resolution phase of inflammation and regulate tissue repair. Previous literature has identified the antimicrobial potential of resolvin D2 (RvD2). Russell et al discusses the role of pro resolution lipid mediators in infectious diseases [5]. Siddiqui et al in a study in 2019 showed that RvD2 when used as an intracanal medicament, induced resolution of periapical inflammation and promoted periapical healing in rats as well as reduction in microbial load. Further, calcified canals apices were observed in RvD2 treated teeth with apex closure [6]. However in the previous study, these properties of RvD2 were observed against a placebo control. There has been no study that has proposed the use of RvD2 in combination with calcium hydroxide which is the gold standard.

Previously our team has a rich experience in working on various research projects across multiple disciplines [7-21] Now the growing trend in this area motivated us to pursue this project. The present study is a preliminary study aimed at identifying the minimum inhibitory concentration of RvD2 against e faecalis and comparing the antimicrobial efficacy of RvD2 with calcium hydroxide as well as determining if the combination of RvD2 and calcium hydroxide has any synergistic antimicrobial effect.

Materials And Method

Chemicals

The test drug RvD2 was purchased from Santa Cruz BioTech and calcium hydroxide was obtained commercially. All media, broth and other chemicals required for the project were obtained from Himedia Laboratories.

Bacterial strains and media

Enterococcus faecalis strain ATCC 29212 was maintained in stock culture at -80ºC in Tripticase Soy Broth containing 25% glycerol. Microorganisms were grown on Tripticase Soy Agar plates, and checked for purity. The bacterial cell suspensions were adjusted to a density containing approximately 1×10^8 CFU/ml and diluted with media to contain 105 CFU/ml. In order to use these microorganisms in the microdilution assay, the appropriate starting concentrations in the assay inoculum were determined from preliminary growth curve studies in the microtiter plates.

Study groups

The following were the study groups:
1: Calcium hydroxide
2: Resolvin D2 100nM
3: Calcium hydroxide and resolvinD2
4: Negative control

Antimicrobial susceptibility testing

A 100 µl of bacterial suspension was spread on each Muller Hinton Agar plate. 20 µl of irrigants Resolvin D2 (100 nM calcium hydroxide and combination of Resolvin D2 and calcium hydroxide were impregnated on sterilized 6 mm blank discs. Distilled water loaded discs were used as negative control. All impregnated discs were ensured to be fully dried in 45ºC incubator for 18 to 24 hours prior to the application of bacteria. The discs which had been impregnated with irrigants using sterile forceps were applied on the inoculated Mueller Hinton agar once it was completely dried. The discs were pressed gently to ensure uniform contact with agar surface. Within 15 min of application, plates were shifted to an anaerobic jar, which was kept in an incubator for 48 h. After incubation was complete, the diameter of the inhibition zone found around the treated discs were measured for the antibacterial activity assessment. If present, their diameters were measured to the nearest whole millimetre with a ruler. All tests were carried out three times to ensure the reliability, and the average of the three replicates of irrigants, and negative control were calculated.

Determination of Minimum Inhibitory Concentration (MIC)

The cultures were then incubated and subsequently serially diluted to reach the density of 2×10^4 cells per ml. Two milliliters of MHB broth was dispensed in tubes, and 100 µL of cell culture was inoculated in it. Then, 100 µL of different concentration of test products was added to each tube. Growth control was run in parallel with every experiment. All the experimental tubes were incubated for 48 h. After completion of the incubation period, the optical density was measured at 600 nm. MIC was defined as the minimum concentration of extract that caused 80% inhibition in growth of test microorganism. Each experiment was carried out in a triplicate set. The lowest concentration prior to colour change was considered as the Minimum Inhibitory Concentration (MIC). The percentage of bacterial inhibition by the test product was computed using the following equation:

Percentage Inhibition = [(OD in control-OD in test)/OD in control] x100

Statistical analysis

For statistical analysis of data, multiple comparisons were performed using one-way analysis of variance (ANOVA) followed by the LSD test for post hoc analysis. Statistical significance was accepted at a level of $P<0.05$. Data was analyzed using SPSS (version 21.0).

Results

The zone of inhibition observed around the disc impregnated with RvD2 (10.8 ± 0.9 mm) was smaller as compared to calcium hydroxide (11.4 ± 0.54mm). However this difference was statistically significant. The maximum zone of inhibition was seen around the disc impregnated with a combination of RvD2 and calcium hydroxide (15.4 ± 0.98mm) which was highly significant. (Table 1 and Fig 1) Resolvin D2 (con 1µg/ml) showed inhibition percentage 51.5%, Hence the MIC which showed 80% inhibition was 1.5 µg/ml. MBC value was calculated based upon the concentration which showed no microorganism growth i.e 100% inhibition which was 2.0 µg/ml. (Table 2)

Discussion

Our institution is passionate about high quality evidence based

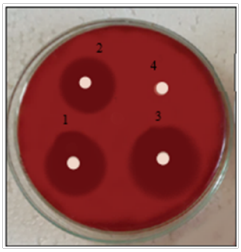
Table 1. Antibacterial activity -Agar well diffusion. NI means no inhibition zone. Each value is expressed as mean ± SD (n = 3). ***p<0.001 statistically significant as compared with negative control. cp<0.05 statistically significant as compared with Resolvin D2 and #p<0.05 statistically significant as compared with Ca(OH)2.

Irrigants	Irrigants Zone of Inhibition (mm)
Resolvin D2	10.8 ± 0.9***
Ca(OH)2	11.4 ± 0.54***
Resolvin D2 + Ca(OH)2	15.4 ± 0.98***c,#
Negative control	NI

Table 2. Absorbance values to determine the minimum inhibitory concentration of resolvin D2.

Drug	Conc (µg/ml)	Absorbance at 600nm	% of Inhibition
Resolvin D2	0.25	0.323 ± 0.22**#	21.02
	0.5	0.284 ± 0.19***#	30.5
	1	0.198 ± 0.11***	51.5

Figure 1. Disc diffusion method showing zone of inhibition.



1- Ca(OH)2; 2- Resolvin D2; 3- ResolvinD2 + Ca(OH)2; 4- Negative control

research and has excelled in various fields [22-32].

Derived from omega 3 fatty acids namely, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) as well as docosapentaenoic acid (DPA); resolvins are specialised pro resolving mediators which restore normal cellular function after [33] tissue injury [34]. It was from the self resolving exudates of murine during the resolution phase of acute inflammation, that RvD2 was first isolated [33]. The biosynthesis involves 17-lipoxygenation of DHA to 17S-hydroperoxy-DHA (17S-HpDHA). This is then further transformed to a 7(8)epoxide-containing intermediate in leukocytes via 5-lipoxygenase (LOX) enzymatically, followed by enzymatic hydrolysis to form RvD2. RvD2 can be endogenously found in human serum, plasma [35], adipose tissue [36], placenta [37], breast milk [38], sepsis patients [39] and lung [40].

Resolution at cellular level involves cessation of PMN entry into the tissue and elevated phagocytosis of apoptotic PMN by macrophages. In human macrophages, RvD2 stimulates phagocytosis and efferocytosis in a DRV2-dependent manner. Resolvin acts by binding to a specific G protein coupled receptor GPR18/DRV2 which activates the cyclic AMP-PKA pathway and phosphorylation of STAT3and increases phagocytosis mediated bacterial clearance [41].

Mizraji et al found that RvD2 prevented alveolar bone loss in murine periodontitis and prevented destructive immunity. It prevented osteoblast-mediated and T-cell-mediated signaling of osteoclast formation by RANKL leading to alveolar bone loss and has also shown defensive properties against P. gingivalis which causes periodontal bone loss [42]. Proresolving mediators have shown promising results in the healing of apical periodontitis with reduction in the size of the periapical lesion and recalcification of bone [43][6]. Resolvins can be administered in active inflammatory lesions without any deleterious effects, the bacterial load is reduced and there is no increase in disease activity [45].

Spite et al observed that RvD2 was able to reduce both systemic as well as local bacterial burden in mice with microbial sepsis induced due to cecal ligation [46]. Human neutrophils have demonstrated enhanced phagocytosis of Escherichia coli in the presence of RvD2 [47]. It has also been suggested that RvD2 helps in controlling infections that are caused secondary to burns by modulating neutrophil chemotaxis [48]. Siddiqui et al observed low levels of residual bacteria in teeth induced with apical periodontitis in murine species that were treated with RvD2 as compared to the control group [6]. Resolvin D2 (RvD2) has also been shown to enhance post ischaemic revascularization while resolving inflammation by promoting apoptosis of polymorphonuclear neutrophils (PMSs), controlling bacterial sepsis as well as promoting arteriogenesis [49]. RvD2 is also known to be capable of inhibiting transient receptor potential channels present in sensory neurons and is thus capable of reducing postoperative pain [50].

Similarly in our study RvD2 has shown comparable antimicrobial activity to that of calcium hydroxide against E faecalis and the combination of the two has shown a significant synergistic effect. The reason for choosing E faecalis was because it is a strain with high resistance and most commonly observed in persistent lesions and failed endodontic cases [51]. However one cannot ignore the fact that an endodontic infection is polymicrobial. Future studies pertaining to the antimicrobial efficacy of RvD2 can focus on a more diverse range of microorganisms. Most often cases of persistent lesions require treatment with triple antibiotic paste(TAP).

TAP is also used in disinfecting canals of immature necrotic permanent teeth before attempting revascularization. However, higher concentrations of TAP has a deleterious effect on SCAP cells and also causes discolouration [52]. On the other hand RvD2 shows promising results in resolution of inflammation, regeneration, periapical healing and control of sepsis. The combination of RvD2 with calcium hydroxide could serve as an alternative medicament in such cases. However further studies clinical studies are required. If the effects of these mediators translate from pre-clinical studies into successful clinical trials, they represent promising new strategies in managing infectious disease.

Conclusion

Resolvin D2 has shown comparable antimicrobial activity to that of calcium hydroxide against E faecalis. The combination of RvD2 and calcium hydroxide has a significant synergistic antimicrobial effect on E faecalis. RvD2 could be a promising new strategy in the management of infectious disease if the translation of the effects of RvD2 from preclinical studies into clinical trials is successful.

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