

## Original Research Article

### Evaluation of agreement between non-surgical management techniques for large periapical lesions

#### ABSTRACT

**Aim:** The aim of this study is to evaluate the agreement between three routinely used non-surgical management techniques for large periapical lesions namely the treatments with Calcium hydroxide, Mineralo-Trioxide Aggregate and Bio-dentine.

**Methods:** Data was collected from 60 patients at the Department of Restorative Dentistry, Faculty of Dental Sciences, University of Peradeniya. The variables age, gender and area of the infected region before and after the treatment and the treatment type were considered. Two homoscedastic and heteroscedastic Mixed-effects models were fitted and the agreement between three treatments were assessed using Concordance Correlation Coefficient (CCC) and Total Deviation Index (TDI).

**Results:** CCC value calculated for treatment types 1 & 2, 1 & 3 and 2 & 3 are (0.905, 0.909, 0.874) for homoscedastic model and (0.989, 0.990, 0.975) for heteroscedastic model. Further, corresponding TDI values for homoscedastic and heteroscedastic models are (3.148, 4.390, 1.647) and (2.963, 4.388, 1.457) respectively.

**Conclusions:** Since all the CCC values are close to 1 and TDI values are low, there is a strong agreement between all three treatments and hence they be used interchangeably. Moreover, the agreement between Treatments with Calcium hydroxide and Bio-dentine is higher ...?? compared to others.

**Keywords:** *Agreement, Concordance correlation coefficient, Mixed effects models, Periapical Lesions, Total deviation index*

#### 1. INTRODUCTION

Inflammatory lesions of the pulp and periapical area which are commonly known as periapical lesions are the most common pathologic condition involving teeth. The lesions are caused by a bacterial infection of the dental pulp.<sup>1</sup> Most of the periapical lesions (>90%) can be classified as dental abscesses granulomas or radicular cysts.<sup>2,3</sup> The occurrence of dental granulomas ranges between (9.3-87.1) % while the incidence of cysts lies within 6-55% and of abscesses between 28.7 and 70.07%.<sup>4,5</sup> A granuloma is formed when the periapical tissues neutralize and confine the irritating toxic products escaping from the root canal. A radicular cyst has its origin from the cell rests of Malassez which are present in periodontal and periapical ligament, and in periapical granulomas. Most radicular cysts originate from pre-existing granulomas. On the other hand, an apical abscess usually develops from a pulpo-periapical inflammatory condition. It also can arise from a pre-existing granuloma or cyst. Cysts and granulomas may present very similarly and on most occasions are hard to distinguish by simple observation. Only a professional can differentiate them. Periapical lesions are

40 diagnosed either during routine dental radiographic examination or following acute pain in a tooth.<sup>6</sup> It  
41 is accepted that all inflammatory periapical lesions should be initially treated with conservative  
42 nonsurgical procedures<sup>7</sup>. Surgical procedures are recommended only in situations where nonsurgical  
43 techniques have failed<sup>8</sup>. In most situations endodontic therapy alone is enough to return the infected  
44 teeth to a healthy state and function without surgical intervention since surgery has many drawbacks  
45 <sup>9,10</sup>, which limit its use in management of periapical lesions. Studies<sup>11</sup> have reported that a high  
46 percentage of 94.4% of complete and partial healing of periapical lesions could be achieved by  
47 nonsurgical endodontic therapy.

48 A nonsurgical approach should always be adopted before resorting to surgery. Patients are also  
49 psychologically more anxious about surgical treatment than a nonsurgical one. There are several  
50 nonsurgical procedures<sup>12,13</sup>, such as Conservative root canal treatment without adjunctive therapy,  
51 Decompression technique, Intra-canal dressing with Calcium hydroxide, Placement of Mineralo-  
52 Trioxide Aggregate (MTA) in the apical 4-5mm of the tooth and Placement of Bio-dentine in the apical  
53 4-5mm of the tooth.

54 Calcium hydroxide is a material widely used in endodontic treatment because of its bactericidal  
55 effects. It is thought to create favorable conditions for periapical repair and stimulate hard tissue  
56 formation. A high degree of success has been reported by using calcium hydroxide beyond the apex  
57 in cases with large periapical lesions.<sup>14</sup> The treatment should be given repeatedly. However this  
58 treatment is economical compared to the others.

59 MTA and Biodentine are more novel materials which are recommended to be used for successful  
60 apical closure in cases with large periapical lesions. They are considered extremely bio-compatible  
61 and have cemento-conductive and osseo-conductive properties. Thus these materials are  
62 increasingly used in the management of large periapical lesions. They are considered more  
63 advantageous considering the time taken for apical closure and the superior apical seal they offer.<sup>15</sup>  
64 However, compared with calcium hydroxide the cost of these two treatment modalities are higher. The  
65 main advantage of these treatment modalities is that the treatment could be dispensed in one visit.

66 The main objective of this study is to evaluate the agreement between three routinely used non-  
67 surgical management techniques for large periapical lesions namely the treatment with Calcium  
68 hydroxide (Treatment 1) which serves as the standard reference method, the treatment with Mineralo-  
69 Trioxide Aggregate (Treatment 2) and the treatment with Bio-dentine (Treatment 3). If the treatments  
70 agree satisfactorily well, then they can be used interchangeably.

## 71 **2. MATERIAL AND METHODS**

72 The data was collected from the Department of Restorative Dentistry, Faculty of Dental Sciences,  
73 University of Peradeniya. Sixty patients were randomly allocated to three groups according to the  
74 treatment given. The variables considered in this study are the age and gender of the patient, area of  
75 the infected region before and after the treatment and the treatment type. The infected area of the  
76 tooth of each patient was recorded under 5-time periods (0, 1, 3, 6, 12 months periods) as realized on

77 periapical radiographs taken using a long cone paralleling technique. The maximum diameter of the  
78 lesions was recorded at each review as understood on an illuminated radiograph viewer under x2.5  
79 magnification.

80 In this study, the Wilcoxon Rank Sum Test was used to test the significant difference between the  
81 Treatment types. The null hypothesis is that there is no significant difference between the two  
82 treatment methods while the alternative hypothesis is that there is a significant difference between the  
83 two treatment methods. If p-value < 0.05, we reject  $H_0$  and conclude that there is a significant  
84 difference between the two treatment methods.

85 At first, the data was modeled using homoscedastic mixed-effects model. Then for the situations  
86 where the key assumptions such as constant error variance (homoscedastic error variance) are  
87 violated, a multiple heteroscedastic mixed effects model was used to model the data. The fitted model  
88 was validated using the 10-fold cross validation technique.<sup>16,17</sup> In order to assess the agreement  
89 between the three treatments, Concordance Correlation Coefficient (CCC) and Total Deviation Index  
90 (TDI) were used.<sup>18</sup> Fisher's z-transformation and the log-transformation were used on the CCC and  
91 TDI respectively for greater accuracy.

92 The CCC is defined as,

$$P_{ccc} = \frac{2\sigma_{12}}{\sigma_1^2 + \sigma_2^2 + (\mu_1 - \mu_2)^2}$$

93 Here  $\sigma_1$  and  $\sigma_2$  are the standard deviations of the two groups being compared while  $\sigma_{12}$  is the  
94 covariance between the two groups.  $\mu_1$  and  $\mu_2$  are the means of group1 and group2 respectively.

95 Total deviation index for the two variables  $Y_1$  and  $Y_2$  is given by,

$$TDI = \sqrt{\chi^{2(-1)}\left(\pi_0, 1, \frac{\mu_d^2}{\sigma_d^2}\right)}$$

96 Here, TDI is the  $\pi_0^{\text{th}}$  percentile of  $|Y_1 - Y_2|$ , for a given large probability  $\pi_0$  where  $0.80 \leq \pi_0 \leq 0.95$ .

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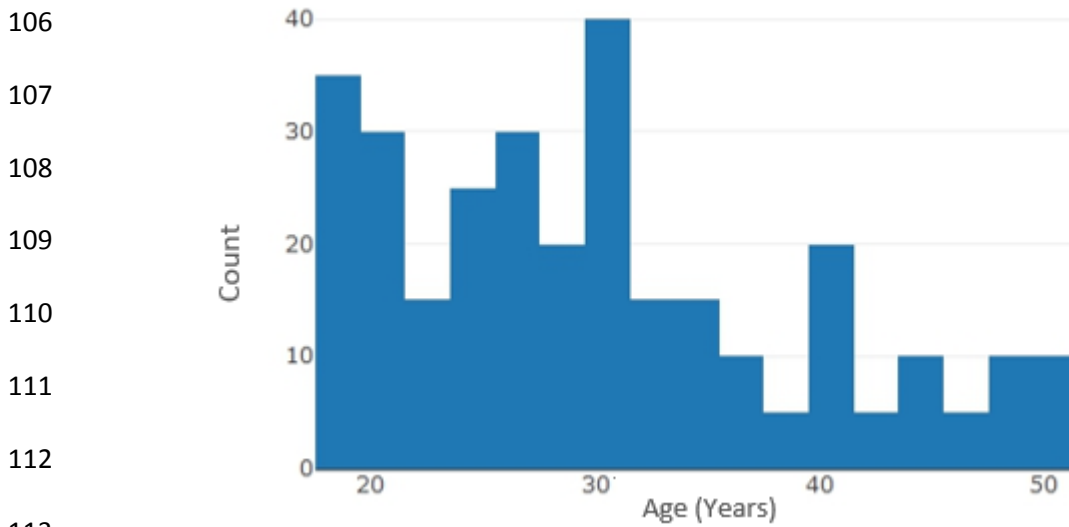
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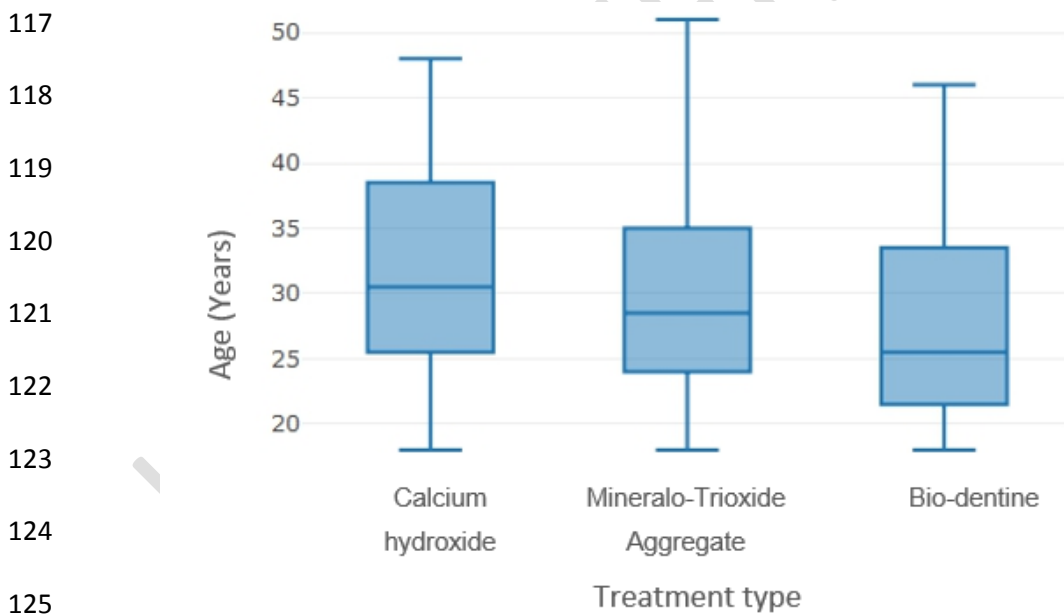
104 **3. RESULTS**

105 Most patients with periapical lesions belonged to the below 30 year age group (Figure 1).



114 **Fig 1: The Plot of count based on the age of the participants**

115 Figure 2 implies that Treatment 1 was mostly given to the patients above 30 years, while the other two  
116 treatments (Treatment 2 and Treatment 3) were given to the patients who are below 30 years.



126 **Fig 2: The variation of the treatment type with age**

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128 The p-values obtained using the Wilcoxon Rank Sum Test are given in Table 1. This suggests that  
129 there is no significant difference between the three treatments.

130 **Table 1: The results of the Wilcoxon Rank Sum Test for checking the significance difference**  
 131 **between the Treatment types.**

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134 Several models were obtained using different variance function classes provided in *nlme* library in the

	<b>Treatment-1 and Treatment-2</b>	<b>Treatment-1 and Treatment-3</b>	<b>Treatment-2 and Treatment-3</b>
<b>w-value</b>	209.5	227.5	213.5
<b>p-value</b>	0.8065	0.2943	0.514

135 statistical software R. AIC and BIC values obtained for the fitted models are given in Table 2.

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137 **Table 2: AIC and BIC values for homoscedastic and heteroscedastic models**

		<b>AIC</b>	<b>BIC</b>	<b>Log Likelihood</b>
<b>Homoscedastic Model</b>	<b>Model A</b>	<b>2962.31</b>	<b>2999.25</b>	<b>-1471.16</b>
<b>Heteroscedastic Model</b>	Model B	2962.53	3006.85	-1469.26
	Model C	2948.87	2985.81	-1464.44
	Model D	2951.38	2999.39	-1462.69
	Model E	2937.23	2977.86	-1457.61
	Model F	2957.14	2997.77	-1467.57
	Model G	2959.53	3000.16	-1468.76
	Model H	3100.65	3141.28	-1539.33
	Model I	2963.32	3003.95	-1470.66
	<b>Model J</b>	<b>2644.27</b>	<b>2699.68</b>	<b>-1307.14</b>

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140 Model A was selected as the best homoscedastic model (Table 2). **Describe the reason** ..This model  
 141 was fitted using the variables time, age, treatment type and their two-variable interaction terms.

142 Fixed effect for model A is the area of the infected region which is explained by time, treatment and  
 143 age with the interaction between time and treatment (interactions between only 2 variables) while the  
 144 random effect is explained for each group where grouping is given by the patient number.

145 Model J was selected as the best model. Describe the reason ... It can be concluded that the area of  
 146 the infected region depends on the age of the patient, time periods, treatment type and their two-  
 147 variable interaction terms. There is a positive impact on the area of the infected region by the  
 148 interaction between the treatment type and age. There are negative impacts on the area of the  
 149 infected region by the treatment type, age, time and the interaction between the treatment type and  
 150 time. According to the model summaries, the highest negative impact on the area of the infected  
 151 region is caused by the treatment type.

152 In order to assess the agreement between three treatment types, CCC and TDI values were obtained  
 153 (Table 3). From both CCC and TDI values given in Table 3, a strong positive agreement is observed  
 154 between all three treatments.

155 **Table 3: CCC and TDI values for models**

<b>Homoscedastic Model</b>				156
	Treatment 1 and Treatment 2	Treatment 1 and Treatment 3	Treatment 2 and Treatment 3	
<b>CCC values</b>	0.905	0.909	0.874	159
<b>TDI values</b>	3.148	4.390	1.647	
<b>Heteroscedastic Model</b>				161
<b>CCC values</b>	0.989	0.990	0.975	161
<b>TDI values</b>	2.963	4.388	1.457	162
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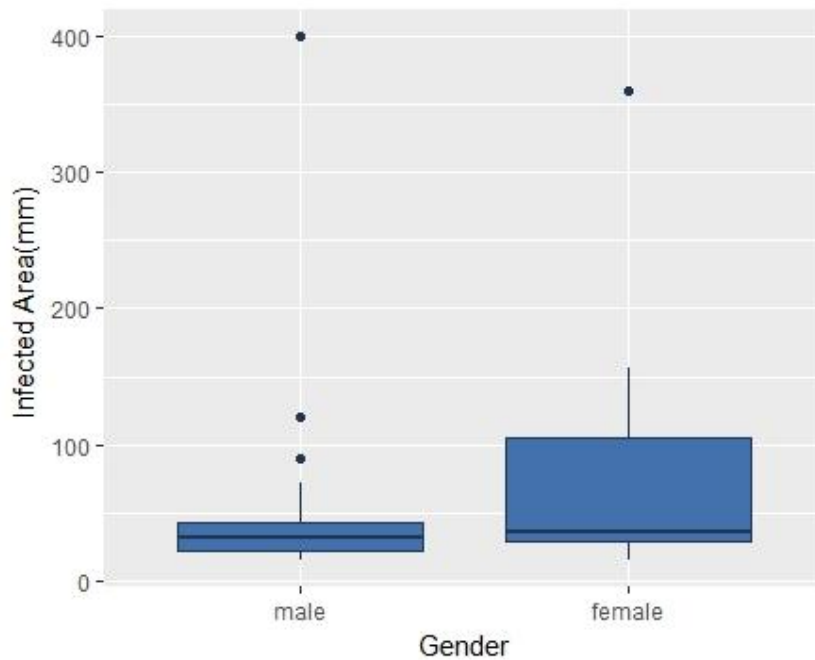
165 **4. DISCUSSION**

166 In the present study, the data of 60 patients who were subjected to endodontic treatment for anterior  
 167 teeth was investigated. They have selected the patients exhibiting well circumscribed periapical  
 168 lesions of **more than 5mm in diameter** (did not mention in the material and method part??) on a pre-  
 169 operative periapical radiograph. Akinyamoju et al <sup>19</sup> found that the age range of the patients having  
 170 periapical lesions was 9 to 80 years with a peak at age group of 20-29 years. In the present study, we  
 171 obtained the similar results reconfirming the fact as given in Figure 1. Furthermore they have found  
 172 that, females were more frequently affected by this condition. The present study has been reported  
 173 the similar observations as in Figure 3.

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**Fig 3: Variation of Infected area with gender**

A similar study was carried out by Dexton et al<sup>20</sup> and the three treatments they compared are Photo Activated Disinfection(PAD), triple antibiotic paste and the calcium hydroxide where all three were used as root canal disinfectant. Moreover, in their study they have found that there is a significant change between calcium hydroxide and PAD using Kruskal-Wallis Test and Bonferroni post hoc test. In the present study the two treatments being compared with the treatment 1 (calcium hydroxide) differ from the previously mentioned study. Although the above-mentioned study has reported a significant difference between the two treatments, no significant difference was found among any of the treatments we considered. As denoted in the Table 1, the p-values obtained using the Wilcoxon Rank Sum Test which are greater than 0.05 suggests that there is no significant difference between the three treatments. **Therefore, mixed effects model analysis' was applied in this study --> Not clear, need to be explained why this 'mixed effects model analysis' was applied in this study instead of for further treatment based on the result of this study???**

The standard mixed-effects model is successful in explaining the data set, in accordance with the literature. The presence of heteroscedasticity is indicated by the situations where the key assumptions such as constant error variance (homoscedastic error variance) are violated. Therefore, in the present study, a multiple heteroscedastic mixed effects model is proposed to model the data and this fitted model is then used to assess the agreement between multiple methods of measurements. This methodology has been indicated by Nawarathna et al <sup>21,22</sup> as a way of measuring agreement in method comparison studies with heteroscedastic measurements.

207 Bland et al<sup>23</sup> affirmed that use of correlation is misleading in comparison of a new measurement  
208 technique with an established one. Furthermore they have suggested an alternative approach based  
209 on graphical techniques and simple calculations. In the current study this evaluation was done using  
210 Concordance Correlation Coefficient and Total Deviation Index where the correlation coefficient is  
211 taken into account.

212 In this study, we only considered 60 patients for the analysis. The results would be more accurate, if  
213 the sample size had been increased. Further, simple random sampling was used with no specific  
214 attention to the gender. Therefore, future studies may include responsiveness of the treatment  
215 conditional on gender.

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## 217 5. CONCLUSION

218 The two treatments; with Mineralo-Trioxide Aggregate and Bio-dentine agreed sufficiently well with the  
219 standard reference method with Calcium hydroxide and hence all three treatments can be used  
220 interchangeably. Moreover, the agreement **between --> with** the treatments using Calcium hydroxide  
221 **and --> or** Bio-dentine is higher compared to other treatments.

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