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COMPARATIVE CLINICAL EVALUATION OF EFFICACY OF BIODENTINE AND BROMELAIN WITH BIODENTINE AS DIRECT PULP CAPPING MATERIALS

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Objectives: This study aimed to evaluate the efficacy of Biodentine and a combination of bromelain with Biodentine as direct pulp capping materials.

Methods: This clinical study included 26 participants with mature permanent mandibular molars exhibiting deep carious lesions without pulpal exposure. The participants were divided into two groups: Group I received Biodentine alone, while Group II received a combination of bromelain and Biodentine. Clinical and radiographic follow-ups were performed at 1, 3, and 6 months to assess the success rates of the treatment modalities.

Results: The clinical success rate of Biodentine as a direct pulp capping agent was 92% at 1 month, 100% at 3 months, and 92% at 6 months follow-up. The radiographic success rate was 100% at all intervals. The clinical success rate of the bromelain with Biodentine group was 85% at 1 month, 91% at 3 months, and 100% at 6 months, with corresponding radiographic success rates of 92%, 91%, and 100% at the respective intervals. Statistical analysis revealed no significant difference in success rates between the two groups.

Conclusions: Both Biodentine and the combination of bromelain with Biodentine demonstrated high clinical and radiographic success rates in direct pulp capping. However, there was no statistically significant difference between the two groups, suggesting that bromelain may not provide additional benefits when combined with Biodentine. Further research with larger sample sizes and longer follow-up periods is needed to explore the potential of bromelain and other combinations for direct pulp capping. These findings contribute to our understanding of effective materials for vital pulp therapy and guide clinical decision-making in dental practice.

Keywords: Biodentine, Bromelain, Direct pulp capping, Pulp vitality.

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The authors certify that there are no conflicts of interest with any financial organization regarding the material discussed in the manuscript.

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ÉVALUATION CLINIQUE COMPARATIVE DE L'EFFICACITÉ DE LA BIODENTINE ET DE LA BROMÉLAÏNE AVEC LA BIODENTINE EN TANT QUE MATÉRIAUX DE COIFFAGE DIRECT DE LA PULPE

Objectifs: Cette étude visait à évaluer l'efficacité de la Biodentine et d'une combinaison de bromélaïne et de Biodentine comme matériaux de coiffage direct de la pulpe.

Méthodes: Cette étude clinique a inclus 26 participants présentant des molaires mandibulaires permanentes matures présentant des lésions carieuses profondes sans exposition pulpaire. Les participants ont été divisés en deux groupes : le groupe I a reçu de la Biodentine seule, tandis que le groupe II a reçu une combinaison de bromélaïne et de Biodentine. Des suivis cliniques et radiographiques ont été réalisés à 1, 3 et 6 mois pour évaluer les taux de réussite des modalités de traitement.

Résultats: Le taux de réussite clinique de la Biodentine en tant qu'agent de coiffage direct de la pulpe était de 92 % à 1 mois, 100 % à 3 mois et 92 % à 6 mois de suivi. Le taux de réussite radiographique était de 100 % à tous les intervalles. Le taux de réussite clinique du groupe bromélaïne avec Biodentine était de 85 % à 1 mois, 91 % à 3 mois et 100 % à 6 mois, avec des taux de réussite radiographiques correspondants de 92 %, 91 % et 100 % aux intervalles respectifs. L'analyse statistique n'a révélé aucune différence significative dans les taux de réussite entre les deux groupes.

Conclusions: Biodentine et l'association de bromélaïne et de Biodentine ont démontré des taux de réussite cliniques et radiographiques élevés dans le coiffage pulpaire direct. Cependant, il n'y avait pas de différence statistiquement significative entre les deux groupes, ce qui suggère que la bromélaïne pourrait ne pas apporter de bénéfices supplémentaires lorsqu'elle est associée à la Biodentine. Des recherches plus approfondies avec des échantillons de plus grande taille et des périodes de suivi plus longues sont nécessaires pour explorer le potentiel de la bromélaïne et d'autres combinaisons pour le coiffage direct de la pulpe. Ces résultats contribuent à notre compréhension des matériaux efficaces pour la thérapie pulpaire vitale et guident la prise de décision clinique dans la pratique dentaire.

Mots clés- Biodentine, Bromélaïne, Coiffage pulpaire direct, Vitalité pulpaire

Introduction

Direct pulp capping is performed frequently as a treatment for deep carious lesions to trigger the formation of a physiologic barrier, the reparative dentin. This barrier preserves and protects pulpal vitality by functioning as a "biological seal" [1]. In cases with deep carious lesions, the inflammation is restricted to the outermost pulp while the deeper tissues remain normal, excluding a few dilated blood vessels [2]. Reports suggest that despite a carious exposure pulp healing can occur if it is in a reversible pulpitis state [3].

For successful therapeutic outcomes in direct pulp capping, the choice of the capping material is crucial [4]. An ideal pulp-capping material should be biocompatible, bioactive, easy to handle, have antibacterial properties, and should be adhesive to dentin to prevent microleakage [5, 6]. Various materials have been produced for direct pulp capping, however, the majority of them do not have all of the aforementioned characteristics.

In this instance, Biodentine introduced in 2009 [7], a calcium silicate-based biocompatible material and a dentin substitute [2] is recognized as a viable option for improved pulp therapy. It stimulates pulp cells to produce reparative dentin, can be placed directly in the cavity without any preconditioning, and has a short setting time (12 minutes) [8, 9].

Bromelain a mixture of proteases obtained from pineapple fruits or stems is known to possess antimicrobial, anticancer, and immunomodulatory effects [10]. Recently it has been discovered that bromelain has anti-inflammatory and mineralization effects on human dental pulp cells [11]. These properties can make bromelain a potent agent for vital pulp therapy.

Therefore, this study attempted to present an in vivo evaluation of the efficacy of biodentine and bromelain with biodentine as direct pulp capping materials. The null hypothesis was that the combination of bromelain with biodentine will perform better over biodentine as a direct pulp capping agent yielding significant results.

Materials and Methods

Ethical clearance and sample size determination

This study is a single-centre, single-blinded, clinical study. The protocol of the study received its approval from the institutional ethics committee (Ref. No. DMIMD(DU)/IEC/2022/876), and then the research was carried in the Conservative Dentistry and Endodontics department.

All the subjects in the experiment were treated in line with the principles outlined in the Helsinki Declaration. In line with a similar study performed by Brizuela C et al., [12] at confidence interval of 95% and power of 80% to the study, a sample size of 26 (n=13 each group) was calculated. Prior to their participation in the experiment, written and informed consent was taken from all the patients. They were provided with a comprehensive description of the experimental need, clinical procedures involved, and possible risks related to their involvement in the study.

Inclusion criteria

Inclusion criteria were patients in between 17–40 years age group, mature permanent mandibular molars with deep carious involvement without pulpal exposure, having response to electric and thermal pulp test similar either to healthy tooth or to pulp in reversible pulpitis, with no periapical pathology evident on radiograph.

Exclusion criteria

Exclusion criteria were primary teeth, teeth with open apex, no pulpal exposure after caries removal, teeth that has irreversible pulpitis (pain that was spontaneous) or necrosed pulp, radiographic examination revealing periapical lesions, teeth with tenderness on percussion, tooth mobility, periodontal disease, associated sinus tract, calcified canals, internal or external resorption, cracked teeth.

Clinical procedure

A standardized operative procedure was implemented throughout the study, and all procedures were performed by a single operator to ensure consistency. In cases where patients reported a history indicative of reversible type of pulpal inflammation, sensibility tests of pulp were conducted with the aid of ROEKO Endo-Frost spray (Coltene/Whaledent, USA) and Digitest II (Parkell, USA) to assess the sensitivity of the pulp [13] and intraoral periapical radiographs were taken and examined to assess the condition of the tooth. To ensure proper isolation, a rubber dam (Hygienic; Coltene, Switzerland) was placed after applying local anesthesia using 2% lignocaine with 1:80,000 adrenaline. Before cavity preparation, the teeth were mechanically cleaned and disinfected using a 0.2% chlorhexidine solution. Nonselective caries excavation was carried out using a bur with round shape (BR-31, by Mani, Japan), starting from the periphery and working towards the center of the cavity. When approaching the pulp, thereafter a sharp spoon excavator (Dentsply B190) was used under magnification loupes (×3.5) to remove any remaining carious tissue. In order to reduce the risk of contamination, a fresh set of sterilized instruments was utilized during this stage to prevent carious tissue debris from contaminating the disclosed area and also the pulp-capping agent. Bleeding was managed by keeping a sterilized cotton soaked in 3% sodium hypochlorite for a duration of 5 minutes. Subsequently, the tooth was thoroughly irrigated using saline to wash off any residual hypochlorite. Cases where the tooth did not show pulpal exposure or hemostasis was not gained in less than 5 minutes, were removed from the experiment to ensure consistency in the sample population [14].

The patients in the study were divided into two groups and received one of the two treatment modalities-

Group I- Biodentine (Septodont, Saint Maur de Fosses, France)

Group II- Bromelain (Brisk Bioscience, Surat, Gujarat, India) with biodentine

In Group I of the study, the exposed pulp and the peripheral dentin were capped using Biodentine of 2 mm thickness. The application of Biodentine followed the recommended manipulation guidelines provided by the manufacturer.

In Group II, equal proportions of biodentine and bromelain were mixed and was placed in the exposed site.

Following the placement of the experimental materials over the exposed pulp, a layer of liner of glass ionomer cement (Vitrebond; 3M ESPE, St Paul, MN) measuring approximately 2 x 2 mm was applied. The glass ionomer liner was then light-cured for 20 seconds using a dental curing light. The final restoration of the tooth was accomplished using a direct composite resin restoration material (Filtek Z350 XT Universal Restorative; 3M ESPE), and the occlusion was evaluated.

Follow-up

Clinical follow-ups were conducted at 1, 3, and 6 months following the procedure. During each follow-up visit, sensitivity tests (electrical and thermal) and a percussion test were done to assess the tooth's response. Radiographic follow-up examinations were also carried out at the same intervals using a parallel technique and a positioner. Clinical success criteria included a sound restoration, no pain/discomfort, no sensitivity to pressure or palpation, normal mobility, absence of sinus or abscess, and no aberrant response to heat or cold stimuli. Intact lamina dura, the absence of periapical lesion, and the no signs of pathologic tooth resorption were all radiographic criteria. Failures were defined as teeth with radiographic or clinical evidence of irreversible pulp necrosis or diseases.

Statistical analysis

The statistical analysis was conducted using the Statistical Package for Social Sciences (IBM SPSS Statistics for Windows, version 21.0, Armonk, NY: IBM Corp.). The analysis was performed with a confidence level of 95% and a statistical power of 80% for the study. Descriptive statistics, including frequency and percentage, were used to summarize the data. The Chi-square test was applied to determine the statistical significance of the differences in clinical and radiographic success rates between Group I and Group II. The threshold for statistical significance was set at $p<0.05$, indicating that results with a probability of less than 0.05 were considered statistically significant.

Results

The results have been tabulated after analysing the rates of clinical and radiographic success and failure of the materials employed as shown in Table 1 and Table 2.

In group I (Biodentine), 1 out of 13 patients gave a history of pain and delayed response at 1 month follow-up. And 1 among the remaining 12 patients showed positive response to vertical tenderness on percussion after 6 months whereas none of the patients reported with any radiographic changes. The clinical success rate of Group I (Biodentine) as a direct pulp capping agent was found to be 92% at 1 month, 100% at 3 months and 92% at a follow-up of 6 months. The radiographic success rate of Group I (Biodentine) was 100% at 1-, 3-, and 6-months interval.

In group II, at a month follow-up, 1 patient gave the history of nocturnal pain, there was tenderness on percussion and periodontal ligament widening was evident on radiograph. Also 1 patient had no symptom but the tooth was non-vital with no changes seen on radiograph. At 3 months follow-up, 1 among the re-

Table 1: Clinical assessment of the success of materials at different time periods. (Group I- Biodentine, Group II- Bromelain with Biodentine, n'- teeth showing successful results, n- total number of teeth at that time interval)

Follow-up	Group I, n'/n (%)	Group II, n'/n (%)	Chi Square	p value
1 month	12/13 (92%)	11/13 (85%)	3.254	0.120
3 months	12/12 (100%)	10/11 (91%)	2.114	0.211
6 months	11/12 (92%)	10/10 (100%)	1.452	0.145

*Statistically significant at $p<0.05$

Table 2: Radiographic assessment of the success of materials at different time periods. (Group I- Biodentine, Group II- Bromelain with Biodentine, n'- teeth showing successful results, n- total number of teeth at that time interval)

Follow-up	Group I, n'/n (%)	Group II, n'/n (%)	Chi square	p value
1 month	13/13 (100%)	12/13 (92%)	1.25	0.456
3 months	12/12 (100%)	10/11 (91%)	0.854	0.235
6 months	12/12 (100%)	10/10 (100%)	0.744	0.122

*Statistically significant at $p<0.05$

maining 11 patient showed positive vertical tenderness on percussion and periodontal ligament widening was evident on radiograph. The clinical success rate of Group II (Bromelain with Biodentine) as a direct pulp capping agent was found to be 85% at 1 month, 91% at 3 months and 100% at 6 months follow-up. The radiographic success rate of Group II (Bromelain with Biodentine) was 92%, 91%, and 100% at 1-, 3-, and 6-months interval respectively.

So, considering the failures, 2 patients from group I and 3 patients from group II were excluded from the study. The overall success rate as a direct pulp capping agent for group I (Biodentine) was 92% (12/13) at 1 month and 3 months, and 85% (11/13) at 6 months. For group II (Bromelain with Biodentine) the overall success rate was 85% (11/13) at 1 month and 77% (10/13) at 3 months, and 6 months interval as shown in figure 1.

This difference in clinical, radiographic or overall success rate showed no statistically significant difference between Group I and II at 1 month, 3 months, and 6 months intervals ($p>0.05$).

Discussion

One of the highly disputed conundrums in the field of endodontics revolves around the handling of deep carious lesions. There are two prominent opposing perspectives when it comes to managing such cases: one advocates for a cautious approach that involves vital pulp therapy, while the other suggests a more invasive yet dependable procedure known as root canal therapy. Direct pulp capping focuses on safeguarding and sustaining the endangered pulp, yet not completely damaged, due to factors like tooth decay, restorations or trauma, with the objective of maintaining its healthful condition [15].

Performing this particular procedure is recommended for teeth experiencing reversible pulpitis, as the primary criterion is the presence of healthy pulp tissue. Nevertheless, accurately assessing the condition of the pulp poses a significant challenge. Clinical signs, symptoms, and sensitivity tests do not provide precise information regarding the pulp's status. Therefore, the ideal outcome in vital pulp therapy is achieved by protecting the healthy pulp while eradicating the inflamed ones, ensuring ideal treatment results [16].

The choice of capping material plays a vital role in the effectiveness of vital pulp therapy. In this course of treatment, calcium hydroxide has long been recognised as the benchmark. The success rates of direct pulp capping using calcium hydroxide have exhibited significant variation over time, ranging from 31.8% after one year [17] to 72.7% after ten years [18]. Nonetheless, calcium hydroxide also has its drawbacks, such as inadequate dentin bonding, tunnel defects, resorption of the material, and also mechanical instability. As a result, calcium hydroxide fails to provide long-term prevention of microleakage. Additionally, the calcium hydroxide suspensions' high pH level (12.5) can cause liquefaction necrosis on the pulp tissue's surface [19].

In recent years, Biodentine™ (manufactured by Septodont Ltd., Saint Maur des Faussex's, France), a novel cement composed of tricalcium silicate (Ca_3SiO_5), has gained significant attention as a "bioactive dentine substitute." It has been recommended for use in pulp capping procedures. The primary composition of the powder is silicates, specifically tricalcium and dicalcium silicate. Additional components include calcium carbonate and oxide as fillers, iron oxide for coloration, and zirconium oxide for radiopacity [20]. Calcium chloride accelerates the system, while a hydrosoluble polymer component reduces water in the mixture. Calcium silicate's interaction with water initiates the hardening and setting of the cement through the hydration of tricalcium silicate, yielding calcium hydroxide and hydrated calcium silicate gel. This process of dissolution occurs on the surface of each calcium silicate grain. Due to medium saturation, the resulting gel and excess calcium hydroxide precipitate on particle surfaces and within powder pores, releasing calcium, phosphate, and hydroxyl ions [21]. In low water content systems, the precipitation process is intensified. Unreacted tricalcium silicate grains are encapsulated by impermeable hydrated calcium silicate gel layers, slowing down subsequent reactions. The formation of the C-S-H gel stems from the continuous hydration of tricalcium silicate, gradually filling the spaces between grains and contributing to the hardening process

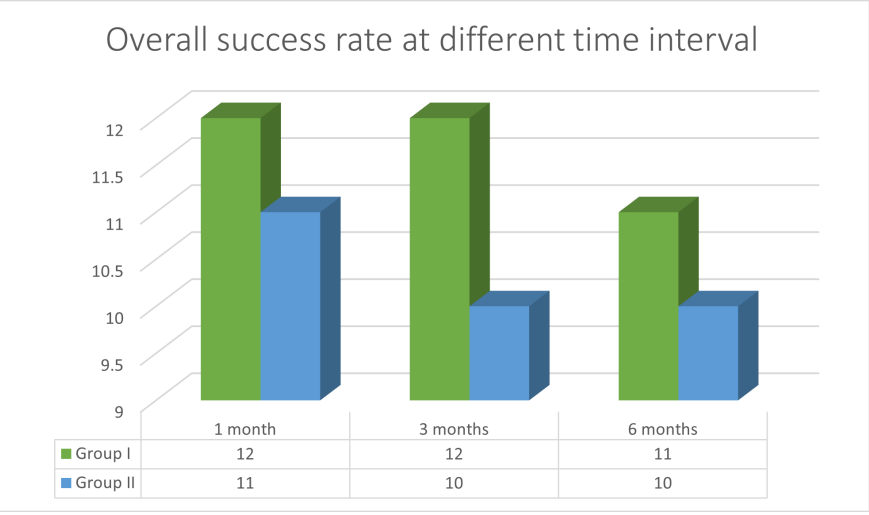

Figure 1. Overall success rate of group I (Biodentine) and group II (Bromelain with Biodnetine) as a direct pulp capping material at different time interval.

through crystal deposition in a supersaturated solution [22].

Studies have demonstrated that Biodentine promotes hard tissue regeneration and does not exhibit any detrimental effects on the pulp tissue [19]. In their study, Nowicka et al. found that using Biodentine as a pulp-capping agent resulted in complete dentinal bridge development without an inflammatory pulp reaction. Further, it was discovered that tubular dentin is formed beneath the osteodentin by layers of odontoblast-like cells that are neatly aligned [9]. The pulp cells incubated with biodentine release a growth growth factor called the transforming factor beta 1 (TGF-β1) [23]. This triggers angiogenesis and differentiation of cells and promotes mineralization, cell migration, and proliferation [24]. The stimulation of differentiation and proliferation of cells is also related to tricalcium silicate (a major component of biodentine) and the release of silicon and calcium ions [9]. This mineralized tissue indicates an early form of reparative dentin as the cells present inside these mineralizations exhibit odontoblastic markers such as dentin sialoprotein and nestin, which aids in mineralization and reparative dentin formation [23].

Bromelain, a potent phytomedicine has plethora of therapeutic properties. It is a proteolytic enzyme derived from pineapple plants. The therapeutic potential of bromelain includes antibacterial, anti-inflammatory, fibrinolytic, oxidizing, antithrombotic, antifungal and proteolytic action. In dentistry bromelain has been studied for its antimicrobial properties, anti edematic, anti-inflammatory, deproteinizing properties [10].

In a study conducted by Hong et al. [10], the effects of bromelain on mineralization and anti-inflammatory responses in lipopolysaccharide-induced human dental pulp cells were investigated. The results indicated that bromelain did not significantly affect the viability of human dental pulp cells at various concentrations (2.5, 5, 10, or 20 microgram/mL). However, bromelain demonstrated a significant decrease in the levels of interleukin-1, 6, 8, ICAM-1, and VCAM-1, which were induced by bacterial lipopolysaccharide in human dental pulp cells. Administration of bromelain led to a considerable reduction in the cytoplasmic and nuclear phosphorylation of p65. Additionally, it markedly reduced the phosphorylation levels of extracellular signal-related kinases and p38 mitogen-activated protein kinases. Bromelain also exhibited an increase in alkaline phosphatase activity and the formation of mineralized nodules. Based on these findings, the researchers concluded that bromelain inhibited the expression of anti-inflammatory cytokines in lipopolysaccharide-stimulated human dental pulp cells. Consequently, bromelain may have potential applications in vital pulp therapy and regenerative endodontics [10]. This anti-inflammatory and mineralizing effect of bromelain on the human pulp cells makes it a potent natural agent for use as a direct pulp capping agent.

A positive electric pulp test suggesting a vital tooth, sporadic sensitivity to cold, and radiographs with no sign of an apical lesion indicating the existence of a vital pulp were among the particular case selection criteria used in this study. A comprehensive inspection of the pulp is required to determine whether it is suitable for preservation because the pulp's state has a significant impact on the outcome of conservative pulp treatment. The extent of pulpal bleeding in situations of clinical pulp exposure has been hypothesised to be a good indicator of the intensity of pulpal inflammation. The difficult to control bleeding signals that the pulp is significantly irritated [25]. According to numerous studies, the recommended "time to stop bleeding" after clinical pulp exposure ought to range between 5 and 10 minutes. This particular quantity acts as a vital threshold for differentiating between pulp conditions that are reversible and those that are irreversible [26]. The "time to stop bleeding" metric in the current study was found to fall within the suggested range of 5–10 minutes. This discovery indicates that the pulp in concern is in good health.

In the cases described in this study, permanent restorations were placed during the same visit. This one-visit procedure offers advantages such as minimizing the risk of failure and restoring the aesthetic appearance of the tooth. However, it is crucial to allow Biodentine and the combination of bromelain with biodentine to set (approximately 12-15 minutes after manipulation) before placing the restoration.

The opaque bridge on the radiograph is one of the key indicators that the direct pulp capping procedure was successful [27]. According to the study by Nowicka et al., the time for dentin bridge formation was only 6 weeks [28]. In contrast, the study by Bui et al., aimed to evaluate the dentin bridge formation after a direct pulp capping procedure using biodentine, found that the dentin bridge formation took 9-12 weeks to be detectable in the x-ray [29].

The present study has defined success rate as the number of patients present at that particular follow-up interval. The following clinical outcomes were obtained from the present study: for the biodentine group, a 92% (12/13) success rate was seen at one month, a 100% (12/12) success rate at 3 months, 92% (11/12) success rate at 6 months follow-up. The radiographic success rate was 100% at 1, 3, 6 months follow-up. Thus, an overall success rate of 92% (12/13) at 1 and 3 months and 85% (11/13) at 6 months follow-up was obtained for biodentine group. In the second group (bromelain with biodentine) the clinical success rate was found to be 85% (11/13) at 1 month, 91% (10/11) at 3 months, and 100% (10/10) at 6 months follow-up. The radiographic success rate was 92% (12/13), 91% (11/12), and 100% (11/11) at 1, 3, and 6 months follow-up respectively. Thus, an overall success rate of 85% (11/13) at 1 month and 77% (10/13) at 3 and 6 months was obtained for the second group. However, the results were

not statistically significant. According to the findings of this study, the success rate of the procedure was optimal when the non-inflammed pulp, effectively controlled haemorrhage, agents (biodentine and bromelain) with no toxic effect on pulp, and effective bacterial sealing with capping agent and permanent restoration was done [15].

The observed positive results in this experiment is likely attributed to several factors. Firstly, the study materials demonstrated a noncytotoxic and nongenotoxic effect on pulp tissues, ensuring their health and viability. Secondly, their excellent sealing ability was evident as it penetrated into the pulp, making tags within the dentinal tubules. This contributed to a tight seal and reduced the risk of bacterial infiltration. Lastly, the interface between enamel, dentin, and dentin-bonding agents exhibited adequate marginal seal, which further enhanced the overall success. Additionally, the achieved microhardness of the restoration was satisfactory, supporting its long-term durability [30].

The information from the failed cases did not offer conclusive evidence regarding the specific factors that led to the unfavorable results. The cases with negative results were associated with pain either due to irreversible pulpitis or due to apical periodontitis. Another possible cause of failure could be the uncontrolled deterioration of the remaining pulp tissue. The unfavorable outcomes also suggest the possibility of flaws in the case selection process, particularly in terms of identifying and managing preexisting pulpal pathosis.

Pulp canal calcification is one of the most common complications in teeth that have undergone vital pulp therapy [31]. Thus has been hypothesized to occur from a persistent stimulatory effect on dentin formation from the pulp capping agent [32]. Previous studies have found PCC occurrences ranging from 0% to 45.0%. The incidence and severity of calcification are influenced by the type of vital therapy, pulp capping material used, follow-up length, stage of root growth, and preoperative diagnosis of the tooth [31]. It has been found that vital pulp therapy performed on cervical pulp exposure obliterates the entrance of the root canal, complicating the subsequent root canal treatment procedure [32]. However, there is disagreement over its management, and there is insufficient data on its negative effects in teeth that have undergone vital pulp therapy [31].

Despite the initial anticipation that the combination of bromelain with biodentine would lead to significantly improved outcomes in the evaluated clinical and radiographic parameters, the results obtained did not demonstrate any statistically significant difference between these two groups. This suggests that the inclusion of bromelain to biodentine may not offer any additional benefits to the existing properties of biodentine as a direct pulp capping agent.

This study does have several limitations, that include a smaller sample size, a relatively short follow-up time of 6 months, the use of equal ratios of bromelain with biodentine, and the absence of cone-beam computed tomography for evaluating dentin bridge formation. These limitations highlight potential areas for future research, which may contribute to the development of a novel combination using bromelain for direct pulp capping that can provide enhanced therapeutic effects on the pulp.

Conclusion

Both bromelain with biodentine and biodentine demonstrated high clinical and radiographic success rates but there was no statistically significant difference between them, suggesting that bromelain may not provide additional benefits when combined with Biodentine. Further research with larger sample sizes and longer follow-up periods is warranted to explore the potential of bromelain and other combinations for direct pulp capping.

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