






## Article

# Comparison of Four Dental Pulp-Capping Agents by Cone-Beam Computed Tomography and Histological Techniques—A Split-Mouth Design Ex Vivo Study

Jayanandan Muruganandhan <sup>1</sup>, Govindarajan Sujatha <sup>1</sup>, Saravanan Poorni <sup>2</sup> , Manali Ramakrishnan Srinivasan <sup>2</sup>, Nezar Boreak <sup>3</sup> , Ahmed Al-Kahtani <sup>4</sup>, Mohammed Mashyakh <sup>3</sup>, Hitesh Chohan <sup>3</sup>, Shilpa Bhandi <sup>3</sup>, A. Thirumal Raj <sup>1</sup> , Alessio Zanza <sup>5</sup>, Luca Testarelli <sup>5</sup>  and Shankargouda Patil <sup>6,\*</sup> 

<sup>1</sup> Department of Oral Pathology and Microbiology, Sri Venkateswara Dental College and Hospital, Chennai 600130, India; drmurugan@outlook.com (J.M.); gsujathareddiffmail.com (G.S.); thirumalraj666@gmail.com (A.T.R.)

<sup>2</sup> Department of Conservative Dentistry and Endodontics, Sri Venkateswara Dental College and Hospital, Chennai 600130, India; poornis@yahoo.com (S.P.); drmsrini@yahoo.com (M.R.S.)

<sup>3</sup> Department of Restorative Dental Science, College of Dentistry, Jazan University, Jazan 45412, Saudi Arabia; nezarboreak@gmail.com (N.B.); dr.mashyakh@gmail.com (M.M.); drhiteshchohan@yahoo.co.in (H.C.); shilpa.bhandi@gmail.com (S.B.)

<sup>4</sup> Department of Restorative Dental Sciences, College of Dentistry, King Saud University, Riyadh 11362, Saudi Arabia; ahkahtani@ksu.edu.sa

<sup>5</sup> Department of Oral and Maxillo Facial Sciences, "Sapienza" University of Rome, 00161 Rome, Italy; ale.zanza@gmail.com (A.Z.); luca.testarelli@uniroma1.it (L.T.)

<sup>6</sup> Department of Maxillofacial Surgery and Diagnostic Sciences, Division of Oral Pathology, College of Dentistry, Jazan University, Jazan 45412, Saudi Arabia

\* Correspondence: dr.ravipatil@gmail.com



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**Abstract:** Dental pulp-capping is done to preserve vital teeth when the pulp is exposed due to caries, trauma or instrumentation. Various materials are used as pulp-capping agents. The introduction of newer materials requires scientific studies to assess their clinical efficacy. The study was designed as a split-mouth randomized analysis of four pulp-capping agents (calcium hydroxide, mineral trioxide aggregate (MTA), Biodentine and EndoSequence root repair material (ERRM)). Based on selection criteria, 15 orthodontic patients requiring the extraction of four premolars (60 teeth total) were included in the study. After pulp-capping, the teeth were extracted after 8 weeks. We analyzed the extracted teeth using cone-beam computed tomography (CBCT) and histological sections to determine the quality of the dentinal bridge and the pulpal response. Ordinal scores were given based on the completeness of the dentinal bridge, the type of bridge and the degree of pulpal inflammation. Results were analyzed using a Kruskal–Wallis test ( $p < 0.05$ ) with post hoc Conover values being used when applicable. All four pulp-capping materials elicited dentinal bridge formation (60/60). MTA had the highest scores (10/15) in dentinal bridge formation followed by ERRM (8/15). Both materials showed more samples with complete dentinal bridges (9/15 each) and a favorable pulpal response (15/15). Teeth capped with calcium hydroxide showed more cases of incomplete bridge formation (9/15) and pulpal inflammation. These differences in dentinal bridge formation and pulpal inflammation were statistically significant ( $p 0.001$  and  $p 0.00005$ , respectively), with post hoc tests revealing no significant differences between MTA and ERRM ( $p 0.49$  and  $p 0.71$ , respectively). MTA and ERRM performed better than the other pulp-capping materials but did not differ significantly from each other. The individual preference for a pulp-capping material may be based on clinical efficacy and handling characteristics.

**Keywords:** Biodentine; calcium hydroxide; dentinal bridge; EndoSequence root repair material; mineral trioxide aggregate; pulp-capping; pulp vitality

## 1. Introduction

Direct pulp-capping is a common procedure for the treatment of unintentional or unavoidable pulpal exposures in clinical practice. Pulp-capping ensures tooth vitality by preserving the integrity of the hard tissues and protective responses to injury [1]. Pulp-capping involves the placement of a material on the pulpal exposure site followed by an intermediate or permanent restoration. The material should stimulate the pulpal cells to produce a reparative dentinal bridge, thereby sealing the pulp. Ideally, these materials are biocompatible and bioactive (stimulating pulpal cells), aid the formation of apatite crystals and provide an adequate seal [2–5]. Table 1 summarizes the ideal properties of a pulp-capping agent.

**Table 1.** The ideal qualities of pulp-capping agents.

<b>Biocompatibility</b>	The agent should not be injurious to tissues or elicit deleterious inflammatory processes.
<b>Workability</b>	The material must be easily prepared and applied to the exposed pulp tissue. It must have some adhesive capability to bind to the dentin and the restoration.
<b>Insolubility</b>	The material as a whole must be stable and insoluble in tissue fluids.
<b>Radiopacity</b>	The material must contain a radiopaque component for radiographic assessment.
<b>Bioactivity</b>	The material must be able to stimulate reparative dentin formation, i.e., a dentinal bridge, thereby sealing the pulp. Preferably tubular dentin.
<b>Anti-caries</b>	The material may also release fluoride and prevent further caries.
<b>Antimicrobial</b>	The material must prevent microbial activity.

Dycal (calcium hydroxide) is the most used material due to its low price and wide availability. The major limitations of Dycal are that it has a lower percentage of complete dentinal bridge formation and an increased risk of tunnel defects, which in turn increases permeability to microbes. In addition, the clinical handling of the material is less desirable [6–9].

Mineral trioxide aggregate (MTA) is a silicate material that is said to aid in faster bridge formation with fewer tunnel defects, less pulpal inflammation and the maintenance of pulpal integrity. It is widely used in pediatric dentistry due to its excellent sealing properties. Its disadvantages include slow setting time, difficulty in handling and tooth staining [10–16].

Synthetic bioceramics were developed in recent years to offset the drawbacks of naturally sourced materials such as MTA [17–23]. Biodentine is composed of tricalcium silicate, calcium carbonate and zirconium oxide. It is claimed to have better handling properties, faster dentinal bridge formation and higher strength compared to MTA, but outcome-based clinical trials have not yet been conducted [24–34]. EndoSequence root repair material (ERRM) is a bioceramic material recommended for perforation repair, pulp-capping and periapical surgery. This agent is aluminum-free, has a high pH, is radiopaque and has shown similar results to MTA in dentinal bridge formation and pulp viability. Long-term clinical trials involving ERRM are not yet available [35–40].

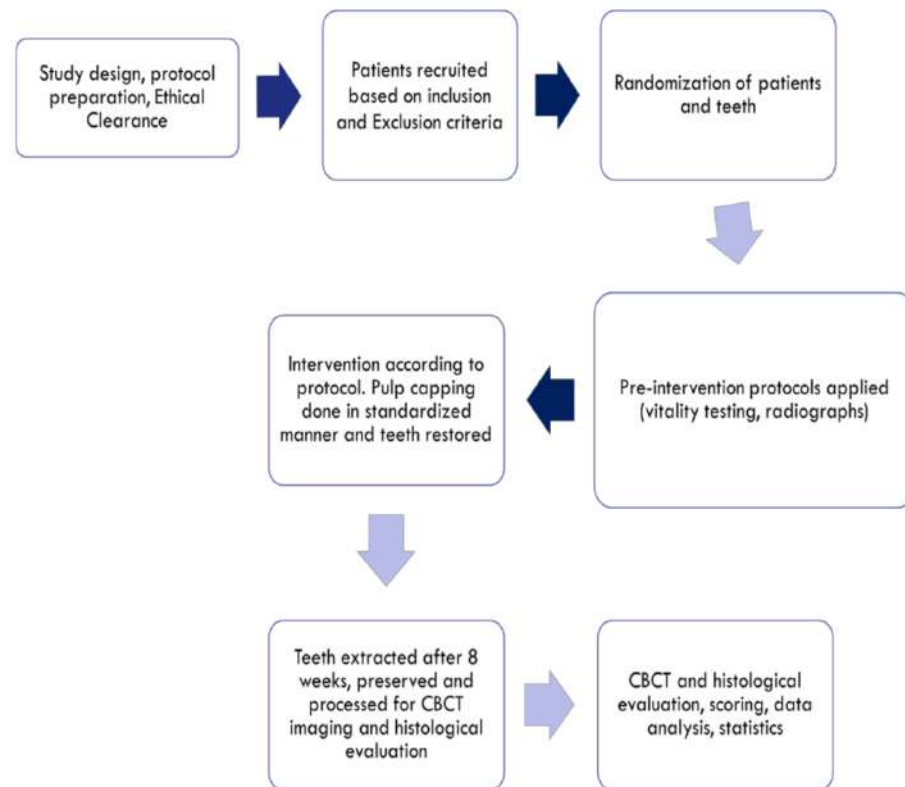
There is a public health incentive in determining the most effective product in the management of pulpal exposure. Thus, the present study was therefore undertaken to compare the clinical efficacy of pulp-capping using calcium hydroxide, MTA, Biodentine and EndoSequence root repair material (ERRM), employing cone-beam CT and histological methods. A literature search revealed that such a split-mouth study employing these four pulp-capping agents in human participants has not been published.

## 2. Materials and Methods

### 2.1. Study Design

To compare the four pulp-capping agents reliably to obtain objective evidence, we selected a split-mouth study where all four agents can be applied and assessed in a sin-

gle participant (Figure 1). The study protocol was reviewed and approved by the Institutional Ethical Committee of Sri Venkateswara Dental College and Hospital, Chennai, India (SVDC/IRB/1/2016). We obtained written informed consent in English and vernacular language from participants and included those who fulfilled the selection criteria. Sample size was calculated as 24 using G\*Power v.3.1 software and assuming an alpha error value of 0.05 with 85% power, employing statistical data from Kim et al. (2016) [34]. Therefore, we planned to use 100 vital teeth (from 25 participants) extracted as part of orthodontic treatment.



**Figure 1.** Flowchart of the process.

## 2.2. Inclusion Criteria

Teeth (1) from healthy patients aged 15–30 years with no systemic diseases, (2) indicated for extraction for orthodontic reasons and (3) free from pulpal lesions or inflammation were considered for inclusion.

## 2.3. Exclusion Criteria

The exclusion criteria were as follows: any systemic conditions that might show pulpal manifestations, calcium disorders, periodontal lesions, history of trauma to teeth, family history of major dental problems, children, pregnancy, lactation, allergy to any of the products used in procedures and bleeding disorders.

## 2.4. Interventions

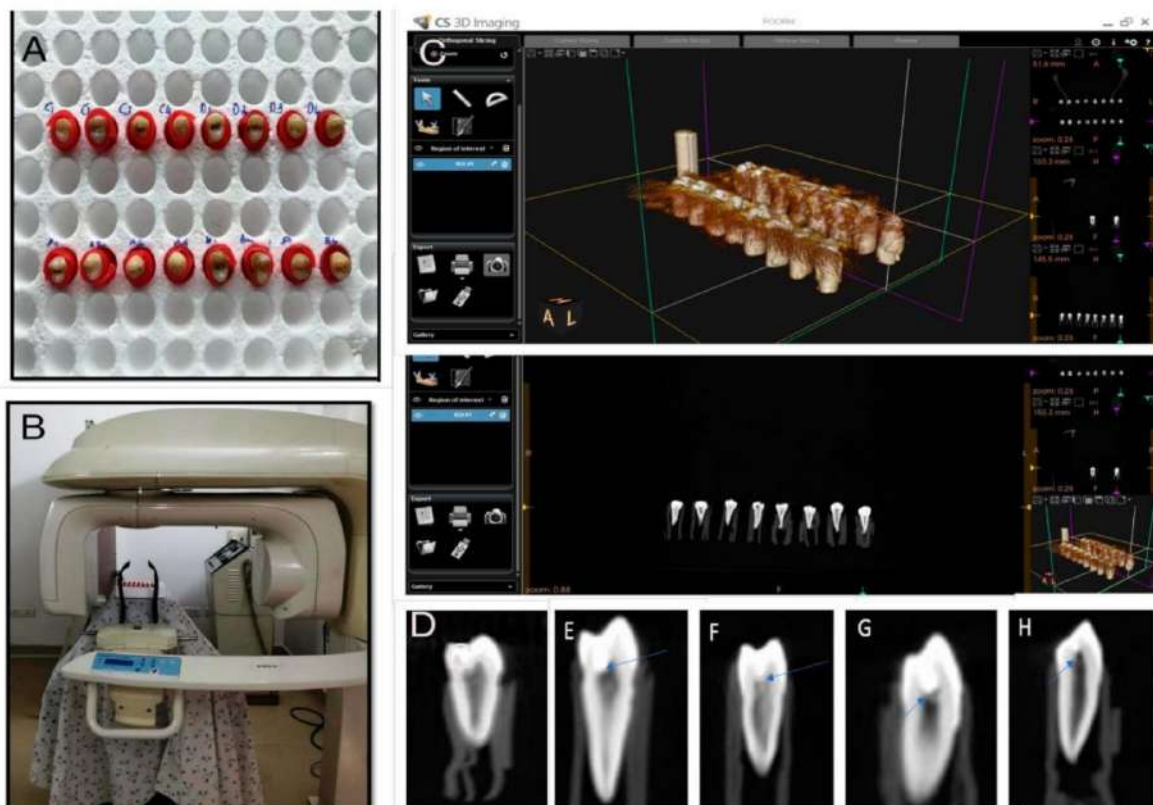
For the assessment of dental vitality and periapical health, we applied a cold test, an electronic pulp (EP) test and intraoral periapical radiography. The participants underwent the interventions with randomization according to the protocol. Participants were randomly assigned the days of appointment based on pick of lots. Each participant had two appointments spaced within a week. At each appointment, maxillary and mandibular premolars on one random side were capped using pulp-capping material, which was also selected based on pick of lots. The capping for the opposite side was performed in the next appointment.

Under local anesthesia, rubber dam isolation, aseptic protocols, cavity preparation and pulp-capping were carried out in a standardized manner across the study groups.

The cavity dimensions were standardized at 2 mm width  $\times$  5 mm length  $\times$  3–4 mm depth, using a straight fissure diamond abrasive. The pulp was exposed using a number 2 round diamond and bleeding was controlled with saline-moistened cotton pellets. The operator performed pulp-capping with one of the following materials: calcium hydroxide (Dycal, Dentsply India Pvt. Ltd., Mumbai, India), mineral trioxide aggregate (MTA Angelus, Angelus Indústria de Produtos Odontológicos S/A, Londrina-PR-Brazil), Biodentine (Septodont Healthcare India Pvt. Ltd. Raigad, Maharashtra, India) and EndoSequence root repair material (Brasseler USA, Savannah, GA, USA) and restored the cavity with a Glass Ionomer restorative (Fuji Type IX, GC America Inc., Alsip, IL, USA) with appropriate post-procedure protocols (Refer Supplementary Materials).

### 2.5. Preparation of Teeth for Analysis

After 8 weeks, we extracted the teeth under local anesthesia and then rinsed them with deionized water to remove blood/debris. We kept the teeth in a beaker containing 10% formaldehyde solution. After 72 h, the teeth were washed for 30 min in running water and sent for imaging using cone-beam Computed Tomography (CBCT). The teeth were stabilized in a Styrofoam tray using beading wax and imaged in a CBCT scan unit (Figure 2). After the imaging, a histopathology laboratory obtained the teeth, performed decalcification using 10% formal-formic acid and stained the tooth sections using hematoxylin and eosin.



**Figure 2.** (A,B) Computed tomography (CT) imaging of the extracted teeth; (C) CT imaging software with tools; dentinal bridge formation (blue arrows) in negative control ((D) no bridge), EndoSequence root repair material (ERRM) ((E) complete bridge), mineral trioxide aggregate (MTA) ((F) complete bridge), Biodentine ((G) partial bridge) and calcium hydroxide ((H) partial bridge).

### 2.6. CBCT and Histological Scoring

In CT images, the presence of a radiopaque structure between the pulp-capping agent and the pulpal space indicates the formation of a dentinal bridge. Two independent investigators who were blinded to the study groups separately assessed the images. The

scoring was based on the presence/absence of a dentinal bridge and the completeness of the dentinal bridge (islands vs. complete bridge) using the method adapted from Nowicka et al. (2015) as follows [32]: score 0—no dentinal bridge formation; score 1—*islands of calcified material*; score 2—*complete dentinal bridge*.

Histopathologists examined the decalcified sections of the teeth to determine the type of calcified material present in the dentinal bridge. Using a BX-43 Olympus microscope under 10x magnification, the teeth were examined and photographed employing the Optika digital micrograph imaging system and the Optika LITEView basic image acquisition software (Optika, Italy).

The dentinal bridge may be composed of any of three tissues that were classified using the scoring adapted from Nowicka et al. (2013) as follows [33]: score 1—*calcified tissue, which does not resemble dentin appearing as structureless calcification with basophilic staining*; score 2—*dentin-like material identified by eosinophilic material with staining similar to dentin, which may contain entrapped cells (osteodentine)*; score 3—*tubular dentin appearing as eosinophilic material resembling dentinal tubules*.

Pulpal responses were recorded using the criteria adapted from Monea and Stoica [2] as follows: 0—*no inflammation*; 1—*mild inflammation*; 2—*moderate inflammation*; 3—*severe inflammation*. Two independent oral radiologists evaluated the CT images, and two independent histopathologists performed the histological examinations.

The participants, after completing the research intervention, proceeded with the orthodontic management according to their original treatment plan, with regular follow-up. They were requested to report in the case of any potential adverse events. Adverse outcomes, including pain and swelling during the 8 weeks, warranted exclusion from the study.

2.7. Statistical Analysis and Report

The ordinal data on the dentinal bridge formation by CT scan, the dentinal bridge quality by histology and the histological pulpal response were tabulated and analyzed using a nonparametric test (Kruskal–Wallis test). A *p*-value less than 0.05 was considered statistically significant.

Out of the 25 study participants, 10 participants were excluded early on before the interventions of the research due to various issues, including the discontinuation of the treatment due to financial restrictions (costs of orthodontic treatment) and the unwillingness to travel for follow-up. The study proceeded with 15 participants on statistical advice. They included eight females and seven males. There were no significant adverse events reported by any of the participants related to the interventions during the study period.

The scores given by the two observers had a 99% consensus. Using the Kruskal–Wallis test, the performance of four pulp-capping agents was compared (Table 2).

**Table 2.** The statistical analysis of the four pulp-capping groups (Kruskal–Wallis test, *p* < 0.05 is significant).

Cone-Beam CT	Scores			<i>p</i> -Value	Post Hoc Test		
	0	1	2				
CH	0	9	6	0.62	Not applicable		
MTA	0	6	9				
BD	0	8	7				
ERRM	0	6	9				
Histopathology	Scores			<i>p</i> -Value	Conover <i>p</i> -Values, Further Adjusted by the Benjamini–Hochberg FDR Method		
	1	2	3				
CH	3	11	1	0.001	BD		
MTA	0	5	10		CH	0.56	
BD	1	13	1		ERRM	0.004	0.001
ERRM	0	7	8		MTA	0.0006	0.0002

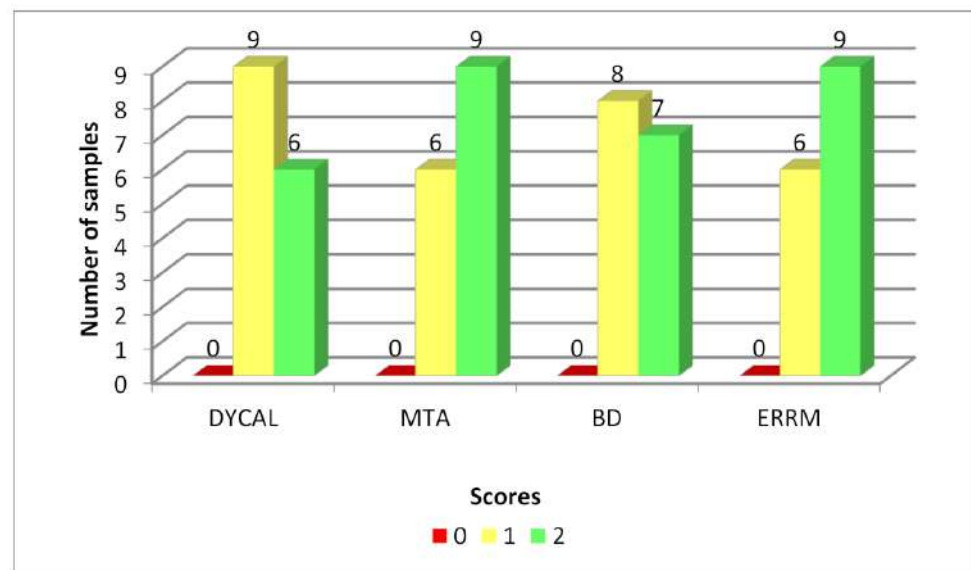
Table 2. Cont.

Pulpal Response	Scores				<i>p</i> -Value			
	0	1	2	3				
CH	3	11	1	0	0.00005	BD	CH	ERRM
MTA	10	5	0	0		CH	0.028	
BD	1	7	7	0		ERRM	0.00004	0.024
ERRM	9	6	0	0		MTA	0.00002	0.012
								0.71

### 3. Results

#### 3.1. CBCT

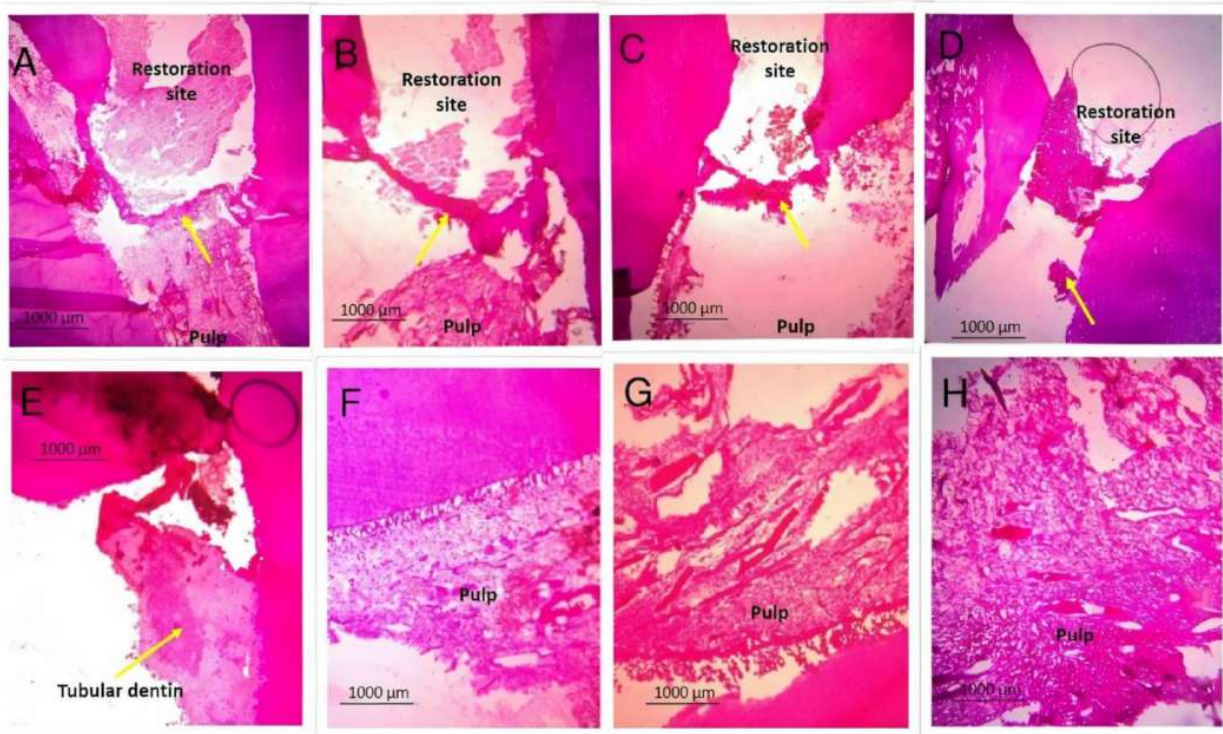
All specimens (100%) developed dentinal bridge formation (Figure 2). Out of these, a complete dentinal bridge formed in 9/15 cases of both MTA- and ERRM-treated teeth (60%). In contrast, only 6/15 calcium hydroxide cases and 7/15 Biodentine cases showed complete bridging (40–46%). These differences were not statistically significant ( $p > 0.05$ ) (Figure 3, Table 2). Figure 2D depicts a tooth restored without any pulp-capping material to act as a negative control. Figure 2E,F depicts complete bridging, and Figure 2G,H depicts partial bridges.



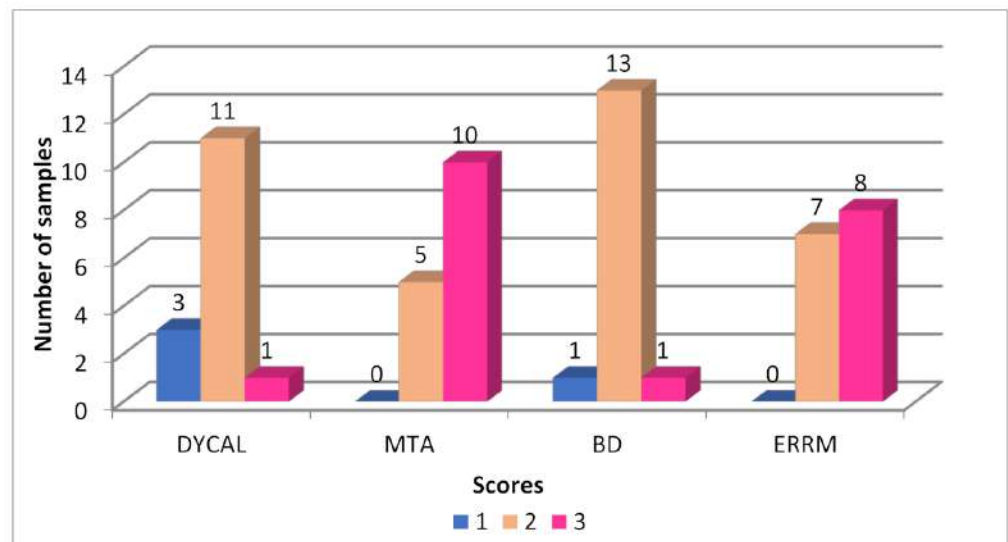
**Figure 3.** CT scan dentinal bridge comparison among the pulp-capping agents (0—no dentinal bridge formation; 1—*islands of calcified material*; 2—*complete dentinal bridge*).

#### 3.2. Histopathology of the Dentinal Bridge

MTA- and ERRM-treated teeth showed dentine-like calcifications in all cases (Figure 4 A,B). Three cases of calcium hydroxide treated teeth and one case of Biodentine-treated teeth showed indistinct calcified masses (Figure 4 C,D). We observed tubular dentin in 10 cases of MTA-treated teeth (67%) and 8 cases (53%) of ERRM-treated teeth (Figure 4E). However, only one case of calcium hydroxide and one case of Biodentine showed tubular dentin formation (6%). These differences were statistically significant (Kruskal–Wallis test,  $p < 0.05$ ) (Figure 5). Post hoc testing revealed that the MTA and ERRM groups differed significantly from the calcium hydroxide and the Biodentine groups. However, there was no significant difference in bridge formation between the MTA and ERRM groups or between the calcium hydroxide and Biodentine groups (Table 2).



**Figure 4.** (A) Complete dentinal bridge (yellow arrows) in EndoSequence root repair material (ERRM)-treated tooth; (B) complete dentinal bridge in MTA-treated tooth; (C) complete bridge in Biodentine-treated tooth with dentin-like mass; (D) incomplete amorphous bridge in calcium hydroxide treated teeth (4×, H and E stain); (E) magnified view of tubular dentin in the dentinal bridge; (F) dental pulp with no inflammation; (G) mild inflammation; (H) moderate inflammation (10×, H and E stain).

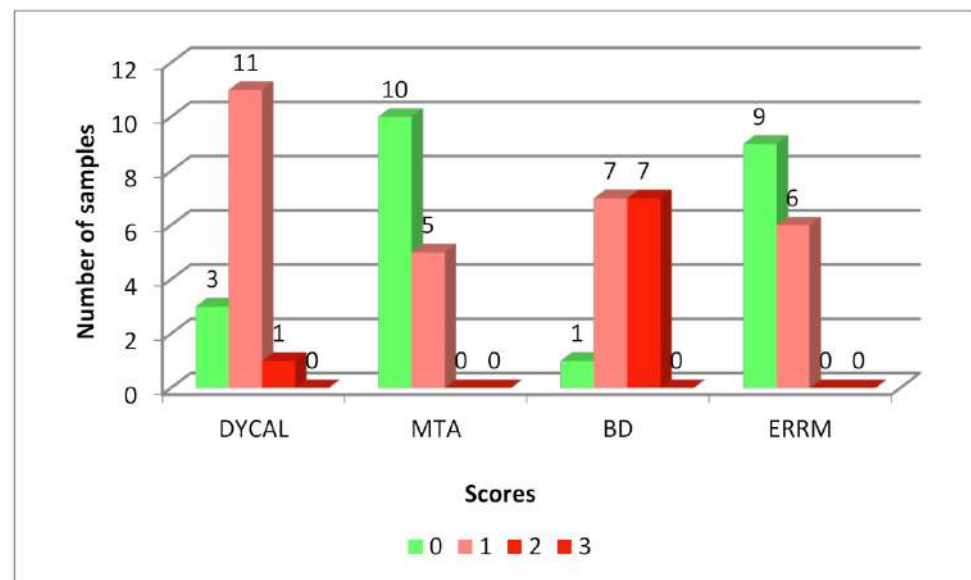


**Figure 5.** A histologic dentinal bridge comparison among the pulp-capping agents (1—calcified areas not confirmative of dentin; 2—amorphous dentin; 3—tubular dentin).

### 3.3. Histopathology of the Pulpal Response

All four pulp-capping agents showed some degree of pulpal inflammation in some cases, though none of them were in a severe category. In 10 cases of MTA-treated teeth and 9 cases of ERRM-filled teeth (67%), tissue sections did not show inflammation of the pulp (Figure 4F). In 11 cases of calcium hydroxide treated teeth and 7 cases of Biodentine-treated teeth, there was mild pulpal inflammation (Figure 4G). Moderate inflammation was

shown by 7 Biodentine-treated teeth, 1 calcium hydroxide treated tooth and none of the MTA- and ERRM-treated teeth (Figure 4H). The histological pulp score differences were statistically significant (Kruskal–Wallis test,  $p < 0.05$ ) (Figure 6). Post hoc testing revealed that the MTA and ERRM groups differed significantly from the calcium hydroxide and the Biodentine groups. There was also a significant difference between the calcium hydroxide and Biodentine groups. However, there was no significant difference in the pulpal response between the MTA and ERRM groups (Table 2).



**Figure 6.** Pulp score comparison among the pulp-capping agents (0—no inflammation; 1—mild inflammation; 2—moderate; 3—severe).

#### 4. Discussion

CBCT demonstrated the superior performance of MTA and ERRM in dentinal bridge formation. All teeth capped with the four agents showed dentinal bridging, thus reinforcing current knowledge that all four materials are acceptable for pulp-capping. Histological analysis of the decalcified teeth sections stained with hematoxylin and eosin revealed that two-thirds (67%) of MTA- and ERRM-treated teeth developed structures similar to tubular dentin in the interface between the capping material and the pulp tissue. Nonspecific calcifications and atubular/amorphous dentin were predominant in teeth filled and capped with calcium hydroxide and Biodentine. As with the CT scan results, the histological findings in the teeth treated with calcium hydroxide are concordant with earlier studies [2,6–14].

Earlier studies by Monea and Stioca (2014) and others [2–4,8,10] reported high scores of dentinal bridge formation by MTA compared to calcium hydroxide in CBCT scan and histological evaluation. Our study affirms the superiority of MTA as a pulp-capping agent and shows that ERRM performs similarly, with identical CT scan scores and slightly lower histological scores. Our findings suggest that ERRM may be a good alternative material to MTA.

The results of our study concerning Biodentine differ from earlier work done by Tran et al. and Nowicka et al. [21,32,33]. Biodentine also stimulated dentin-like material, but in fewer teeth compared to MTA and ERRM. Histologically, Biodentine stimulated a stronger pulpal response compared to the other agents. This may be due to its chemical composition and workability characteristics. Laurent et al. reported a higher TGF secretion by pulpal cells treated with Biodentine. The scientific file of the manufacturer states that “when compared to ProRoot MTA, Biodentine demonstrates at least equivalent biocompatibility”. The file further notes that VEGF and FGF-2 (angiogenic mediators) were found to be enhanced in Biodentine-induced pulpal cells [24]. Therefore, we may infer that such mediator stimulation may be proinflammatory for the pulp. Biodentine is available as a



powder liquid formula, thereby making the mixing ratio subject to worker errors. The presence of a hydro-polymer might also be an inflammatory stimulus for the pulp. The inflammatory response of calcium hydroxide treated teeth is similar to that of Biodentine-treated teeth, which is in line with many studies on calcium hydroxide as a pulp-capping material [32–34].

Bioceramics have been developed for several applications. They are defined as “ceramic products or components employed in medical and dental applications, mainly as implants and replacements that have osteoinductive properties”. MTA is one of the earliest bioceramic materials introduced [17]. MTA has been used in dental clinics for more than 2 decades since its discovery by Torabinejad in 1993 and FDA approval in 1997. The active components are tricalcium silicate, dicalcium silicate and tricalcium aluminate. Torabinejad et al. reported a close physicochemical seal between MTA and dentine, with faster initial dentine bridge formation and good healing. The major advantage of MTA is its stability in moist tissue. It is reported to have an inductive and a supportive function in the formation of dentinal bridges with fewer tunnel defects [10–14]. The drawbacks of MTA include its handling characteristics and long setting time (2 h 45 min) requiring two visits to complete the restoration. Grey MTA may cause an aesthetic compromise due to the presence of iron compounds. White MTA has been reported to cause discoloration due to the presence of the bismuth oxide radiopacifier, requiring a search for alternatives. Mixing results in a grainy mass that is difficult to introduce and condense at the exposure site [3,10–18].

The unpredictable properties of MTA mainly stem from its manufacture from natural materials, which results in compromises on purity, particle size, etc. Thus, efforts have been made to synthesize similar materials. These efforts spawned a new class of calcium silicate materials, including Bioaggregate, Biodentine, EndoSequence materials and iROOT BP Plus. Calcium silicate based cement (MTA, Biodentin and iRoot) showed good pulp-capping properties (biocompatibility, inductive effect and tissue response), and no material was superior to the other. They all seemed to form good quality dentinal bridges with minimal inflammation [19–21]. Recent evidence suggests that immediate adhesive restoration after the use of silicate materials such as MTA produces acceptable results. MTA can therefore be used in immediate restorations in a single sitting [22]. Biodentine was formulated by Septodont in 2009 as an alternative to MTA. However, the calcium silicate is completely synthetic with a uniform particle size and is free from impurities. The presence of a hydrosoluble polymer (super-plasticizer) reduces porosity. It is marketed as a “dentine substitute material”, claiming properties and behaviors similar to those of dentine. Biodentine is claimed to possess superior compressive strength (304 MPa vs. 67 MPa after 21 days) and flexural strength compared to MTA [20]. Reparative dentin formed with Biodentine-restored vital pulps was a tubular orthodentin, without the tunnel defects observed in calcium hydroxide. Additionally, the absence of disadvantageous weak aluminates (present in MTA) seems to contribute to its strength [23–25].

A recent systematic review evaluated the material properties and clinical applications of Biodentine and found superior strength and less microleakage when compared to MTA. Both materials were associated with TGF- $\beta$  expression in pulp cells and performed similarly as pulp-capping materials [26]. Therefore, Biodentine is seen as a good alternative to MTA, with better handling, short setting time, higher strength and improved calcium release. However, more data on long-term clinical outcomes are required [27–34].

ERRM is a bioceramic material recently developed by Brasseler USA. It is composed of calcium silicate, zirconium oxide, tantalum oxide, calcium phosphate and fillers. ERRM is premixed and hardens in the presence of moisture and therefore is ideal against dentinal walls [35]. Cell culture studies have reported its biocompatibility and antibacterial effects. The alkaline pH induced by the material is said to result in increased calcium release and hydroxyapatite formation. The antibacterial effects are persistent even after setting [36,37]. The results of the present study are largely in agreement with a 2016 study that compared MTA and ERRM as pulp-capping agents and found that both MTA and ERRM stimulate well-formed dentin-like tissue with minimal inflammation. There were no statistically

significant differences between the two agents. However, they observed that MTA was superior in forming the dentinal bridge [38]. Although there are promising results obtained with newer materials like ERRM, it is vital to acknowledge that long-term studies similar to those of MTA are lacking with ERRM [39,40].

## 5. Conclusions

The results of the study indicate that the completeness and the quality of dentinal bridge formation are significantly greater in MTA and ERRM than in calcium hydroxide. The pulpal inflammatory responses to MTA and ERRM were less than those to calcium hydroxide and Biodentine. MTA exhibited superior performance in dentinal bridge formation when compared to the other agents. The results obtained with ERRM are probably due to its reported biocompatibility, anti-inflammatory and inductive properties. Therefore, ERRM may be a good alternative to MTA.

**Supplementary Materials:** The following are available online at <https://www.mdpi.com/article/10.3390/app11073045/s1>.

**Author Contributions:** Conceptualization, J.M. and G.S.; methodology, S.P.; software, M.R.S.; validation, N.B., A.A.-K. and M.M.; formal analysis, H.C.; investigation, A.Z.; resources, L.T.; data curation, S.B.; writing—original draft preparation, J.M.; writing—review and editing, A.T.R.; supervision, L.T. and S.P. All authors have read and agreed to the published version of the manuscript.

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**Informed Consent Statement:** Informed consent was obtained from all subjects involved in the study. Written informed consent was obtained from patients to publish this paper.

**Data Availability Statement:** Not applicable.

**Conflicts of Interest:** The authors declare no conflict of interest.

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