


Efficacy of Platelet Rich Plasma and Platelet Rich Fibrin for Direct Pulp Capping in Adult Patients with Carious Pulp Exposure- A Randomised Controlled Trial

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ABSTRACT

Objective: This study evaluated the effectiveness of Platelet Rich Plasma (PRP), Platelet Rich Fibrin (PRF) and Mineral Trioxide Aggregate (MTA) as direct pulp capping materials in patients with carious pulp exposure using cone beam computed tomography.

Methods: This parallel, triple blinded, randomised trial was done on 30 permanent posterior teeth chosen as candidates for direct pulp capping based on stringent inclusion and exclusion criteria. The samples were allocated based on sequentially numbered opaque sealed envelope method into three groups: MTA, PRP and PRF for direct pulp capping. The treated teeth were restored with Glass Ionomer cement liner and light-cured resin composite. Patients were followed up for a period of 12 months. Statistical analyses were performed with statistical software SPSS version 25. Data were analysed for normality using Shapiro Wilk's test. Dentine bridge volume analysis across the groups were done using Kruskal Wallis test with the significance level at $P=0.05$. As the test revealed a significant difference, post hoc analysis was done with Dunn test.

Results: CBCT analysis revealed that the volume of dentine bridge formed by PRP and PRF was significantly higher than the volume of dentine bridge formed by MTA ($P<0.001$; CI: 90%). There was no significant difference in the efficacy between the three direct pulp capping agents based on clinical assessment. A total of 27 teeth (90%) showed positive response to pulp sensibility testing and evidence of dentine bridge formation in radiograph at 12 months. No adverse events were encountered.

Conclusion: Platelet concentrates could be the future of vital pulp therapy for adult permanent teeth with reversible pulpitis.

Keywords: Carious pulp exposure, cone beam computed tomography; direct pulp capping; mineral trioxide aggregate; platelet rich fibrin; platelet rich plasma; reversible pulpitis

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HIGHLIGHTS

- Pulp capping is a promising treatment for adult permanent teeth with a clinical diagnosis of reversible pulpitis and carious pulp exposure during excavation.
- Platelet concentrates could be the future of regenerative procedures in endodontics.
- Current imaging techniques are valuable tools in assessing hard tissue formation.

INTRODUCTION

Vital pulp therapy involves treating exposed pulp in order to repair its damage and maintain its vitality (1). Direct pulp-capping is one such therapies that prevents pulpal injury by protecting it from various chemical, bacterial, mechanical, and thermal attacks (2). Currently there are two approaches to treat pulpal injury. The first is the traditional approach that employs newer synthetic ma-

terials that provide better seal than calcium hydroxide (3). Mineral Trioxide Aggregate (MTA) is a tricalcium silicate based material that is considered to be a promising direct pulp capping agent according to various *in vitro* (4), and human studies (5, 6). MTA has numerous disadvantages, including its tendency to discolor tooth, the presence of toxic elements such as arsenic, difficult handling properties, and high cost (7).

The second is the biologic approach that explores the molecular and cellular mechanisms behind pulp tissue regeneration and identifies a biological strategy for the treatment of clinical exposures.

The biological approach is achieved by reducing further damage to remaining odontoblasts and potentiating the differentiation of new odontoblasts (3).

A recent development in the field of endodontics has been the refinement of regenerative concepts for various procedures such as pulpotomies, apexogenesis, and osteogenesis after endodontic surgery using platelet concentrates (8-10). Platelet rich plasma (PRP) has been proposed as a potential pulp capping agent because of its excellent tissue compatibility (11). It is also stated that PRP is found to aid in recruitment and proliferation of the mesenchymal stem cells of the pulp and promotes mineralization of dental pulp stem cells (DPSC) (12). Platelet-rich fibrin (PRF) is a second generation platelet concentrate introduced by Choukroun in 2001 that contains components of blood that are conducive to healing (13). According to Ehrenfest, the advantages of PRF over PRP are that it is purely autologous, relatively simple to prepare, no external agents are required in its preparation and has sustained release of growth factors (14). A PRF membrane can sustain the release of several key growth factors for at least one week and up to 28 days, which means that it can release growth factors in conjunction with its own biological scaffold to promote wound healing (14).

Although histological evidence of dentine bridge formation is regarded as the gold standard for assessing the success of a direct pulp capping procedure, it involves destroying the tooth, while clinical success depends solely on the health of the pulp. There is no reliable method to assess dentine bridge formation and correlating it with clinical symptoms following direct pulp capping therapy. CBCT is a three-dimensional diagnostic modality that permits evaluation of dentine bridge formed after direct pulp capping (15). This study aimed to assess (1) the volume of dentine bridge using CBCT, and (2) the pulp sensibility, after direct pulp capping using PRF and PRP in comparison with MTA in adult permanent posterior teeth with carious pulp exposure. The null hypothesis was that there is no difference in the volume of dentine bridge formed with MTA, PRP and PRF as direct pulp capping agents in adult posterior teeth with carious pulp exposure.

MATERIALS AND METHODS

Allocation of participants

Thirty healthy participants (18 males and 12 females) were recruited between the age group of 18-45 years. Asymptomatic maxillary and mandibular molars and premolars with caries involving only the occlusal surface, not tender to percussion; ideal periodontal probing depth of 2 to 3 mm; normal response to cold and electric pulp testing; radiographic evidence of deep caries approximating the pulp chamber with no evidence of thickening/ widening of periodontal ligament, absence of furcation radiolucencies and periapical pathology were included in the present study. The exclusion criteria were as follows: symptomatic teeth (history of spontaneous pain), radiographic evidence of periapical changes or pathology, negative response to pulp sensibility testing, history of systemic diseases, tooth not conducive

for rubber dam isolation, history of previous restoration in the tooth under consideration for pulp capping, periodontally compromised teeth, patients with bleeding disorders, platelet count less than $1,50,000/\text{mm}^3$, patients with unsatisfactory oral hygiene maintenance and pregnant and lactating females.

Thirty carious premolars and molars which fulfilled the inclusion criteria were chosen for the study. The complete treatment procedure was explained to the patients and a written informed consent was obtained from all the patients selected for the study. The study was conducted in accordance with the Declaration of Helsinki Ethical principles for medical research involving human subjects after being independently reviewed and approved by the Institution's Ethical Committee (Ref No 0430/DE/2010).

Study design

This prospective, randomised, non-inferiority, parallel, three-arm active controlled triple blinded study compared MTA (Angelus, Londrina, PR, Brazil), PRP and PRF as direct pulp capping agents. Sample size was calculated using G power software applying the data obtained from pilot study with 5 samples in each group. The effect size of 0.8803 was obtained using the mean (\pm SD) values of volume and dentine bridge thickness formed in MTA, PRP and PRF group. Considering a dropout of 25%, 10 subjects were chosen per group to get a power of 90% in detecting the statistical significance among the 3 groups (Fig. 1). Allocation ratio for the test and control groups was 1:1. The procedure was performed by a single independent operator. Randomisation was done by the lot method with allocation concealment using the SNOSE method (sequentially numbered opaque sealed envelope method). The 30 subjects were randomly divided into 3 groups.

MTA group: (n=10) Direct pulp capping with MTA

PRP group: (n=10) Direct pulp capping with PRP

PRF group: (n=10) Direct pulp capping with PRF

Preoperative assessment

Medical and dental history were recorded for all the patients selected for the study. Intra oral examination was done to assess the nature of presenting illness, the oral hygiene status, periodontal condition and restorability of the involved tooth. Preoperative intra oral periapical radiographs were obtained for each subject included in the study. Electric and thermal (cold) pulp testing were performed to assess the sensibility of the pulp. Oral prophylaxis was done prior to the commencement of the treatment. Teeth with clinical signs and symptoms with sensibility tests suggestive of reversible pulpitis were further recruited for the study.

Direct pulp capping procedure

Patients were given a prophylactic oral rinse of 0.2% Chlorhexidine (Rexidine mouth rinse, ICPA products) before the procedure. Under local anaesthesia (Lignocaine with 1:80,000 Adrenaline (Lignox 2%, Warren, Indoco Remedies Ltd, India) and rubber dam isolation, caries detector dye (Caries Indicator,

Prime Dental Products Pvt Ltd, India) was applied to the tooth for 30 seconds and rinsed for 10 seconds to disclose the infected dentine. Caries excavation was done using sterile round diamond points (BR 41, Mani Dia-Burs, Tochigi, Japan) and Straight fissure (SF 11, Mani Dia-Burs, Tochigi, Japan) with high speed airtor hand piece (NSK, Tokyo, Japan) till the stained tooth structure was completely eliminated. At this stage, teeth with carious pulpal exposure (0.5 to 1 mm diameter) were further chosen for direct pulp capping.

After excavation, the cavities were inspected visually for haemostasis. If bleeding persisted a sterile cotton soaked in 1% NaOCl was used to establish haemostasis. If the selected tooth fulfilled the inclusion criteria, the exposed pulps were pulp capped with any of the following three pulp capping agents.

MTA

MTA was mixed with the liquid supplied by the manufacturer on a sterile glass slab using a stainless steel spatula. MTA was placed in thickness of 2 mm over the pulp exposure site. After placement, the cavity floor was dabbed with moist sterile cotton pellet.

PRP and PRF group

PRP was prepared prior to the operative procedure in accordance with the protocol developed by Sonnleitner et al. (16) and PRF was prepared in accordance with the protocol developed by Choukroun et al. (13) The prepared PRP and PRF were

then carried to the exposure site in a highly resorbable sterile collagen membrane (Kolspon, Eucare Pharmaceuticals Pvt Ltd., India) and positioned with the tine of a sterile explorer.

Restorative procedures

After placement of the pulp capping agents, the floor of the prepared cavities were lined with type II GIC (Fuji II, GC Tokyo, Japan). After ensuring set, the cavity was etched with 37% Orthophosphoric acid (Tetric Etch, Ivoclar Vivadent) for 20 seconds, rinsed and dried followed by application of bonding agent (Tetric Bond, Ivoclar Vivadent). Final restoration was done with light-cured resin composite (Tetric N Ceram, Ivoclar Vivadent) and assessed for the presence of premature contacts and visible marginal defects. The restoration was finished and polished with composite finishing kit (Shofu, Kyoto, Japan). The patients were reviewed clinically at regular intervals of 3, 6 and 12 months. CBCT assessment was done at 6 months.

Post-operative follow up

Out of the 30 cases treated, one patient in each group complained of pain at various time points after 6 months. 27 cases were available for follow up till 12 months. The primary outcome measure was the assessment of the quality of dentine bridge induced. The secondary outcome measures were clinical and radiographic assessment mentioned below. The clinical and radiographic assessments were done by blinded and trained professionals. No adverse effects were reported in any of the groups treated.

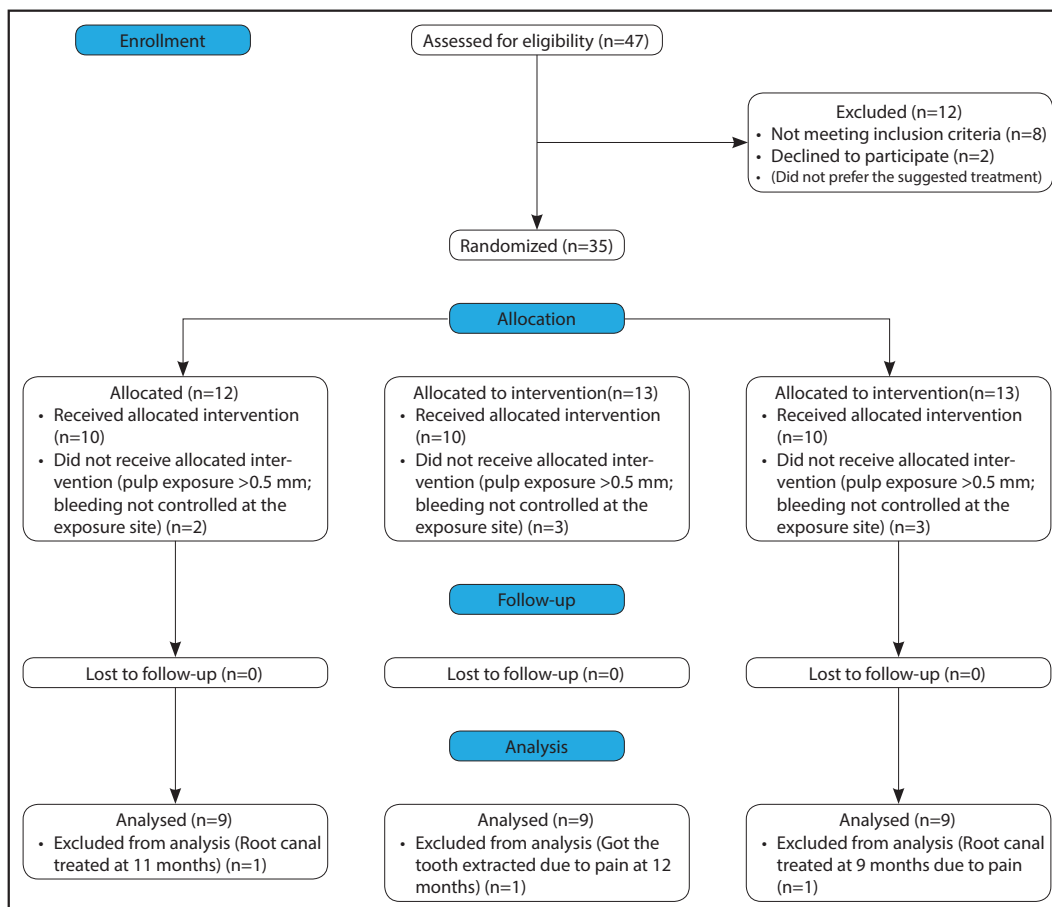


Figure 1. Consort flow diagram

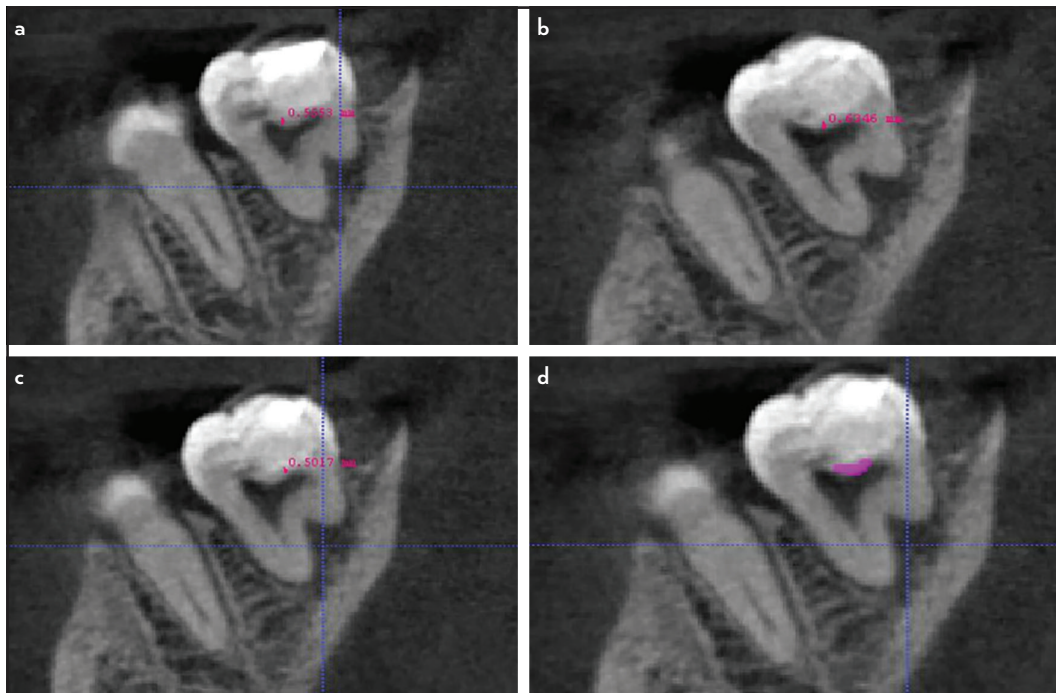


Figure 2. Measurement and marking of the formed dentine bridge in MTA group for volumetric analysis. (a-c) Localisation of three focus points below the exposure site for volumetric analysis. (d) Dentine bridge below the exposure site marked for image segmentation and 3D image generation

MTA: SMineral trioxide aggregate

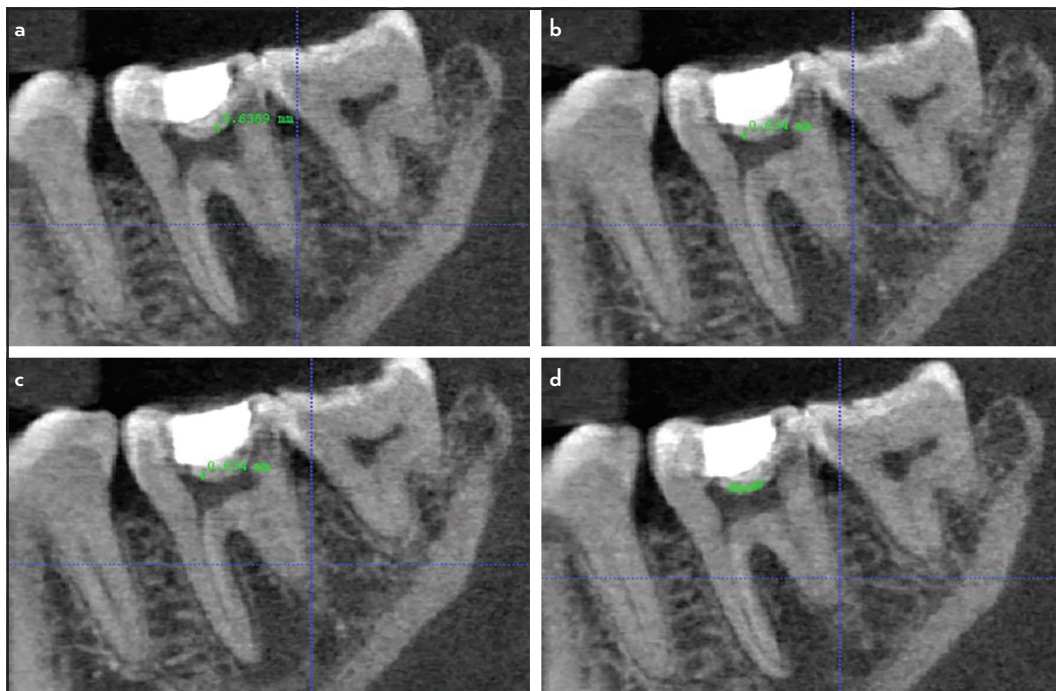


Figure 3. Measurement and marking of the formed dentin bridge in PRP group for volumetric analysis. (a-c) Localisation of three focus points below the exposure site for volumetric analysis. (d) Dentin bridge below the exposure site marked for image segmentation and 3D image generation

PRP: Platelet rich plasma

Clinical assessment

During each follow up visit at 3, 6 and 12 months, the pulp capped teeth were evaluated for pulp sensibility using cold and electric pulp testing, periodontal probing depth, mobility, pain and tenderness to percussion.

Radiographic assessment

The pulp capped teeth were radiographically evaluated using Digital radiography (X Ray Vision software, Dr Suni Plus) with XCP film positioning device and standard exposure modes of 100 ms, 4 mA and 60 kVp during every postoperative visit of 3,

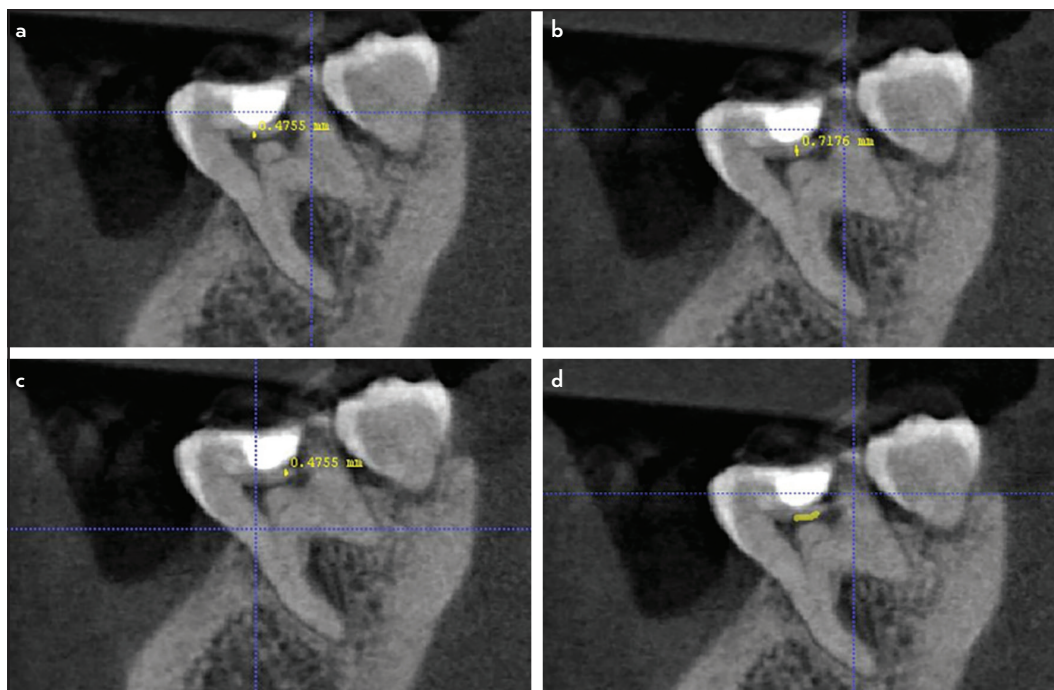


Figure 4. Measurement and marking of the formed dentin bridge in PRF group for volumetric analysis. (a-c) Localisation of three focus points below the exposure site for volumetric analysis. (d) Dentine bridge below the exposure site marked for image segmentation and 3D image generation

PRF: Platelet rich fibrin

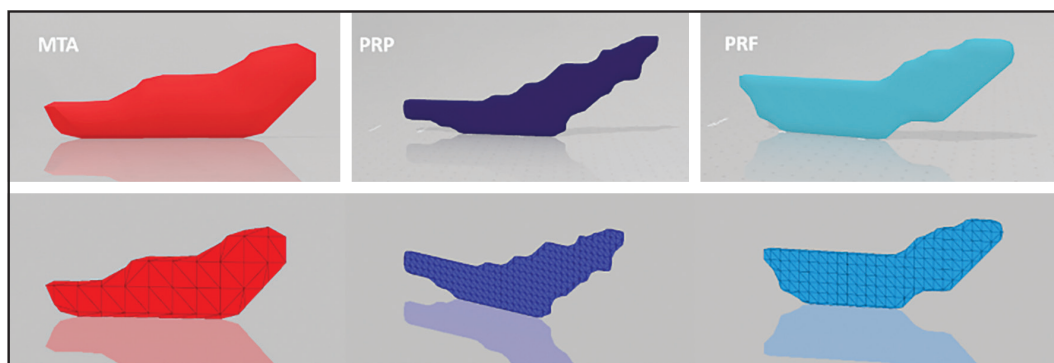


Figure 5. Three-dimensional reconstructed image of the dentine bridge

MTA: Mineral trioxide aggregate, PRP: Platelet rich plasma, PRF: Platelet rich fibrin

6 and 12 months. Interpretation of intra oral radiographs were done by 3 independent assessors for the presence or absence of hard tissue formation on a dichotomous scale (2 endodontists and 1 radiologist).

CBCT assessment

The pulp capped teeth were subjected to CBCT analysis using CS 9300 (Carestream, Rochester, New York, USA) with small field of view (FOV) of 5×5 cm, ultra-high resolution of 90 μ m (voxel size), 75 kV, 4 mA, 20 seconds exposure time, 350 mGy/cm² after 6 months. The CBCT images were analysed using ITK-Snap software version 3.8.0 (Fig. 2-4). Interpretation of CBCT was done by 3 independent assessors (2 endodontists and 1 radiologist). The assessors evaluated the CBCT for presence/absence of dentine bridge formation, and the volume of the formed dentine bridge in mm³. The zone below the pulp capping was oriented by visualizing

the site of exposure in the CBCT slice and was marked for three-dimensional assessment using a cursor. The marked zone was obtained in .STP three-dimensional file extension format. The obtained three-dimensional file was visualized in Microsoft 3D application and the mesh data of the formed dentine bridges was obtained as an image (Fig. 5). For assessing these parameters, assessors had been trained repeatedly before the evaluation. The average of the three individual values given by each assessor were taken as the final value for each sample. The same procedure was followed for all the subjects.

Statistical analysis

Statistical analyses were performed with IBM SPSS statistics for Windows (IBM Corp, New York, USA). Data followed a non-normal in distribution as analysed using Shapiro Wilk's test. Volumetric analysis across the groups were done using Kruskal

Wallis test with the significance level at 0.05 (P=0.05). As the test revealed a significant difference, post hoc analysis was done with Dunn test.

RESULTS

Clinical assessment

At the end of 12 month review period, 90% of the samples in MTA, PRF and PRP group showed positive response to EPT and Cold test. None of the subjects were observed to have an abnormal periodontal probing depth at the observed intervals of time (Table 1).

Radiographic assessment

90% (27 cases) of the samples showed evidence of dentine bridge formation at the end of 12 months. None of the subjects were observed to have periapical pathology at the observed intervals of time. 10% of cases were observed to have periodontal space widening in the periapical region.

CBCT assessment

The volume of dentine bridge formed at 6 months revealed that PRP and PRF formed significantly higher volume of dentine bridge than MTA (P<0.001) (Tables 2, 3).

DISCUSSION

Adult permanent molars and premolars with all four walls intact were chosen for the study so that the operator has a better command over the margins of the restoration. Mature adult permanent teeth with clinical signs and symptoms of reversible pulpitis were selected co-relating clinical signs and symptoms, pulp sensibility tests and radiographic presentation. Caries indicator dye was used to assess complete caries removal as it is one of the most reliable method to ensure removal of infected dentine, and also prevents inadvertent removal of healthy tooth structure (17). Bleeding at the exposure site, if present was controlled using 1% NaOCl as it is a strong prognostic indicator of pulp capping (18). At the end of 12 months, 90% of teeth showed positive response to pulp sensibility test and tested negative to pain and tenderness on percussion. However, none of the teeth that were reviewed demonstrated increased periodontal probing depth at 12 months. There was radiographic evidence of dentine bridge formation in 27 teeth out of the 30 treated. 2 out of 30 cases presented with increased periodontal ligament space widening: one from MTA (at 9 months) and PRF group (at 11 months) which were root canal treated. One teeth in PRP group was extracted due to pain at the 12th month follow up. MTA induces the proliferation of pulp cells, releases cytokines, and promotes hard tissue formation (7). MTA also elaborates TGFβ1 which plays a key role in migrating the progenitor cells of the pulp and differentiating them to form odontoblast like cells (19). These differentiated cells form dentinoid tissue which is suggestive of more of a reparative process than regeneration (12). PRP significantly increased the ALP activity and FGF (Fibroblast Growth Factor) in PRP regulates the structures of regenerated dental pulp and calcified tissues and acts synergistically with TGF-β1 and IGF-1 to positively influence their inductive effects on odontoblastic differentiation (20). Even though bovine

TABLE 1. Pulp sensibility test results at 12 months

S. no	Cold test			Electric pulp test		
	Number of cases treated (Number of cases with positive response)			Number of cases treated (Number of cases with positive response)		
	MTA	PRP	PRF	MTA	PRP	PRF
	10 (9)	10 (9)	10 (9)	10 (9)	10 (9)	10 (9)
% of cases with positive response at 12 months	90	90	90	90	90	90

MTA: Mineral trioxide aggregate, PRP: Platelet rich plasma, PRF: Platelet rich fibrin

TABLE 2. Volume of dentine bridge formation in the three groups – Kruskal Wallis test

Group (n=10)	Mean (mm ³)	Standard deviation	P
MTA	0.0720	0.0181	<0.001
PRP	0.1392	0.0161	
PRF	0.1368	0.0128	

MTA: Mineral trioxide aggregate, PRP: Platelet rich plasma, PRF: Platelet rich fibrin

TABLE 3. Pairwise comparison between MTA, PRP and PRF

Group	Test statistic	Standard error	P
MTA vs PRF	-14.850	3.855	<0.001*
MTA vs PRP	-15.150	3.855	<0.001*
PRP vs PRF	0.300	3.855	0.938

*Denotes statistical significance. mm³: volume of dentine bridge in cubic millimetres, MTA: Mineral trioxide aggregate, PRP: Platelet rich plasma, PRF: Platelet rich fibrin

thrombin used in the preparation of PRP may be associated with the development of antibodies to the factors V, XI and thrombin, hypothesised to cause coagulopathies (20), none of the studies published so far have reported any adverse events with the use of PRP (8-10). Owing to these controversies linked to the use of PRP, second generation platelet concentrates are being preferred. PRF is rich in leukocytes that are responsible for additional growth factor release apart from imparting immunity. The fibrin scaffold also entraps growth factors and is responsible for the sustained release (21). All these bioactive elements are secreted by platelet concentrates. Though PRP contains concentrated growth factors, the maximum release is attained only immediately after activation, that is after the addition of bovine thrombin (14).

So far, no clinical study has been performed comparing MTA, PRP and PRF as pulp capping agents to compare the results with our study. In studies conducted so far comparing MTA/PRF (22) or PRP/PRF (23) or MTA/PRP (24) for regenerative procedures, the outcomes of the materials have been comparable. The success rate of direct pulp capping in our study is consistent with

the results of various other studies in the literature (25, 26). Thus, the null hypothesis is rejected in the current study.

A complete removal of carious dentine was carried out in this study. The bioactive factors released from demineralized dentine are therefore not available for stimulating the DPSCs into odontoblast-like cells, and all reconstructive processes are attributable to the pulp capping agents applied (27). In 6 months, CBCT measurements were made to assess the formation of the dentine bridge using radiodensity values, which indicate the extent of mineralization of dentine that cannot be determined histologically. The three-dimensional reconstructed image of the formed dentine bridge and the resultant volume could be assessed using the ITK snap software.

Nowicka A et al. (15) has utilised CBCT as an imaging modality to assess dentine bridge formation in third molars indicated for extraction and correlated the findings with histomorphometric analysis. The present study has utilized CBCT to assess dentine bridge formation *in situ*. There has been no destruction of samples in the study. Elmsmari (2019) considered 6 months adequate to assess the outcomes of pulp capping in his study (28). Hence in our study, 6 months has been used as the optimal time frame for CBCT assessment; clinical and radiographic assessments were done at 12 months though.

This study employed a small FOV of 5×5 cm for endodontic applications. According to Ludlow et al. (29) the effective dose following adult exposure at 5×5 cm FOV was found to be as low as 3 μS with reduction in radiation exposure ranging between 0-85% based on the varying exposure parameters such as kilovoltage potential, current, exposure time and FOV. The overall performance of PRF was found to be better as a pulp capping agent. This outcome can be attributed to the slow and sustained release of growth factors from PRF.

CBCT revealed that MTA produced similar clinical results to PRP and PRF, although the amount of dentine bridge formed by MTA was considerably less than the other two groups. This could be because MTA is only a biomaterial and not a biological alternative like PRP and PRF. Though MTA is proven to induce dentine bridge formation by inducing biochemical pathways, platelet concentrates provide the necessary bioactive substances in readymade form and they circumvent the natural biological process of induction.

We found that both of the experimental materials formed dentine bridges comparable to MTA. The success rates of MTA, PRP and PRF as direct pulp capping agents did not differ significantly. To our knowledge, PRP and PRF have not been evaluated *in vivo* as direct pulp capping agents in combination with CBCT. Based on the clinical, radiographic and CBCT observations of the current study, it could be inferred that platelet concentrates could be a promising alternative to MTA for direct pulp capping in adult permanent teeth with carious exposure. However, the study should be done on a larger sample size in different clinical set-ups with longer follow-up periods to validate the results of the current study.

Within the limitations of this study, it can be concluded that the two novel pulp capping agents namely PRP and PRF produced promising results comparable to the current gold standard material MTA. Based on the clinical, radiographic and CBCT observations of the current study, it could be deduced that both PRF and PRP could be promising alternatives to MTA for direct pulp capping in adult permanent teeth with carious exposure. There was no significant difference in success rates between MTA, PRP and PRF.

Disclosures

Conflict of interest: The authors deny any conflict of interest.

Ethics Committee Approval: This study was approved by The Tamilnadu Government Dental College Ethics Committee (Date: 29/04/2014, Number: 0430/DE/2010).

Peer-review: Externally peer-reviewed.

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