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Human pulpal response to mineral trioxide aggregate (MTA), bioactive glass and calcium hydroxide: A histologic study

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***Abstract*---**Aim:The aim of this study was histological evaluation of the relative success of white mineral trioxide aggregate (MTA), bioactive glass (BAG), and calcium hydroxide ($Ca(OH)_2$) when used as pulp capping agents in human teeth. Materials and Methods:45 healthy premolars scheduled to be extracted for orthodontic reasons were divided into three groups of 15 teeth in each group. The exposed pulps were capped with MTA, Bioglass or Calcium hydroxide. At the end of two months the teeth were extracted and subjected to histological analysis. The sections were blindly evaluated by an experienced and calibrated pathologist. Results: Statistically significant differences were observed among the groups for histological

evaluation. A clear superiority of MTA over the other two materials in terms of all the histological criteria evaluated was observed. Conclusions:MTA was observed to be superior to BAG and $Ca(OH)_2$ in terms of histological analysis. Although results favour the use of MTA, more studies with larger samples and a longer follow-up are suggested.

***Keywords*---**pulp capping, pulp exposure, humans, mineral trioxide aggregate, bioactive glass, calcium hydroxide, biocompatibility, dentine bridge.

Introduction

Direct pulp exposures can be a challenging problem and such pulp exposure presents a treatment dilemma[1]. Direct pulp capping is the coverage of exposed pulp by a biocompatible material after traumatic or carious exposure. The purpose of this procedure is to seal it against bacterial leakage, stimulate dentinal barrier formation and maintain vitality of the pulp[2]. Calcium hydroxide has been indicated to promote healing in many clinical situations. They provide an option for reparative dentin formation, but long term studies have shown results to be variable & somewhat unpredictable[1].The spectrum of success rates for calcium hydroxide ranges from 13% to 96%[3].Due to its biocompatible & anti bacterial properties, Bioglass can be the material of choice for pulp capping & periapical bone healing. Studies have shown bioactive glass to be superior to Calcium Hydroxide as pulp capping material in primary teeth[6, 7]. Mineral trioxide aggregate became known as an appropriate material for pulp capping, because of its several good features such as high sealing effect and high pH, biocompatibility, long term stability, prevention of bacterial leakage, and stimulation of cementum, bone and dentin formation[2]. Dentin bridge formation with MTA seems to be more homogenous[3], but it is a technique sensitive material that can be difficult to place and it takes about fours hours to set when in contact with moisture[8].

To date researchers have been unable to identify a reliable pulp capping material on direct pulp exposures. Controversies surround the pulp capping materials and identifying a reliable non absorbable bioactive pulp capping material that consistently stimulates cellular repair mechanism, seals the dentin and promotes formation of a biologically stable reparative dentin is the goal. Although studies have evaluated the effect of these materials individually, no comparative studies have been done to evaluate their performance as direct pulp capping agents on permanent teeth. Several clinical and radiographic studies conducted previously have evaluated the effect of pulp capping in human teeth, only few histological studies have been conducted to evaluate histological response in human teeth. Moreover, the true “gold standard” of pulp status is histological analysis[4]. Hence the aim of this study was to Evaluate and Compare Histological responses of the effects of White Mineral Trioxide Aggregate, Bio-active glass and Calcium Hydroxide used as direct pulp capping agents in human permanent teeth.

Materials and Methods

45 Maxillary and mandibular intact premolars with healthy periodontium, without evidence of caries, fractures, restorations, were selected after examinations. The patients and/or their parents signed consent forms after receiving a detailed explanation about the experimental rationale, clinical procedures, and possible risks. The research protocol was reviewed and approved by the Research & Ethical review committee from the K.V.G Dental College & Hospital. Medical and dental history was recorded from the subjects to rule out systemic diseases contradicting the procedure. The patients had no medical problems and the subject teeth had no previous operative procedures. The teeth were subjected to pulp vitality testing. Custom made ice sticks, gutta-percha sticks, electric pulp tester was used to check the vitality of the teeth scheduled for pulp therapy and their adjacent teeth. Electric pulp testing was done using Digitest pulp tester (Parkell Corp).

All the teeth were anesthetised using 2% Lignocaine with 1:80000 adrenaline (LIGNOX 2% A, Warren Pharma). After obtaining profound anaesthesia, rubber dam (HYGENIC, COLETENE WHALEDENT) isolation was done. Occlusal cavities were prepared by means of sterile 0.5mm round diamond burs (DENTSPLY CORP) at high speed under water/spray coolant. The dimensions of the cavity were occlusal depth, 3.0 + 0.2mm. The cavity depth was checked with a periodontal probe in an attempt to standardize the cavity. Pulp exposure was performed in the centre of the pulpal floor by means of the sterile round bur under water cooling. One bur was used for each cavity. Haemostasis was established with sterile cotton pellet soaked in saline solution.

The 45 teeth were then divided into three experimental groups. In group 1, White Mineral Trioxide Aggregate (DENTSPLY Tulsa Dental Specialities Johnson City, TN) was mixed with saline in a 3:1 ratio with a stiff metal spatula and them was placed over the exposed pulp. A wet cotton pellet was placed over the pulp capping material and the cavity restored with Type III, Class I Intermediate Restorative Material (DENTSPLY Caulk, Milford, DE) for 3-4 hrs. IRM and cotton pellet were removed. A thin layer of Light Cure Glass Ionomer Cement (GC, Fuji II) was applied. Total Etch adhesive system (SINGLEBOND, 3M), a single step etch-and-rinse adhesive was used for all groups. Enamel and dentin were conditioned with 35% phosphoric acid for 20 secs. The acidic agent was rinsed out and the dentin was slightly dried in such a way that the surface stayed visibly moist with a shiny appearance. The bonding resin was subsequently applied and light-cured for 10 seconds. Increments of Z-250(3M ESPE) was used to restore the cavities. Each increment (+ 2mm) was light-cured for 40 seconds. When necessary, the material excesses were removed by using an ultra fine diamond bur at high speed under water cooling.

In Group 2 –Bioglass powder (NovaBone Products, FL) was used as the pulp capping material. It is available as a crystalline powder. It was mixed with small amount of saline and placed over the exposure. Light cure GIC based was placed and posterior composite restoration done using the same technique as in group 1.
In Group 3,Dycal (DENTSPLY Caulk, Milford, DE), a two paste system was used in our study. The base paste and catalyst paste was mixed and placed directly

over the pulp, followed by light cure GIC base and posterior composite restoration.

Teeth from all the 3 groups were extracted after 60 days for histological examination. The extraction was performed under local anaesthesia. The apical third of all the roots was sectioned in 5mm to facilitate fixation in 10% buffered formalin solution for 72 hrs. The teeth were decalcified in 5% nitric acid for 6-8 weeks, prepared according to routine histologic techniques and embedded in paraffin. Six micrometer thick sections were cut with a Hard Tissue Microtome parallel to main vertical axis of the tooth. The number of sections obtained per tooth was not fixed. On the average, 10-12 slides containing 4-5 six-micrometer-thick sections were obtained. The sections, mounted on glass slides were stained with hematoxin-eosin and viewed under light microscopy.

The sections were blindly evaluated by an experienced and calibrated pathologist. The multiple sections were used to achieve an overall assessment for each tooth for:

1. Hard Tissue Bridge (regular, irregular or absent).
2. Inflammation (absent, mild or moderate)
3. Pulp cells – odontoblasts (normal or irregular).
4. Pulp capping material (absent, mild or moderate).
5. Calcifications (present or absent).

The scores attributed to each group were subjected to nonparametric Kruskal-Wallis analysis. This test was performed separately for each clinical, radiographic and histologic examination. The comparisons between averages were performed by comparing the ranks with appropriately computed critical values using the Unpaired “T” test and ANOVA test.

Results

MTA showed better dentin bridge formation (40% of regular & 60% of irregular) compared to BAG 73.3% (20% of regular & 53.3% irregular) and Ca (OH) $_2$ (40% irregular & 60% absent).Higher failure rates were observed in group III – Ca (OH) $_2$ over a two month evaluation period. Highest inflammatory response was seen in Group III - Ca (OH) $_2$ 100% (60% mild & 40% moderate response) and Group II – BAG with 66.7% mild inflammatory response. Group I - MTA showed 100% regular odontoblasts whereas Group II – BAG showed 80% normal cells and Group III - Calcium hydroxide only 26.7%. Least percentage of normal odontoblasts (26.7%) was seen in group III – Ca (OH) $_2$. Group I – MTA showed only 13.3% of remnants of pulp capping material while group II – BAG had 93.3% and group III – Ca (OH) $_2$ showed 60%. Highest amount of remnants were seen in the calcium hydroxide samples. Group I – MTA & group II – BAG showed 66.7% of calcification whereas group III – Ca (OH) $_2$ showed 73.3%.

Table 1:Percentage of scores (%) attributed for each group in hard tissue bridge formation designated as regular, irregular or absent

			GROUP			Total
			Bioglass	CaOH	MTA	
	Regular	Count	3	0	6	9
		%	20.0%	.0%	40.0%	20.0%
	Irregular	Count	8	6	9	23
		%	53.3%	40.0%	60.0%	51.1%
	Absent	Count	4	9	0	13
		%	26.7%	60.0%	.0%	28.9%
Total		Count	15	15	15	45
		%	100.0%	100.0%	100.0%	100.0%

a x2=15.993 p=0.003 hs

Table 2: Percentage of scores (%) attributed for each group in inflammation designated as no inflammation, mild and moderate inflammation

			GROUP			Total
			Bioglass	CaOH	MTA	
	No inflammation	Count	5	0	11	16
		%	33.3%	.0%	73.3%	35.6%
	Mild	Count	10	9	4	23
		%	66.7%	60.0%	26.7%	51.1%
	Moderate	Count	0	6	0	6
		%	.0%	40.0%	.0%	13.3%
Total		Count	15	15	15	45
		%	100.0%	100.0%	100.0%	100.0%

a X2=26.071 p<0.001 vhs

Table 3:Percentage of scores (%) attributed for each group in evaluation of Pulpal cells – Odontoblasts designated as normal and irregular

			GROUP			Total
			Bioglass	CaOH	MTA	
	Normal	Count	12	4	15	31
		%	80.0%	26.7%	100.0%	68.9%
	Irregular	Count	3	11	0	14
		%	20.0%	73.3%	.0%	31.1%
Total		Count	15	15	15	45
		%	100.0%	100.0%	100.0%	100.0%

a x2=20.115 p<0.001 vhs

Table 4: Percentage of scores attributed for each group for evaluation of remnants of pulp capping materials designated as absent and moderate

		GROUP			Total
		Bioglass	CaOH	MTA	

	Absent	Count	6	1	13	20
		%	40.0%	6.7%	86.7%	44.4%
	Moderate	Count	9	14	2	25
		%	60.0%	93.3%	13.3%	55.6%
Total		Count	15	15	15	45
		%	100.0%	100.0%	100.0%	100.0%

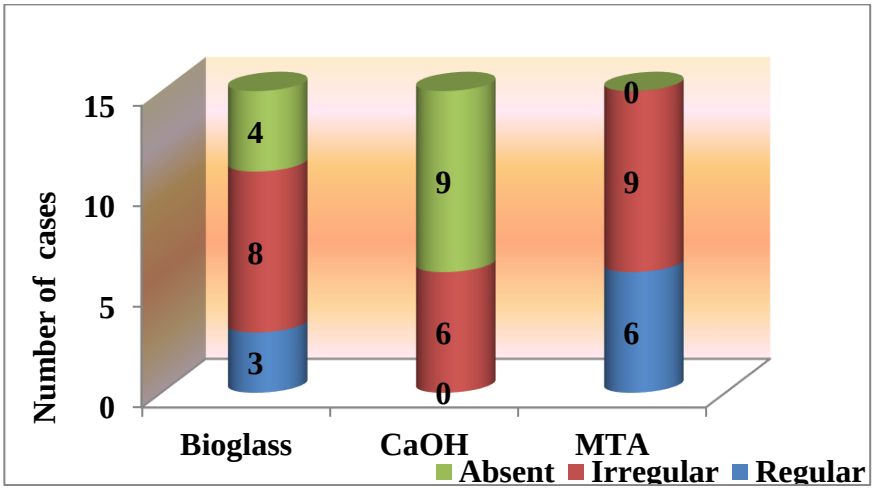
a x2=19.62 p<0.001 vhs

Table 5: Percentage of scores (%) attributed for evaluation of pulpal calcifications designated as present or absent

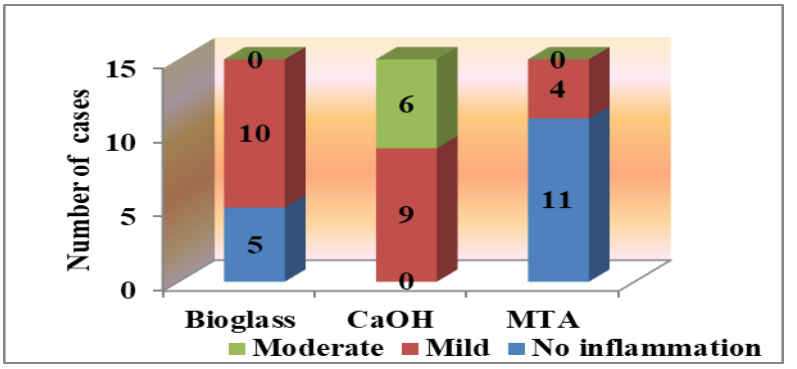
			GROUP			Total
			Bioglass	CaOH	MTA	
	Present	Count	10	4	10	24
		%	66.7%	26.7%	66.7%	53.3%
	Absent	Count	5	11	5	21
		%	33.3%	73.3%	33.3%	46.7%
Total		Count	15	15	15	45
		%	100.0%	100.0%	100.0%	100.0%

a x2=6.429 p=0.04 sig

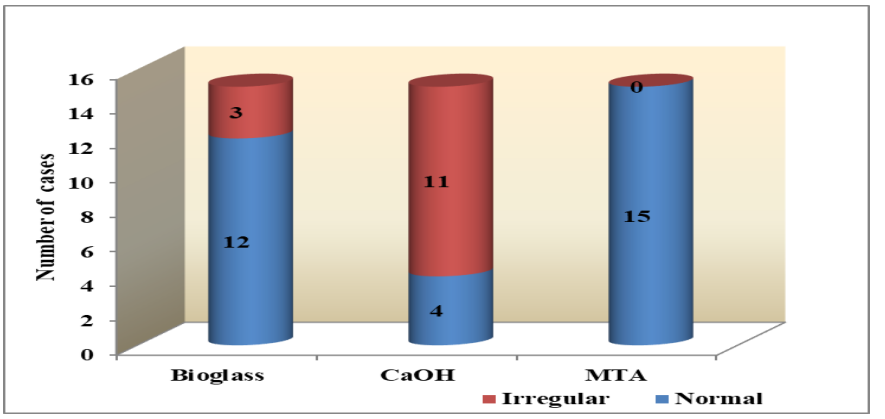
Graph 1:Hard tissue bridge formation observed histologically over a period of 2 months



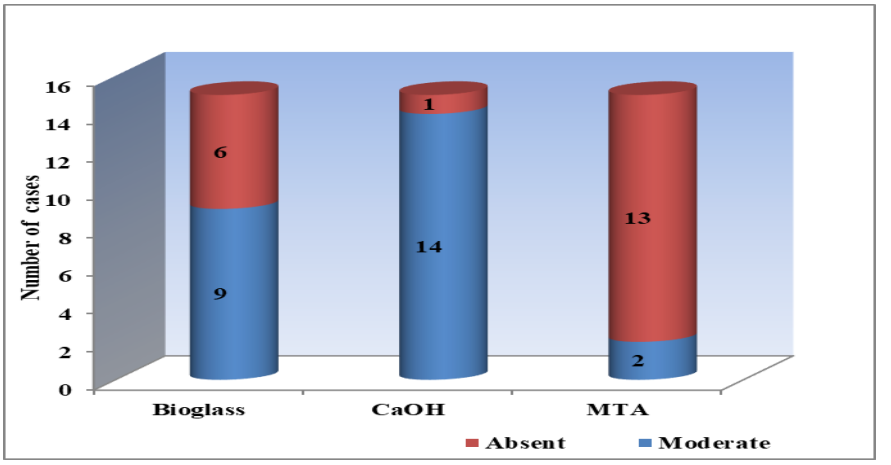
Graph 2:Assessment of inflammatory changes observed histologically over a period of 2 months



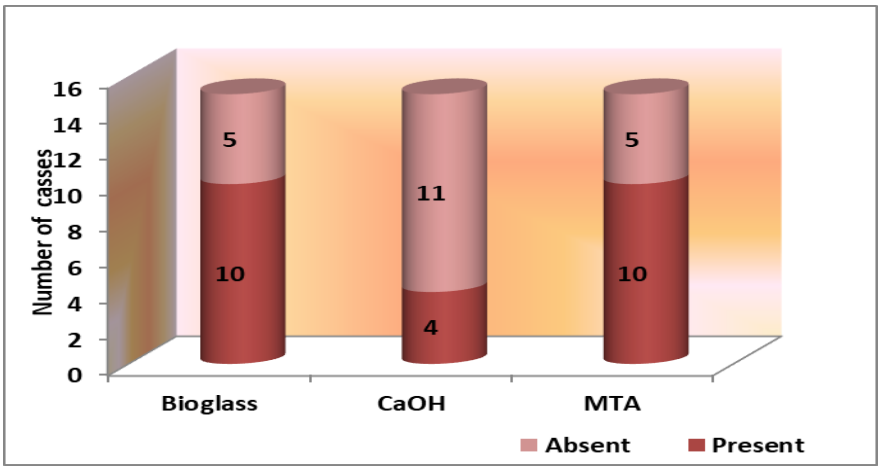
Graph 3: Histological evaluation of pulp cells – odontoblasts observed over a period of 2 months



Graph 4:Remnants of pulp capping material evaluated histologically over a period of 2 months



Graph 6:Evaluation of calcifications observed histologically over a period of 2 months



Discussion

The pulp of a tooth can be exposed due to several causes: caries, trauma or mechanical reasons, the latter typically due to misadventure during tooth preparation. Some studies have shown that a tooth is more likely to survive direct pulp capping if the initial exposure is due mechanical reasons rather than caries. Caries penetration to the pulp will result in bacterial invasion of the pulp, resulting in pulpal inflammation. This leaves the pulp less able to respond and heal, compared to a mechanical exposure in which pre-existing inflammation is not present. A logical extension of this is that teeth are asymptomatic and exhibit no clinical or radiologic signs of pathology at the time of pulp capping tend to fare better than those teeth with such factors present. Much research on pulp capping has been accomplished in animals, from lower species, such as mice and dogs, to primates. However, the results of pulp capping in animals often does not reflect what will happen in humans. It is necessary to be very cautious in taking the results of animal pulp capping studies and applying them to human patients[32]. Subjects recruited in our study for direct pulp capping procedures were orthodontic patients requiring extraction of intact premolars.

The ultimate goal of research such as this is to derive conclusions based on evidence that can be applied to clinical practice. In any study the treatment outcome is largely determined by the evaluation criteria and the material used to determine whether any particular treatment procedure has been “successful”. Unfortunately, the true state of pulpal health or pathology cannot be determined by clinical signs, symptoms or radiographic appearance. The true “gold standard” of the pulp status is histological analysis. Numerous studies including histological analysis have demonstrated a chronically inflamed pulp, but the patients reported no symptoms and no apical/radicular pathology were noted on radiographs[32]. However in a clinical setting histological examination is not possible when reviewing treatment outcome and therefore the lack of both clinical and radiographic signs is the usual criterion applied.

Calcium hydroxide was used for pulp capping for the 1st time by Hermann (1930), and from then it has been the most used material for pulp capping and has a long-term track record[35]. Calcium hydroxide has excellent antibacterial properties. One study showed a 100% reduction in micro-organisms associated with pulp infections after one hour contact with calcium hydroxide. Calcium hydroxide has some disadvantages as well. Calcium hydroxide has no inherent adhesive qualities and provides a poor seal. Another criticism noted of calcium hydroxide is the appearance of so called "tunnel defects" in the reparative dentin formed underneath calcium hydroxide pulp caps[32]. In a review by TJ Hilton conclusion were drawn regarding calcium hydroxide as the "gold standard" for direct pulp capping. It is the most cost effective material and is likely, the effective component in MTA[32].

Since the introduction of Mineral trioxide aggregate in 1995, it has developed considerable interest as direct pulp capping agent in recent years. MTA is considered silicate cement rather than an oxide mixture, and so its biocompatibility is due to its reaction products. As a result, many of the advantages and potential mechanisms of action for MTA are comparable to calcium hydroxide, including its antibacterial properties and biocompatibility properties, high pH, radiopacity and its ability to aid in the release of bioactive dentin matrix proteins[32]. A review of animal direct pulp capping studies comparing MTA to calcium hydroxide generally reveals better pulp healing with MTA[2]. Most human studies show similar pulp capping outcomes of MTA and calcium hydroxide.

Another material of interest containing oxides of calcium is Bioactive glass. They have been studied for more than 30 years as bone substitutes, but introduced to dentistry in 1985. They react with aqueous solutions and produce a carbonated apatite layer. BAG is biocompatible and can bind to the bone. Presently third generation of biomaterials are available. The materials are resorbable and are bioactive. They are designed to activate genes that stimulate regeneration of living tissue[19]. Based on studies, BAG is able to stimulate hard tissue formation and mineralization. Results of studies by Haghgoo have shown that BAG can repair bone lesions through osteoblastic potential so it is logical that odontoblastic activity of BAG is survived. Haghgoo and Naderi studied the histological response of pulps capped with BAG and Ca $(OH)_2$ in primary teeth. They found BAG to be superior to calcium hydroxide when used as a pulp capping agent[7]. Hence the present study aimed at evaluating MTA, BAG and Ca(OH)2 as a direct pulp capping agents.

The main indicator of success in direct pulp capping or pulpotomies is the formation of dentin bridges, according to Zander and Hess. Considering formation of regular/irregular hard tissue, the present study showed all the groups achieved pulp healing to a lesser or greater extent. Group I (MTA) showed high success rate (100%) with thicker and uniform dentin bridge followed by BAG (73%), and $Ca(OH)_2$ (40%). However, Myers *et al.*(1996) found no significant differences in pulpal status or bridging between MTA and calcium hydroxide groups. Alexander *et al* have shown 100% of the specimens capped with MTA presenting a compact thick dentin bridge similar to $Ca(OH)_2$ which is in contrast with the present study.

Similar results were seen in a study by Lourdes *et al* evaluating reparative dentin bridge formation after 60 days of pulp capping[27].

The present study showed regular type of hard tissue bridge formation in 100% of MTA samples. In the BAG group, 20% regular and 53.3% irregular type was seen. The $Ca(OH)_2$ group showed 40% irregular type and no regular type of hard tissue bridge formation. Similar results were demonstrated with MTA showing dentin bridge formation to be more homogenous and continuos when compared to pulps capped with $Ca(OH)_2$[22]. Dentin bridges form as result of pulp irritation and/or inflammation, or alternatively due to stimulus from the material placed over the exposed pulp[25].

The ability of MTA to induce the formation of a dentine bridge may be due to its excellent sealing ability (Torabinejad *et al.* 1993, Bates *et al.* 1996, Fischer *et al.* 1998, Wu *et al.* 1998) or biocompatibility (Kettering and Torabinajed 1995, Torabinejad *et al.* 1997, 1998 Holland *et al.* 1999 Mitchell *et a*l. 1999, Kieser *et al.* 2000). Studies by Tziafas *et al.* have shown hard tissue bridge formation with MTA in 2 weeks to be irregular and can be clearly observed in 3 weeks. In the present study $Ca(OH)_2$ group showed higher rate of failure and more irregular type of dentin bridge formation. It has not been possible to identify whether the inductive effects of $Ca(OH)_2$ are due to release of calcium or hydroxyl ions (Schibich *et al.* 1978) and early work has suggested calcium ions are not necessary for the repair process (Glass and Zander 1949, Seltzer and Bender 1958). Despite many studies, the mechanism of action of this material remains unknown (Pashley 1996)[11].

BAG showed a higher rate of dentin bridge formation compared to $Ca(OH)_2$ in the present study. Similarly Haghoo and Naderi in their study on primary teeth reported that BAG was better than $Ca(OH)_2$ in terms of dentin bridge formation. BAG are biomaterials having osteoconductive property and can restore pulpal histology. It has been shown that BAG improves osteointegration. BAG has the capacity to serve as inductive material for had tissue bridge formation and mineralization but it has been shown that microscopic calcific bridges formed by $Ca(OH)_2$ does not constitute a continuos seal and may allow bacterial leakage through numerous defects[26 19].

Least inflammation was seen in MTA group (26.7%) followed by BAG (66.7%) and $Ca(OH)_2$ (100%). Mild inflammation was observed with MTA and BAG whereas $Ca(OH)_2$ group showed mild – moderate inflammation. The findings of the present study corroborates with a study by Briso & others when MTA showed decreased inflammatory infiltrate compared to $Ca(OH)_2$[30]. Abedi *et al.* (1996) found a significantly higher frequency of calcific bridge formation and less inflammation with MTA compared with calcium hydroxide[11]. However Iwanato *et al.* reported no difference between MTA and $Ca(OH)_2$ regarding hard tissue bridge & inflammatory infiltrate[11].

All samples capped with $Ca(OH)_2$ showed pulpal inflammation. In accordance with the present study, Junn *et al.* reported significant differences between amount of inflammation and degree of dentinal bridge formation in the MTA and calcium hydroxide groups[11]. Salako *et al*, found samples capped with BAG showed less

inflammation and normal pulp tissue than samples capped with $Ca(OH)_2$[26] which is in concurrence with the present study. Reasons attributed to this may be due to the biocompatibility and anti bacterial properties of BAG, whereas $Ca(OH)_2$ destroys the underlying healthy pulp tissue leaving a necrotic layer because of its alkaline pH.

In this study there were (100%) normal odontoblasts seen in the MTA group followed by BAG (26.7%) and $Ca(OH)_2$ (26.7%). Irregular type of odontoblasts were observed more in the $Ca(OH)_2$ group. It is believed that MTA has different effects on different tissues. In this study normal and regular odontoblasts were found, which may be due to the action of oxides and trioxides of MTA on the cells. MTA also stimulates the release of bone-like cells, which actively promote the formation of hard tissue. Sarkar *et al.* found that when in contact with synthetic tissue fluid, MTA triggers the precipitation of hydroxyapatite (HA) on its surface and in the surrounding fluid. Similar reports have been shown by Aeinechi *et al.* and Chacko and Kuriose in their studies comparing MTA and $Ca(OH)_2$. Sarkar *et al* found that MTA has different effects on different tissues[25]. Dammaschke *et al* in a study have mentioned that $Ca(OH)_2$ promotes the differentiation of odontoblast or odontoblast like cells and MTA has the same effects because of release of calcium and hydroxyl ions. Takita *et al* compared the effects of MTA and Dycal on human cells and concluded that MTA stimulated the proliferation of cells within 12 days whereas dycal showed no such effects. In vitro studies have showed that MTA is able to induce differentiation of pulp cells into odontoblast-like cells and the formation of reparative tertiary dentin[35].

Another finding that deserves attention is the remnants of pulp capping material assessment, which was done as further away from Dentin Bridge. In the present study $Ca(OH)_2$ groups had highest amount of remnants of pulp capping material (93.3%) and least with MTA (13.3%). Studies by Lourdes *et al.* have shown in 70% of the cases “little black coloured particles” of $Ca(OH)_2$ surrounded by macrophages after 30 days which was not observed in MTA groups. Because these particles might induce calcification similar to what occurs with dentin chips, their presence could have been responsible for retarding the healing process of $Ca(OH)_2$, although controversy exists as to whether these particles that have been accidentally forced into the pulp promote or retard healing[27].

Bioglass groups showed moderate amount of pulp capping material (60%) and absence of materials in 40% of the samples and. has shown to be more successful compared to calcium hydroxide among all the criteria evaluated. The present third generation of bioactive materials are being made resorbable and resorbable polymers are being made bioactive. Bioglass have the concept of osteoproduction and osteostimulation. They form a chemical bond with living tissues maintaining a rigid scaffold upon which cells migrate and grow. Progenitor cells are seeded onto these biologically active resorbable scaffolds. The cells grow outside the body and become differentiated and mimic naturally occurring tissues. With time the scaffolds are resorbed and replaced by host tissues that include a viable blood supply and nerves[19].

Histological evaluation of the pulp capping materials tested shows; MTA to be a superior material for pulp capping of mechanically exposed human pulps. The

results of this study should be carefully evaluated because the capping procedure was accomplished in sound teeth. In most clinical scenarios, the pulp exposure frequently occurs by a carious process in which the level of inflammation in much higher. The ideal would be testing these procedures under the aforementioned condition to verify the reproducibility of the findings reported in this clinical evaluation. However, although the use of vital healthy teeth for this kind of study has limitations, it still has the benefit of standardization and can be regarded as acceptable in respect to material selection and handling. Moreover further research with larger samples and longer follow-up is warranted.

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