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ORIGINAL ARTICLE

Direct pulp capping using Simvastatin and MTA in dogs' teeth: marginal adaptation SEM study

ABSTRACT

Aim: *To investigate the marginal adaptation of Simvastatin (Smv), Mineral Trioxide Aggregate (MTA), and the combination of the two materials after direct pulp capping (DPC) in dogs' teeth after three months.*
Methodology: *DPC was performed at random on 18 maxillary and mandibular incisors of two dogs. The pulpal exposures in class V cavities were capped with either Smv or Smv+MTA or MTA. All cavities were restored with Intermediate Restorative Material (IRM). After a 90-day follow-up period, the dogs were euthanised and the incisors were sectioned into two halves and studied under the scanning electron microscope (SEM). The interface between the DPC materials and pulp as well as dentine is examined for gap mean percentage to the total area of the DPC material.*
Results: *There was a statistically significant difference between Smv and Smv+MTA groups (P<0.05). Statistically, significant difference was neither observed between MTA and Smv nor between MTA and Smv+MTA groups (P>0.05). The highest mean gap area percentage value was recorded in the Smv+MTA group (3.750±1.802) followed by the MTA group (2.121±1.166) while the lowest gap percentage was recorded in the Smv group (1.339±1.271).*
Conclusions: *Simvastatin showed a good marginal adaptation property that encourages its use as DPC material.*

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Introduction

Direct pulp capping (DPC) is a procedure where a biocompatible material is applied on a vital exposed pulp to seal it preventing aggression of micro-organisms (1). Mineral Trioxide Aggregate (MTA) is a bioactive and cytocompatible material displaying consistent outcomes for pulp capping (2-4). It encourages pulp cell differentiation into dentinoblast-like cells as well as increasing angiogenic factors secretion (5). Comparing MTA to calcium hydroxide as a DPC agent, MTA exhibits a higher incidence of dentine bridge formation and a minor extent of pulpal inflammation (6). MTA yields great alkalinity of pH. Former studies of MTA physical properties have supported its effective marginal adaptation, sealing ability and low or no solubility. But still, its high cost and tooth discoloration are some of the main drawbacks (5, 6).

Simvastatin (Smv) is a 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor used as a drug to lower cholesterol. It is well established that Smv has multiple influences on the induction of angiogenesis and bone formation (7-9):

-has a beneficial effect on repair and regeneration especially when an implant is needed (10);

-showed good results in the treatment of periodontal diseases (11);

-reduces periodontal ligament spaces subjected to the induction of periapical disease of rats' teeth (12).

Previous trials have confirmed that dental pulp stem cells (DPSC) handled with Smv at 1 µmol/L displayed increased growth factors angiogenesis and dentinoblastic differentiation in addition to improved Alkaline Phosphatase activity and development of mineralized nodes (13-16). Similarly, an animal experiment obtained an enhancement of DPSC induced pulp regeneration after pulpotomy with Sim at 1 µmol/L (14).

A recent study investigated the dentine thickness and continuity after direct pulp capping using Smv and MTA. There was no statistically significant difference between MTA and Smv at 0.5% and 1.5% (17). Moreover, Smv has a strong anti-inflammatory action preventing the inflammatory process induced by lipopolysaccharide (LPS) (18).

Marginal adaptation is one of the essential physical properties of a proper DPC material to have to resist the microleakage throughout its entire thickness. Consequently, the biological response of the pulp towards the DPC will be improved (19). Numerous studies analyzed the MTA marginal adaptation as a retrograde filling using a Scanning Electron Microscope (SEM), where it showed a good adaptation (19-21). Some researchers examined the dentinoblastic activity of MTA using SEM in DPC or in pulpotomy procedures. MTA showed the highest biological response (22, 23). Smv sealing ability was tested in the case of furcal perforation using dye extraction method and showed poor results (24). Several histological studies have been conducted to examine the histological response of pulp tissues to MTA and Smv but no immunohistochemical assessment of the dentine formed was done. No published data investigated the marginal adaptation of using Smv and MTA as pulp capping agents, especially in an animal model. So, we have adopted one animal model, where DPC procedure was performed on dogs' teeth.

Later, the work was divided into two parts according to the point of assessment. In the first part, the marginal adaptation of either Smv to pulp and dentine was assessed in comparison to MTA or their combination using SEM. In the second part, the biological behavior of the same tested materials using a histopathological and immunohistochemical evaluation was accomplished.

This paper is concerned about the marginal adaptation of the DPC materials. The rationale of this study is to find out a material that is comparable to MTA regarding the minimum micro-gaps at the interface between Smv and dentine as well as the pulp.

Our null hypothesis that there is no sig-

nificant difference among the three tested DPC agents; Smv, Smv+MTA and MTA. The present study was designed to compare the marginal adaptation of using Smv, Smv+MTA and MTA as DPC materials in dogs' incisors, over three months using SEM.

Materials and Methods

The present part of the animal study started after the approval of Research Ethical Committee (REC), Faculty of Dentistry, Suez Canal University, Ismailia, Egypt (Registration No. 212/2019). We worked according to the ethical guidelines and regulations of the International Guiding Principles for Biomedical Research Involving Animals (Geneva, 2012). This study was carried out on 2 Mongrel dogs at the age of 2 years old and with a weight of 15-18 kg having permanent dentition. Housing, operative procedures, and sacrificing were done at the Department of Veterinary Surgery, Faculty of Veterinary Medicine, Suez Canal University.

Sample size determination
G* power statistical analysis software was used to determine sufficient sample size (25). The sample size was determined on a sample population of 18 incisors with an α error probability of 0.05, effect size f of 0.82 , and a 0.8 power (1-β). Five maxillary and four mandibular incisors were capped for a total of nine incisors in each dog (total sample size=18) (26).

Operative procedure
Dogs were kept under the same managemental and nutritional regimens during the experiment. Food and water were withheld 6-8 hrs before anesthesia. Each dog was premedicated with I/M injection of chloropromazine hydrochloride (Misr Co. Pharm. Industries, S.A.A, Cairo, Egypt) in a dose of 1mg /kg. The site of operation was aseptically prepared, and then general anesthesia was conducted by I/V injection of thiopental sodium (Sandoz GmbH, Kund, Austria) 2.5% solution until the main reflexes disappeared. After ensuring dryness of the field using cotton rolls and separating the jaws by a modified plastic syringe, the teeth were subjected to a class V preparation on their labial surface coronal to the gingival margin. Inverted cone bur size 1 (Dentsply Maillefer, Tulsa, Oklahoma, USA) at high speed (30,000 rpm) contra-angle handpiece (NSK, Tokyo, Japan) was used under a water coolant until the pink color was noticed at the floor of the cavity but without exposure. Later, the exposure was achieved by a sharp probe to standardize the size. Bleeding was controlled after a few seconds with a moistened cotton pellet by 2.5 % sodium hypochlorite NaOCl (Clorox; Household Cleaning Products of Egypt, Cairo, Egypt) and sterile cotton pellets pressed over the exposure site (17). Rinsing the cavity was done using normal saline (El Fath, Cairo, Egypt) and later the cavity was dried and prepared to receive the DPC material.

Grouping of teeth according to the experimental DPC material
Samples randomization
One of the co-authors who was not involved in the clinical procedure performed the blind allocation of the teeth after running randomization that was done for grouping by Microsoft Excel. Incisors were randomly and equally divided into three groups according to the DPC material applied to the exposure site (n=18) according to the following:
Group A (n=6): using Smv (Sigma-Aldrich, St. Louis, MO, USA); tablet was ground and weighted to obtain 1.5 mg (13, 17, 18) and then mixed with distilled water to produce a creamy mix.
Group B (n=6): using Smv+ MTA (Angelus, Londrina, Brazil); the mixture was prepared where the ratio of the powder of ground tablet Smv (1.5 mg) to MTA to the distilled water is 1.5:1.5:1 to obtain a creamy mix.
Group C (n=6): using MTA; it was prepared where the ratio of the powder to the distilled water is 3:1, according to the manufacturer's instructions.
The DPC material was then applied to the exposure site using a plastic instrument and compacted with a hand plugger. Later, final restoration was placed using Inter-

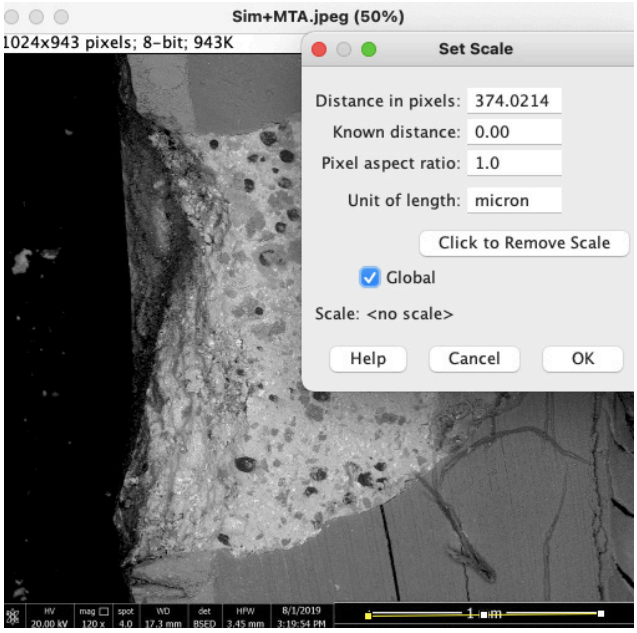

Figure 1
Photograph showing image analysis by image J software for setting image scale.

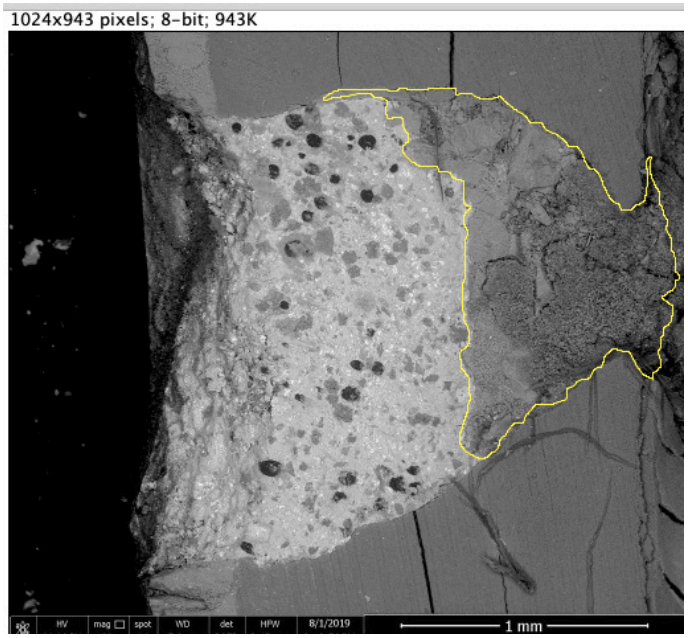

Figure 2
Photograph showing image analysis by image J software for total area selection of the DPC material.

mediate Restorative Material (IRM) (Dentsply, Charlote, U.S.A).

Euthanasia and jaw sectioning
Dogs were clinically observed daily for a follow-up period of 90 days during the study period for recording any postoperative complications. They were then euthanised by thiopental sodium overdose. The teeth contained within bone pieces were removed and reduced in size to fragments measuring approximately 3 mm of coronal height and 3 mm of root height. The samples were stored in buffered 10% formalin at 4 °C for 72 h. Then teeth were then dried before the SEM evaluation.

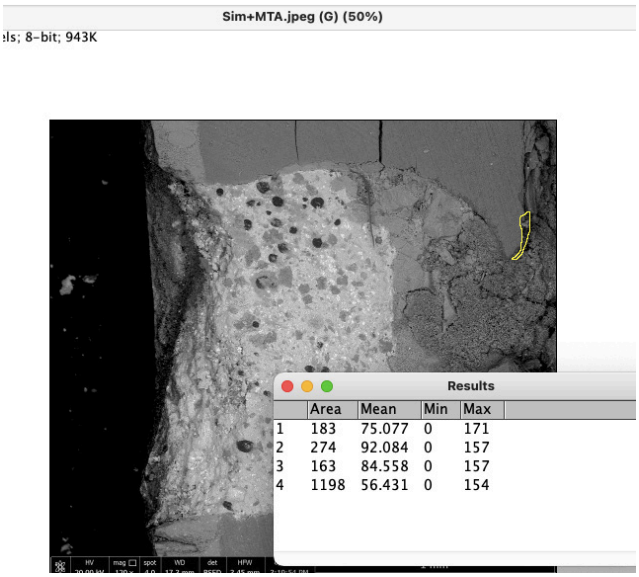

Figure 3
Photograph showing image analysis by image J software for measuring and analysis of gap area.

SEM evaluation
Sectioning of the teeth
The teeth were carefully notched in a labiolingual direction by a diamond disc to obtain a crack. Afterward, by using an isomet low-speed the samples were cut into two halves. The samples were washed using saline and only the better half was used for the evaluation.
Preparation of samples for SEM evaluation
The samples were dehydrated in sequence with 80% alcohol for 15 minutes, 90% alcohol for 15 minutes, and 100% alcohol for 20 minutes. The coronal portion of the samples was viewed under SEM (Model Quanta, FEI, Eindhoven, Netherlands) at 20 kV with 120-180X, 1000X, and 4000X magnifications. The marginal

adaptation of the DPC material to the pulp and dentine was evaluated using an image analysis software (Image J version 1.53e; National Institutes of Health, Bethesda, MD, USA). The scale measurement was calibrated for each image to micron (Figrure 1). Each photomicrograph was analyzed by measuring the total area of the DPC (Figure 2), then the gap percentage was measured to the total area after adding all areas of gaps at the interface of the DPC material to the pulp and dentine (Figure 3) according to the following equation (Gap%=addition of the gap areas at the interface between the DPC material and pulp and dentine/total area of the DPC material X100). Two calibrated examiners assessed readings blindly, where each one of them repeated the assessment two times within a week to check the intra-examiner reliability. Additionally, comparing both examiners showed the reliability between them (inter-examiner reliability).

Statistical analysis

The raw data were subjected to preliminary testing to verify the normality of the results using Kolmogorov-Smirnov and Shapiro-Wilk tests. The mean and standard deviation (SD) values were calculated for each group. Comparison among the 3 groups was conducted using the One-Way Analysis of variance (ANOVA) test at a significance level of P≤0.05. Then multiple pairwise comparisons between groups were performed using Tukey's post hoc test using SPSS software version 26 (IBM, Armonk, NY, USA).

Results

One-way ANOVA test displayed a statistically significant difference between groups at p-value ≤0.05 (p=0.032). Analysis of Tukey's post hoc test revealed a significant difference between Smv and Smv+MTA groups (p=0.028). Whereas there was no statistically significant difference between the MTA and Smv+MTA groups (p=0.157). Additionally, no significant difference between MTA and Smv groups (p=0.624). The highest mean gap area percentage value was recorded in Smv+MTA group (3.750±1.802) followed by MTA group (2.121±1.166) while the lowest gap percentage was recorded in Smv group (1.339±1.271) (Table 1, Figure 4).

Discussion

The prognosis of DPC depends upon many factors. One factor is the quality of the DPC material adaptation to prevent microbial ingress; accordingly pulpal healing predictably happened (27). Poor adaptation of DPC materials to dentine results in gaps and causes fluid fluctuations into dentinal tubules (28). Whenever the DPC material is capable of providing the biological seal, the result will be towards dentine bridge formation and regeneration (26, 27, 29). Dogs were selected as an animal model due to the similar dentine synthesis as human beings. Despite the difference in the rate reparative dentine formation, dogs' pulps are equivalent to that of humans. Interestingly, the size of the pulp offers a proper sample for the histopathological

Table 1

Mean and standard deviation of gap area percentage values in the three tested groups

Groups	No. of samples	Mean±SD	P-value
Smv	6	1.339^{b}±1.271	0.032*
Smv+MTA	6	3.750^{a}±1.802	
MTA	6	2.121^{ab}±1.166	

Mean values with the same superscript letters are not statistically significant at P≤0.05.
Mean values with different superscript letters are statistically significant at P≤0.05.

evaluation. Furthermore, dogs afford a wide range of teeth that can permit the comparison of different materials in the same dogs (22, 30). DPC was conducted and then the assessment was done in two parts. The first part was completed to evaluate the marginal adaptation of the tested materials. The second part was completed to examine the biological effect of the tested materials through histopathological and immunohistochemical analysis.

This article is concerned about the marginal adaptation of Smv, a mixture of Smv+MTA and MTA using SEM after 90 days to assess the long-term adaptation of the tested materials and hence the advanced pulpal response. Adaptation of Smv as a DPC material was not investigated previously. That is why we have chosen this point of investigation in an animal model to simulate the clinical situation. MTA is considered the gold standard DPC material of choice (5, 6).

In a recent study by Dianat et al. they recommended that the addition of Smv to MTA may enhance the pulpal repair (17). Proper partial isolation was followed in the study before starting the cavity and it was ensured through the procedure (30). Class V cavity in anterior teeth was chosen rather than Class I in posterior teeth to avoid any variation in the occlusal force that might affect the results (22). Mechanical Pulpal exposure was achieved by a sharp explorer to prevent pulpal damage that might be

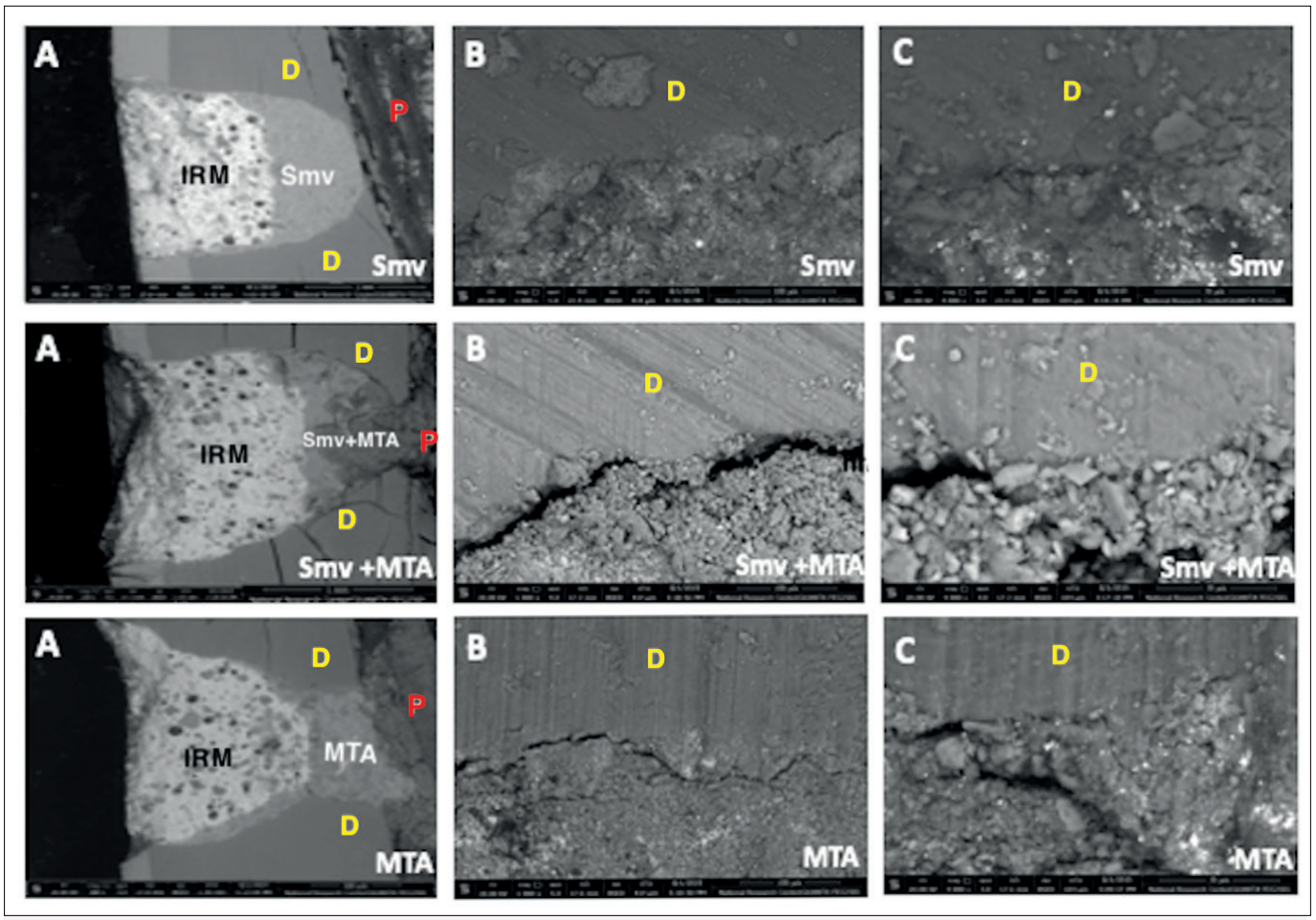

Figure 4
Representative SEM micrographs displaying cavities filled with Smv, Smv+MTA, MTA then IRM at A) 120X, B) 1000X, C) 4000X representing the interfaces between DPC materials and dentine as well as pulp. Where D stands for Dentine and P for Pulp.

happened by using a bur, to ensure that pulpal exposure would be consistent in size (29). IRM was used as a coronal restoration as it was recommended due to its acceptable compressive strength and hardness that could be placed for a year (31). SEM was used for evaluation because it is considered the main tool to measure the tooth structures/material interface (19, 20, 22, 23, 27, 28). However, using a non-destructive tool such as micro-computed tomography (μCT) could be beneficial. This might be a limitation in our study, but the use of μCT is costly and difficult to work with.

We partly rejected the null hypothesis, as we found a significant difference between Smv+ MTA and Smv groups. On the other hand, a significant difference was neither obtained between Smv and MTA, nor between MTA and Smv+MTA groups. The highest mean of gap area percentage value was obtained in the Smv+MTA group. Previously, combining Smv+MTA showed lower cell growth, decreased Alkaline Phosphatase activity , and decreased levels of mineralization markers than combining Smv + αTricalcium phosphate cements (32). On the other hand, Dianat at al. demonstrated that 1.5% Smv gel below MTA showed active pulpal repair with well-formed dentine when placed as a DPC material in all of the samples treated with this combination (17). Different study designs, concentrations, and forms of the Smv combination might be the reason for such discrepancies in results. High gap (%) in this group might be because of the lack of any chemical or mechanical bond to both dentine and pulp. Smv group revealed the lowest mean of gap area percentage value. Many studies showed the beneficial action of Smv on DPSC differentiation and its potent anti-inflammatory action that can enhance pulpal regeneration (13-18). Likewise, its valuable effect on apical periodontitis adds to its advantages (12). Nevertheless, a recent study exhibited an adverse effect of Smv on osteoblast differentiation but it was a time-dose dependent reduction in cells (33). They found a decrease in cell viability and a significant increase of mineralization in a late mineralization stage while the alkaline phosphatase turnover was unaltered (33). Higher concentrations of Smv have caused increased rates of cell death. The use of simvastatin as a pulp capping material requires a thorough evaluation of the optimum dose (13, 17, 34, 35). That is why we used 1.5 mg of Smv in the current study. Although there was no statistically significant difference between MTA and Smv, MTA group showed a higher mean of gap area percentage than Smv of mean 2.12 μm, but lower than the previous study where the mean value was 4.92 μm (36). MTA has a slow setting reaction that might participate in leakage and surface disintegration that causes loss of marginal adaptation (31).

In accordance with the mean of gap area percentage we detected in the MTA group, Torbinejad et al. noticed a gap equal to 2.5 μm (20). A study emphasized the superior sealing ability of MTA due to 1.5 μm MTA particles which are smaller than the diameter of some dentinal tubules (2-5 μm) (37). They added that formation of a hydraulic seal after hydration is one of the main causes of sealing ability (37). Likewise, an insoluble barrier might be formed against microleakage (20). All the previously mentioned studies were carried out to assess MTA marginal adaption as a retrograde filling material. Smv showed a comparable marginal adaptation as good as MTA. Further long-term studies are required to support our findings with larger sample size. More physical properties are required to be studied such as push-out bond strength, compressive strength, and hardness of Smv.

Conclusions

Under the limitation of this study, taking into consideration Smv's low price, superior Smv marginal adaptation in the present study favors its use as a DPC material.

Clinical Relevance

This study emphasizes that simvastatin has a good marginal adaptation in comparison to the gold standard direct pulp capping agent (MTA). Thus, Smv can be a

promising material to be used in direct pulp capping treatment with favourable outcome. It is important to find an inexpensive alternative to MTA which displays good biological and physicochemical properties.

Conflict of Interest

The authors declare that there is no conflict of interest.

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