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In Vivo Evaluation of Treatment Outcomes of Pulpotomy Medicaments with and Without Simvastatin - A Longitudinal Study

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Abstract

Introduction: In modern day dentistry, the usage of regenerative materials has caught the attention of many clinicians. Simvastatin which is a cholesterol lowering agent enhance the healing potential of these materials and this study aimed to evaluate and compare clinical and radiographic success of Biodentine and alpha -TCP with and without simvastatin as a pulpotomy medicament in primary molars at 3,6 and 9 months intervals.

Method: 60 primary molars were selected from 44 children based on the selection criteria. They were randomly divided into 4 groups of 15 teeth each. Group 1(Biodentine) Group 2(Biodentine + Simvastatin) Group 3(Alpha-TCP) and Group 4(Alpha-TCP+ Simvastatin.) The pulpotomized teeth were evaluated clinically and

radiographically at 3, 6 and 9 months interval. The data was subjected to Fisher exact test and Cochrane test.

Results: The results showed a 100 % clinical success in the Biodentine + Simvastatin group which was followed by Biodentine (84.6%). Radiographic success was also higher in Biodentine+Simvastatin (83.3%) group, followed by Biodentine, Alpha-TCP+Simvastatin and Alpha-TCP.

Conclusion: Biodentine + Simvastatin can used as a medicament for pulpotomy in primary teeth. Simvastatin enhances the pulp healing potential of both Biodentine and α-TCP.

Keywords: Biodentine, Simvastatin, Alpha TCP, Pulpotomy.

Introduction

Pulpotomy is still the most common treatment for cariously exposed pulps in asymptomatic primary molars. A wide range of materials and techniques, such as formocresol (FC), glutaraldehyde, ferric sulfate (FS), calcium hydroxide (CH), mineral trioxide aggregate (MTA), electro surgery, and lasers, have been used over the years in primary molar pulpotomies. Although FC has long been considered the gold standard for pulpotomy studies, concerns about FC have led clinicians to use alternative techniques or agents that are more tissue compatible. Studies have been conducted on the effectiveness and safety of more biocompatible and regenerative alternatives. Regeneration approach includes pulpotomy agents that have cell-inductive capacity to either induce existent cells or replace lost cells to differentiate into specialised tissues [1]. Hence, priority has changed from preservation to regeneration, materials with better biologic properties such as improved antibacterial activity, ability to form odontoblast like cells, less cytotoxic activities have been introduced. Biodentine™ (Septodont), a new tricalcium silicate-based restorative material, is one of them. It presents good biocompatibility with human dental pulp cells and has high antibacterial and antifungal property [2]. Alpha-tricalcium phosphate (alpha-TCP), a biodegradable ceramic having osteoinductive and bone regenerative potential, has also been reported to be a promising material. Simvastatin is widely used as a cholesterol lowering agent in the prevention and treatment of atherosclerosis and has certain pleiotropic effects including an anti-inflammatory effect and improves angiogenesis and vascular endothelial cell function [3]. Various studies have been performed in the field of dentistry to determine the effect of statin and has proved to be effective as a pulp capping material where it accelerates reparative dentin formation. Hence, the current study evaluated and compared the use of Biodentine and alpha-Tricalcium phosphate (TCP) as pulpotomy agents with and without simvastatin.

Methodology

60 carious teeth selected from 44 children aged between 4-9 years fulfilling the selection criteria were included in this study.

Inclusion criteria:[4]

- Healthy cooperative patient.
- Carious exposure of vital pulp.
- No clinical and radiographic evidence of pulpal degeneration.
- Radiographic evidence of presence of 2/3rd of the root.
- Possibility of proper restoration of primary molars.
- Children with prior parental consent.

Exclusion criteria:[4]

- Continuous pain.
- Abscess or fistula in relation to teeth.
- Tooth close to natural exfoliation.
- Presence of inter radicular bone loss.

- Evidence of internal resorption.

Topical anaesthesia was applied with 8% lidocaine and 0.8 % dibucaine gel before 2% lignocaine with 1:80000 adrenaline local anaesthetic solution was administrated. Isolation was obtained with rubber dam. Caries was removed with slow speed No.6 round bur and the cavity outlines was established with high speed straight fissure diamond burs. The pulp chamber was then deroofed followed by irrigation to remove dentinal debris. Coronal pulp amputation was achieved with slow speed No.6 round bur. The remaining pulp tissue was excavated with sterile spoon excavators and the chamber was irrigated with saline. Hemorrhage was controlled by applying pressure with wet sterile cotton pellets. On achieving haemostasis, the radicular pulp was assessed and the freshly prepared mixture of respective medicaments was placed accordingly.

Group 1 (15 teeth) Bio-dentine.

Group 2 (15 teeth) Bio-dentine + Simvastatin.

Group 3 (15 teeth) α-Tricalcium phosphate.

Group 4 (15 teeth) α-Tricalcium phosphate + Simvastatin

The access cavity was then restored with resin modified glass ionomer cement. The tooth was then be restored immediately, with a stainless-steel crown cemented with glass ionomer cement. All the patients were followed for 3,6 and 9 months and assessed both clinically and radiologically.

Clinical and radiographical evaluation at 3,6 and 9 months intervals were done using following criteria. [5]

Clinical criteria:[5]

1. Pain
2. Percussion
3. Swelling
4. Fistula formation
5. Pathologic tooth mobility

Radiological criteria: [5]

1. Pathological interradicular radiolucency
2. Internal resorption
3. External root resorption
4. Widening of periodontal space
5. Calcification of canal

If the tooth exhibited any one or more than one of the above features, the pulpotomy will be considered as failure. The results obtained were subjected to statistical analysis.

Statistical Analysis

Fisher exact test was used to compare the clinical & radiographic parameters between the four groups at each time interval. Cochran's Q test was used to compare the clinical & radiological parameters between the time intervals in each group. The level of significance was set at $P<0.05$.

Results

Table 1: Shows the comparison of clinical success of the materials at 3,6 and 9 months 100% success was seen in Biodentine + Simvastatin group at 3,6 and 9 month. Whereas, there is a decrease in success rate in biodentine group from 92.3% at 3rd month to 84.6% at 6 and 9 months. In TCP group, the success rate was 83.3% in 3rd month, which decreased to75% at the end of 6 and 9 months. The alpha TCP +simvastatin group showed a decrease in success rate from 84.6% at the 3rd month to 69.2% at the end of 6 and 9 months. However, there was no statistical significant difference between the groups.

Table 2: The radiographical success of Biodentine + Simvastatin group was 83.3% in the 3rd month, which decreased to 75% in the 6 months but at the end of 9 months it increased to 83.3% as 1 tooth showed the signs of healing. Whereas, biodentine group showed decrease in the success rate from 92.3% in the 3rd month to 69.2% at 6 and 9 months. In TCP +simvastatin group

showed decrease in success rate from 69.2% in the 3rd month to 61.5% at the end of 6 and 9 months and in alpha-TCP group the success rate was 58.3% in the 3rd month, which decreased to 50% at the end of 6 and 9 months There was no statistical significant difference between the groups.

Discussion

Untreated caries is one of the possible causes of pulp exposure which was traditionally treated with root canal therapy. However today, the management strategies of exposed pulp aim to overcome the limitation of pulpectomy, which makes the tooth non-vital to the selection of the vital pulp techniques such as pulpotomy as the treatment of choice.[6]

For the past 90 years, formocresol has been the most preferred pulpotomy medicament for primary molars[8]. However, due to its undesirable consequences such as mutagenicity and carcinogenicity, the usage of formocresol has been questioned.[7]Owing to these concerns, various other medicaments such as glutaraldehyde, ferric sulfate were tested and have shown a varied clinical success. In spite of clinical success, these pulpotomy technique has been questioned for safety and effectiveness. The paradigm shift from mere preservation to regeneration in endodontics has promoted materials like MTA, Biodentine, Pulpotec, freeze dried-bone, Emdogain as an alternative vital pulp therapy medicament. With improvement of medicaments, that are not only biocompatible but also bio inductive, the focus has been directed from preservation and conservation to regeneration of the remaining pulp tissue. In the recent years special attention has been given to Biodentine in vital pulpotomy of primary teeth.

Biodentine was firstly introduced in 2009 by Septodont and it is another calcium silicate cement with high alkaline pH 12.[2,9] It is non-cytotoxic and non-genotoxic in pulp fibroblast at any concerntration and stimulates dentine regeneration by inducing odontoblasts differentiation from pulp progenitor cells and promotes mineralization, generating a reactionary dentine as well as dense dentine bridge.[9] A new material similar to hydroxyapatite has been widely studied for reconstruction of osseous defects in orthopedic surgeries, neurosurgeries, and maxillofacial surgeries.[10] It is the alpha-tricalcium phosphate (α-TCP) bone cement that is an apatite carbonate formed by the mixture of the α-TCP with calcium carbonate and monocalcium phosphate monohydrate powder. The α-TCP is more soluble and biodegradable than β-TCP.[11] Calcium and phosphate ions act as a signal for regulating cell function/differentiation in addition to acting as one of the building blocks for hydroxyapatite mineral. Tada et al, suggested that elevated extracellular calcium and phosphate increases BMP-2 expression through cyclic adenosine monophosphate–dependent protein kinase and extracellular signal regulated kinase 1/2 pathways in HDPCs[12]. This increase in calcium and phosphate ions further act as a signal for cell proliferation and mineralization in the TCP group.[12] Because of its biodegradable, osteoinductive, osteoconductive and bone regenerative potential recently, this, fast-setting α-Tricalcium-phosphate (TCP) cement was used as in pulp capping process and reported to be a promising material.

Statins are widely used as a cholesterol lowering agent in the prevention and treatment of atherosclerosis. Simvastatin has certain pleiotropic effects including induction of angiogenesis, osteoblastic differentiation and thereby promoting mineralization in non-mineralizing osteoblasts through the induction of BMP-2(bone morphogenic protein-2) and osteocalcin, anti-inflammatory effect and improves vascular endothelial

cell function. Various studies have been performed in the field of dentistry to determine the effect of statin in vitro and in vivo[13], Simvastatin-treated dental pulp stem cells have been reported to exhibit odontogenic differentiation in vitro.

When combined with Biodentine, calcium silicate cement (biodentine), which already has properties favourable for dentin and bone repair, it's plausible that the combination could enhance the regenerative capacity of Biodentine.[13] This combination might lead to improved outcomes in procedures like regenerative pulpotomies, where preservation of dental pulp and promoting dentin regeneration are crucial. The addition of simvastatin could potentially enhance the dentin regeneration process, leading to better healing and possibly even faster recovery times.

Studies have demonstrated a considerable increase in cell proliferation, an increase in ALP activity (an odontoblast differentiation marker), and a quicker cellular attachment when simvastatin is combined with α-TCP, a biodegradable ceramic. Research has also demonstrated that the osteoconductive effects of α-TCP is increased, when it is coupled with simvastatin, leading to an increase in odontoblastic differentiation property.[14] The studies done by Mahendran et al in 2020, demonstrated that mineralized tissue development of α-TCP treated with simvastatin was similar to that of MTA.[10] Statin which are widely used as a cholesterol lowering agents is found to have an anti-inflammatory effect.[14]This property of statins also helps to restore the inflamed pulp tissue. The combinations of simvastatin with α-TCP opens a new avenue in regenerative endodontics as pulpotomy agents. However, till date there are no in vivo studies, that have evaluated the effect of simvastatin with Tricalcium phosphate and Tricalcium silicate cements as pulpotomy agents. Hence, the study aimed to compare and evaluate the clinical and radiographic success of Biodentine, Biodentine + simvastatin, TCP and TCP +Simvastatin at 3,6 and 9 month follow-ups.

The study demonstrated a good success rate in Biodentine +Simvastatin group both clinically and radiographically, as a pulpotomy medicament in primary teeth followed by Biodentine, α-TCP+Simvastatin, α-TCP. It was interesting to note that the radiographic success of Biodentine + Simvastatin increased from 75% in the 6th month to 83.3% in the 9th month as a tooth with internal resorption showed signs of healing, Parisa Sanaei et al, 2021 reported that Biodentine can be successfully used to manage internal resorption due to its dentine regeneration property.[21] In biodentine the hybrid zone formed is impermeable to toxins and there is increase in carbonate content of interfacial dentin, preventing the microleakage which might be a reason for healing of internal resorption as reported by the study done by Atmeh AR et al.[22] Clinical success rate of Biodentine +Simvastatin was 100%, Mundy et al, concluded statins has a ability to accelerate mineralized tissue formation in vivo and it is also shown to accelerate BMP-2 expression and enchance bone formation.[18] When simvastatin which is an anti-inflammatory was coupled with biodentine, it enhances odontoblastic differentiation in Human Dental Pulp Stem Cells.[13] The ability of biodentine to release calcium is the key factor for success as calcium increases differentiation, proliferation and mineralization of pulp cells.[17] Ramanandvignesh et al, Ying et al, reported similar clinical success rates after 1 year.[15,16]

In the present study α-TCP + simvastatin group showed better radiographical success when compared to α-TCP group alone. An invitro study done by Kavitha et al,2019 found that simvastatin with alpha TCP was effective in

inducing dentin bridge formation, comparable to MTA.[10] Research has also demonstrated that the osteoconductive effects of α-TCP is increased, when it was coupled with simvastatin, leading to an increase in odontoblastic differentiation and anti-inflammatory effects[14]. Chohayeb et al stated that TCP can be used as potential alternative for pulp capping agents in exposed pulp.[23] Nyan et al, 2010 showed that when combined with Alpha TCP particles ,0.1 mg of simvastatin was optimal for stimulation of maximum bone regeneration in rat calvarial defects without inducing inflammation.[19] The present study has 0.05 mg of Simvastatin. More studies with bigger sample size and varying concerntration of simvastatin should be done to evaluate the effect of these material.

Conclusion

Combination of Biodentine + Simvastatin group showed 100% clinical success. However, there was no statistical significant difference between the groups. Simvastatin when combined with biodentine enhances the anti inflammatory action, stimulates growth factors and promotes reparative dentine formation. Hence, the combination of simvastatin with biodentine can be used as a promising alternative for vital pulpotomy materials in primary teeth.

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Legend Tables

Table 1:

	Clinical	3 Months	6 Months	9 Months	Cochran test
Biodentine	Success	12 (92.3)	11 (84.6)	11 (84.6)	Cochran's Q=2 P=0.999 P=0.368
	Failure	1 (7.7)	2 (15.4)	2 (15.4)	
	Total	13 (100)	13 (100)	13 (100)	
B+S	Success	12 (100)	12 (100)	12 (100)	NA
	Failure	0 (0)	0 (0)	0 (0)	
	Total	12 (100)	12 (100)	12 (100)	
TCP	Success	10 (83.3)	9 (75)	9 (75)	Cochran's Q=2 P=0.999 P=0.368
	Failure	2 (16.7)	3 (25)	3 (25)	
	Total	12 (100)	12 (100)	12 (100)	
TCP+S	Success	11 (84.6)	9 (69.2)	9 (69.2)	Cochran's Q=4 P=0.333 P=0.135
	Failure	2 (15.4)	4 (30.8)	4 (30.8)	
	Total	13 (100)	13 (100)	13 (100)	

Table 2:

	Radiological	3 Months	6 Months	9 Months	Cochran test
Biodentine	Success	12 (92.3)	9 (69.2)	9 (69.2)	Cochran's Q=6 P=0.111 P=0.05
	Failure	1 (7.7)	4 (30.8)	4 (30.8)	
	Total	13 (100)	13 (100)	13 (100)	
B+S	Success	10 (83.3)	9 (75)	10 (83.3)	Cochran's Q=1 P=1.000 P=0.607
	Failure	2 (16.7)	3 (25)	2 (16.7)	
	Total	12 (100)	12 (100)	12 (100)	
TCP	Success	7 (58.3)	6 (50)	6 (50)	Cochran's Q=2 P=0.999 P=0.368
	Failure	5 (41.7)	6 (50)	6 (50)	
	Total	12 (100)	12 (100)	12 (100)	
TCP+S	Success	9 (69.2)	8 (61.5)	8 (61.5)	Cochran's Q=2 P=0.999 P=0.368
	Failure	4 (30.8)	5 (38.5)	5 (38.5)	
	Total	13 (100)	13 (100)	13 (100)	