A. Agrafioti, D.G. Giannakoulas*, C.G. Filippatos, E.G. Kontakiotis

Department of Endodontics, School of Dentistry, National and Kapodistrian University of Athens, Athens, Greece
**School of Dentistry, National and Kapodistrian University of Athens, Athens, Greece*

email: agrafiot@dent.uoa.gr

DOI: 10.23804/ejpd.2017.18.04.03

Analysis of clinical studies related to apexification techniques

ABSTRACT

Aim *The aim of this study was to gather all the clinical studies regarding apexification and artificial apical barrier techniques, point out the possible differences of the clinical procedures and investigate how these are changing over time.*

Materials and methods *An electronic search was carried out in PubMed, covering the period from March 1968 to July 2015. More articles were retrieved by hand-searching or by the reference section of the included articles. Specific criteria were set in order to determine the relevance of each study.*

Results *One hundred and thirty eight articles were included, 53% of them concerned apexification with MTA plug. Long term apexification studies demonstrated 13% for a single change of the intracanal medicament and 85% for two or more. In 13% of the studies concerning artificial apical plug, the procedure included a single visit. Calcium hydroxide was left in the root canal for 3–12 months in 59% of the long term apexification studies, for 12-24 in 42% and for 24 months or more in 10%.*

Conclusion *Both techniques can lead to favourable clinical outcomes. There is a tendency for the artificial apical barrier apexification over the years, which usually includes the use of intracanal medicament for a short time.*

Keywords *Apexification; Calcium hydroxide; MTA; Open apex.*

Introduction

Teeth with necrotic pulp and open apex bring about several challenges to clinicians due to the lack of natural apical constriction and the thin root walls that are prone to fracture [Trope, 2006, Camp, 2008]. In order to confine filling materials into the root canal space and prevent overfilling, the placement of an artificial apical barrier and/or the closure of the apex are necessary before obturation of the root canal system [Trope 2006].

The traditional approach to handle cases with open apex is the multiple-visit apexification treatment with the use of calcium hydroxide (CH) as intracanal medicament [Seltzer, 1988]. The frequency of changes of CH from the root canal constitutes a controversial topic as there are studies that propose that a single placement of this medicament is enough to achieve predictable outcomes [Chawla 1986], whereas others claim that multiple replacements of CH could lead to a more rapid formation of a calcified tissue barrier [Abbot 1998]. The time required for the calcified tissue barrier to form varies from 5 to 20 months [Sheehy and Roberts, 1996] and seems to be influenced by several factors such as opening of the apex, frequency of intracanal medication replacement, age of the patient and the presence of periapical radiolucency [Mackie et al., 1988; Finucane and Kinirons, 1999; Kleier and Barr, 1991].

CH apexification has high clinical success rates and most of the teeth exhibit a calcified barrier at the blunt apex [Sheehy and Roberts, 1996; Mendoza et al., 2010]. However, despite the high success rate of CH apexification, several limitations led to seek for alternative treatment modalities. The long time for the apical barrier to be formed, the multiple visits for completion of the treatment, the possibility for coronal microleakage during treatment as well as the lower resistance to fracture of the teeth are some of those disadvantages [Andreasen et al., 2002; Andreasen et al., 2006; Rosenberg et al., 2007].

Torabinejad and Chivian [1999] proposed the use of mineral trioxide aggregate (MTA) as an artificial apical plug for the treatment of teeth with open apex. MTA has the main advantages of inducing a hard tissue barrier in contact to its surface [Shabahang et al., 1999] and setting up in the presence of moisture [Torabinejad et al., 1995]. MTA apexification treatment can be completed in a single visit or in two or more visits with the use of CH as intracanal medicament [Witherspoon et al., 2008; Nayar et al., 2009]. In a systematic review of the literature, Chala et al. [2011] report that the clinical success of MTA plug apexification does not differ from that of CH apexification. More recently, other biomaterials such as Biodentine (Spetodont) and calcium-enriched mixture (CEM) have also been used as artificial apical barriers in cases of pulpless teeth with open apex [Khetarpal et al., 2014; Asgary and Fazlyab, 2014].

In recent years, regenerative endodontic procedures (REPs) have been used to treat teeth with necrotic pulp and open apex [Kontakiotis et al., 2014]. Those techniques aim

to achieve healing of apical periodontitis, and thickening and/or lengthening of the root walls based on the core principles of tissue engineering [Kontakiotis et al., 2015]. Since 2001, many studies have been published in the literature presenting the use of REPs with signs of clinical success [Kontakiotis et al., 2014; Kontakiotis et al., 2015].

Apexification treatment has been implemented in teeth with open apex for more than 40 years. Several differences can be found among the relevant studies in the way the apexification procedures are carried out. Regardless the type of apexification (long-lasting use of CH or use of artificial apical barriers), the type of apical barrier, the number of visits, the use of intracanal medicaments and its time of permanence in root canal, apexification procedures appear to lead to favourable clinical outcomes. Certainly, it is pretty important and helpful to clinicians to gather and analyse the clinical articles related to apexfication treatment via a systematic approach of the international literature. Regenerative endodontic procedures were not taken into account in this review, as there are already studies that have gathered the related clinical articles and analysed the implemented protocols [Kontakiotis et al., 2014; Kontakiotis et al., 2015].

The purpose of this review was to retrieve all clinical studies related to apexification treatment in teeth with open apex, point out the differences in treatment procedures among them, detect how these procedures are changing over time, as well as to survey the percentages of clinical success and apical closure of the aforementioned techniques.

Materials and methods

An electronic search in PubMed database was carried out covering the period from March 1968 to the second week of July 2015. Appropriate MeSH (Medical Subject Headings) terms for this search were formed: (((open[All Fields] AND ("Apex"[Journal] OR "apex"[All Fields])) OR (("calcium hydroxide"[MeSH Terms] OR ("calcium"[All Fields] AND "hydroxide"[All Fields]) OR "calcium hydroxide"[All Fields]) AND ("apexification"[MeSH Terms] OR "apexification"[All Fields]))) OR (("pemetrexed"[Supplementary Concept] OR "pemetrexed"[All Fields] OR "mta"[All Fields]) AND apical[All Fields] AND plug[All Fields])) OR (("mineral trioxide aggregate"[Supplementary Concept] OR "mineral trioxide aggregate"[All Fields]) AND ("apexification"[MeSH Terms] OR "apexification"[All Fields])). There was also a hand-search of 4 relevant dental journals: Journal of Endodontics, International Endodontic Journal, Pediatric Dentistry, and International Journal of Paediatric Dentistry. The reference section of each study included in this review was used as an additional article source. The relevance of each article was initially evaluated by scanning its title and abstract. In cases of uncertainty for the article's relevance, full texts were retrieved.

The criteria for the definitive inclusion of each article after full text retrieval were:

1) clinical studies, case series or case reports that included calcium hydroxide apexification treatment or apexification procedure with the use of artificial apical barriers in teeth with open apex;
2) adequate information with regard to the technique and the materials used;
3) outcome based on clear data from clinical and radiographic examination;
4) articles written in English language.

Exclusion criteria were:

1) articles irrelevant to apexification procedures;
2) animal studies, reviews, in vitro or ex vivo studies;
3) inadequate data regarding the application of the treatment protocol;
4) articles written in languages other than English.

The criteria were applied to each article independently by the reviewers for more reliable results. A consensus was achieved after discussion in cases of disagreement.

The information selected from each article concerned: the type of each study, the cause of open apex, the type of apexification procedure (calcium hydroxide or artificial apical barrier), the type of artificial apical barrier, the number of visits for the completion of treatment, the time that calcium hydroxide was left in the root canals, the clinical success of the treatment as well as the apical closure. In cases of clinical studies that included multiple categories, all of them were counted.

Results

One thousand two hundred and thirty-five (1235) results were found after the aforementioned electronic search, 1114 of which were not included in this review due to the exclusion criteria. The sample was formed at 121 articles. Seventeen more studies were retrieved after hand-searching in the specific journals or by the reference section, so the final sample was 138 articles (Fig. 1).

The results of this study are shown in Table 1. Fifty-three percent of the studies included in this review referred to MTA apical plug technique, whereas in the last decade the same percentage was 71%. The percentages regarding the number of visits of CH apexification were 13% and 85% for two visits and multiple visits, respectively. As far as the duration of the treatment is concerned, CH remained in the root canal space for 3-12 months in 59% of the studies, for 12-24 months in 42%, and 24 months or more in 10% of the studies.

The apical plug technique was completed in one visit in 13% of the studies; in two visits in 75% and in more than two visits in 20%, whereas, the intracanal medicament was left for up to 3 weeks in 74% of the studies in which it was used.

Long-term apexification presented higher percentages of apical closure than artificial barrier apexification.

Discussion

Pulp necrosis is caused by trauma or other insults, and it usually results in the arrest of root development of permanent immature teeth; immature pulpless teeth remain with open apex and thin and short root walls [Holden et al., 2008]. Other causes of open apex are: chronic periapical periodontitis that leads to apical resorption, apical resorption due to trauma, destruction of apical constriction during mechanical debridement, apicoectomy without use of root-end filling materials and horizontal root fracture [Kusgoz et al., 2009; Stefopoulos et al.; 2012; Mente et al., 2013]. In the case of immature teeth with open apex and fragile root walls, apart from the risk of extruding root filling materials in the periradicular tissues, there is also the risk of root fracture during or after the completion of treatment [Holden et al., 2008].

Two of the most popular techniques to confront teeth with open apex are: the long-lasting apexification treatment with use of CH, and the apexification procedure with placement of artificial apical barriers at the blunt apex. The present study targeted clinical articles related to apexification procedures. The number of articles that complied with the inclusion criteria of this study was one hundred thirty eight. Gathering all these articles and analysing in detail the treatment procedures is helpful to uncover possible preferences to a specific treatment protocol or a specific biomaterial and to understand how these preferences are changing over time as well as to clear up their correlation with the treatment outcome.

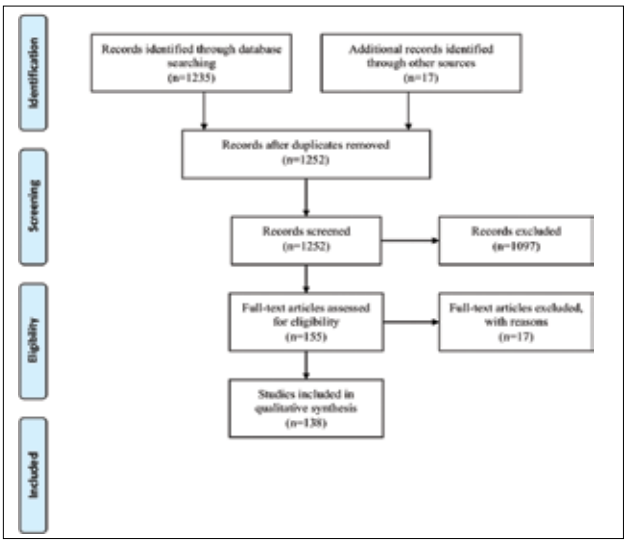

FIG. 1 PRISMA 2009 flow diagram.

According to the findings of the present study, all clinical articles published from 1976 to 2002 are related to CH apexification. However, it seems that in the last decade the use of artificial apical barriers has restricted the use of CH technique, as in this decade 75 out of 105 relevant studies (71%) are related to MTA apical plug technique and, additionally, there are a few cases of apical plug technique in which Biodentine and calcium-enriched mixture (CEM)

Study	Type of study	Cause of open apex	Barrier	One or two visits	Duration of CaOH	Clinical success	Apical closure	Recall Period
Umashetty et al, 2015	Case report	Immature teeth	MTA	2 visits with $Ca(OH)_2$	2 weeks	4/4	2/4	15 months
Yadav et al, 2015	Case report	Immature tooth	MTA + PRF membrane	2 visits with $Ca(OH)_2$	1 week	1/1	0/1	2 years
Chalakkal et al, 2015	Case report	Immature tooth	Mineralised tissue barrier	1 visit (Metapex)	1 year	0/1	1/1	1 year
Mente et al, 2015	Cohort clinical study	Apicoectomy	MTA	1 or 2 visits (n=9) Multiple visits (n=14) with $Ca(OH)_2$	Not mentioned	20/23	Not Mentioned	35 months
Galhotra et al, 2015	Case report	Immature tooth	Mineralised tissue barrier	1 visit (Metapex)	1 year	Not clear due to extrusion	Not clear due to extrusion	2 years
Kumar et al, 2014	Case report	Immature tooth	MTA + PRF membrane	Multiple visits with triple antibiotic paste + $Ca(OH)_2$	3 weeks	1/1	1/1	1 year
Narang et al, 2015	Pilot clinical study	Immature teeth	MTA	2 visits with triple antibiotic paste	Not mentioned	5/5	0/5	18 months
Silva et al, 2015	Case report	Immature tooth	Mineralised tissue barrier	4 visits with $Ca(OH)_2$	9 months	1/1	1/1	6 years
		Immature tooth	MTA	2 visits with Ca(OH)2	3 weeks	1/1	1/1	
Badole et al, 2015	Case report	Immature teeth	MTA	2 visits with $Ca(OH)_2$	1 week	2/2	0/2	1 year

TABLE 1A Presentation of the data collected from the clinical studies on apexification techniques.

Study	Type of study	Cause of open apex	Barrier	One or two visits	Duration of CaOH	Clinical success	Apical closure	Recall Period
Bonte et al, 2015	RCT	Immature teeth	Mineralised tissue barrier	6 visits with $Ca(OH)_2$	1 year	12/16 75%	8/16 50%	1 year
			MTA	2 visits with $Ca(OH)_2$	2 weeks	14/17 82.4%	13/17 76.5%	1 year
Kumar et al, 2014	Case report	Immature teeth	MTA	2 visits with $Ca(OH)_2$	2 weeks	2/2	2/2	8 months
Khetarpal et al, 2014	Case report	Immature tooth	Biodentine	2 visits with $Ca(OH)_2$	1 week	1/1	1/1	18 months
Shekhar et al, 2014	Case report	Immature tooth	MTA	2 visits with $Ca(OH)_2$	1 week	1/1	1/1	6 months
Pace et al, 2014	Case series	Immature teeth	MTA	2 visits with $Ca(OH)_2$	1 week	15/16	Not mentioned	10 years
Alobaid et al, 2014	Retro cohort study	Immature teeth	MTA	Multiple visits with $Ca(OH)_2$	Not mentioned	5/5	Not mentioned	22 months
			Mineralised tissue barrier	Multiple visits with $Ca(OH)_2$	Not mentioned	7/7	Not mentioned	
Asgary & Fazlyab 2014	Case report	Immature tooth	C.E.M	1 visit	-	1/1	1/1	2 years
Sinha et al, 2014	Case report	Immature tooth	Biodentine	2 visits with triple antibiotic paste	-	1/1	1/1	1 year
Chacko & Pradhan 2014	Case report	Immature tooth	Mineralised tissue barrier	Multiple visits with $Ca(OH)_2$	2 years	1/1	1/1	2 years
Ghosh et al, 2014	Comparative study	Immature teeth	Mineralised tissue barrier	Multiple visits with $Ca(OH)_2$	7.6 months	44/51 86.3%	37/51 72.5%	7.6 months
Nayak & Hasan 2014	Case report	Immature tooth	Biodentine + collagen membrane	2 visits with $Ca(OH)_2$	1 month	1/1	1/1	1 year
Kumar et al, 2014	Case report	Immature tooth	MTA	2 visits with $Ca(OH)_2$	5 month	1/1	1/1	28 months
Dixit et al, 2014	Case report	Immature teeth	MTA	2 visits with $Ca(OH)_2$	2 weeks	2/2	2/2	5 years
			mineralised barrier	2 visits with $Ca(OH)_2$	6 months			
Nagy et al, 2014	RCT	Immature teeth	MTA	2 visits with triple antibiotic paste	Not mentioned	9/9	Not mentioned	18 months
Khetarpal et al, 2013	Case report	Immature tooth	MTA + PRF membrane	2 visits with $Ca(OH)_2$	1& 2 weeks	Inadequate recall period	Inadequate recall period	3 months
Cetenovićet al, 2013	Case report	Immature teeth	MTA	4 visits with $Ca(OH)_2$	6 months for the first 3/ 4 months for the other	4/4	0/4	6 months (3 first)/ 3 months
Gawthaman et al, 2013	Case report	Immature tooth	mineralised barrier	2 visits with $Ca(OH)_2$	3 months	Inadequate recall period	1/1	3 months
			MTA	2 visits with $Ca(OH)_2$	5 days	Inadequate recall period	Inadequate recall period	-
Floratos et al, 2013	Case report	Immature teeth	MTA	2 visits with $Ca(OH)_2$	2 weeks	2/2	2/2	12&16 months
Costa et al, 2013	Case report	Immature tooth	mineralised barrier + MTA	Multiple visits with $Ca(OH)_2$	18 months	1/1	1/1	16 months
Shekhar & Shashikala 2013	Case report	Immature tooth	MTA	2 visits with $Ca(OH)_2$	1 week	1/1	1/1	24 months
Chang et al, 2013	Case reports	Immature teeth	MTA	2 visits $Ca(OH)_2$	2 weeks	3/3	Not clear	11-24 months
				3 visits $Ca(OH)_2$	3 weeks		Not clear	
				2 visits $Ca(OH)_2$	1 week		1/1	

TABLE 1B Presentation of the data collected from the clinical studies on apexification techniques.

Study	Type of study	Cause of open apex	Barrier	One or two visits	Duration of CaOH	Clinical success	Apical closure	Recall Period
Fayazi et al, 2013	Case report	Immature tooth	MTA	2 visits $Ca(OH)_2$	1 week	1/1	1/1	6 months
Vijayran et al, 2013	Case report	Immature tooth	MTA	2 visits $Ca(OH)_2$	13 months	Inadequate recall period	Inadequate recall period	-
Souza et al, 2012	Case report	Overinstrumentation - destruction of AP	Ca(OH)2 plug	2 visits with $Ca(OH)_2$	2 weeks	1/1	1/1	8 years
Paul et al, 2012	Case report	Immature tooth	MTA	2 visits with $Ca(OH)_2$	3 weeks	1/1	1/1	6 months
Mente et al, 2013	Retro cohort study	Immature (12)	MTA	2 or more visits with $Ca(OH)_2$	Not mentioned	11/12 92%	Not mentioned	1 year
		Overinstrumentation (110)				103/110 94%		
		Root resorption due to A.P. (105)				89/105 85%		
		Root resorption Due to trauma (25)				24/25 96%		
Silva & Zaia 2012	Case report	Immature tooth	Mineralised tissue barrier	Multiple visits with $Ca(OH)_2$	18 months	1/1	1/1	2 years
de Jesus Soares et al, 2012	Case report	Immature tooth	Mineralised tissue barrier	2 visits with $Ca(OH)_2$	9 months	1/1	1/1	4 years
Jeeruphan et al, 2012	Retro study	Immature teeth	MTA	1 visit	-	13/19	Not mentioned	>6 months
			Mineralised tissue barrier	Multiple visits with $Ca(OH)_2$	17 months	17/22	Not mentioned	
Stefopoulos et al, 2010	Case report	Apicoectomy	MTA	2 visits with $Ca(OH)_2$	2 weeks	1/1	1/1	4 years
Rudagi & Rudagi 2012	Case report	Immature tooth	MTA	2 visits with $Ca(OH)_2$	1 week	1/1	1/1	1 year
Albadri et al, 2012	Case report	Immature teeth	MTA	2 visits with $Ca(OH)_2$	Not mentioned	2/2	2/2	6-18 months
		Root fracture				1/1	1/1	
Gunes & Aydinbelge 2012	Case report	Immature teeth	MTA	2 visits with $Ca(OH)_2$	2 weeks	3/3	3/3	18 months
Aggarwal et al, 2012	Case report	Immature tooth	Not clear	Multiple visits with $Ca(OH)_2$ Points	2 months	1/1	Not clear	24 months
Bezgin et al, 2012	Prospect Clinical study	Immature tooth	Mineralised tissue barrier	Multiple visits with Ca(OH)2 Points	9.6 months	11/12	11/12	12 months
			Mineralised tissue barrier	Multiple visits with Ca(OH)2 Paste	9.6 months	10/10	10/10	
Asgary & Ehsani S 2012	Case report	Immature tooth	MTA	2 visits with $Ca(OH)_2$	2 weeks	1/1	1/1	7 years
Nosrat et al, 2011	Case series	Immature teeth	CEM/MTA	2 visits with $Ca(OH)_2$	2 weeks	7/7	7/7	12-24 months
		Resorption due to AP				6/6	6/6	
Yassen et al, 2012	Prospective study	Immature teeth	Mineralised tissue barrier	2 (74%) 3 (22%) 4 (4%) -visits with $Ca(OH)_2$	6-12 months	23/23	23/23	13 months
Ajwani & Saini 2011	Case report	Immature tooth	MTA	2 visits with $Ca(OH)_2$	1 month	1/1	0/1	6 months
Paula-Silva et al, 2011	Case report	Immature tooth	MTA	Multiple visits with $Ca(OH)_2$	14 months	1/1	1/1	12 months

TABLE 1C Presentation of the data collected from the clinical studies on apexification techniques.

Study	Type of study	Cause of open apex	Barrier	One or two visits	Duration of CaOH	Clinical success	Apical closure	Recall Period
Beslot-Neveu A et al, 2011	RCT	Immature teeth	MTA	2 visits with $Ca(OH)_2$	2 weeks	Not mentioned	Not mentioned	12 months
			Mineralised tissue barrier	4 visits with $Ca(OH)_2$	6-12 months			
Shadmehr & Farhad 2011	Case report	Immature tooth	MTA+ Calcium hydroxide plug	3 visits with $Ca(OH)_2$	2 weeks	1/1	0/1	18 months
Moore et al, 2011	Comparative clinical study	Immature teeth	MTA	2 visits with $Ca(OH)_2$	At least 1 week	21/22 95,5%	14/22 63,6%	23,4 months
Kumar et al, 2011	Case report	Overi-nstrumentation	MTA	2 visits with $Ca(OH)_2$	1 week	1/1	0/1	6 months
Kahler 2011	Case report	Immature teeth	MTA	2 visits with $Ca(OH)_2$	1 month	2/2	0/2	12 months
Mohammadi & Yazdizadeh 2011	Case report	Immature tooth	MTA	Not mentioned	Not mentioned	1/1	1/1	1 year
Warner & Al-Salehi 2011	Case report	Immature tooth	MTA	2 visits with $Ca(OH)_2$	1 month	1/1	0/1	2 months
Asgary et al, 2011	Case report	Immature teeth	CEM	1 visit without $Ca(OH)_2$	-	1/1	0/1	40 months
				2 visits with $Ca(OH)_2$	6 weeks	1/1	0/1	
Mendoza et al, 2010	Clinical Study	Immature teeth	Mineralised tissue barrier	Multiple visits with $Ca(OH)_2$	8,6+/- 3,36 months	28/28	28/28	24 months
Cehreli et al, 2011	Case report	Immature teeth	MTA	2 visits without $Ca(OH)_2$	Not mentioned	2/2	0/2	18 months
Sridhar et al, 2010	Case report	Immature teeth	Mineralised tissue barrier	3 visits with Metapex®	12 months	3/3	3/3	12 months
Chhabra et al, 2010	Case report	Immature tooth	MTA+ Demineralized freeze-dried bone allograft	2 visits with Metapex®	2 weeks	1/1	0/1	24 months
Lee et al, 2010	Clinical study	Immature teeth	Mineralised tissue barrier	4 visits with $Ca(OH)_2$	10-14 weeks	32/32	32/32	Not ment-ioned
Vellore 2010	Case report	Immature teeth	Mineralised tissue barrier	3 visits with $Ca(OH)_2$	3 months	2/2	2/2	-
Araújo et al, 2010	Case report	Apical resorption	MTA+ Calcium sulphate matrix	1 visit without $Ca(OH)_2$	-	1/1	0/1	12 months
Khatavkar & Hegde 2010	Case report	Immature tooth	MTA+ Calcium sulfate barrier	2 visits with $Ca(OH)_2$	1 week	1/1	0/1	3 months
Vanka et al, 2010	Case report	Immature teeth	MTA	Multiple visits with $Ca(OH)_2$	16 months	1/1	0/1	6 months
			MTA+ absorbable collagen sponge	2 visits with $Ca(OH)_2$	2 weeks	1/1	1/1	Not mentio-ned
Wang et al, 2010	Case report	Immature tooth	Mineralised tissue barrier	Multiple visits with $Ca(OH)_2$	5 months	1/1	1/1	12 months
Schmitz et al, 2010	Case report	Immature teeth	Mineralized tissue barrier	Multiple visits with $Ca(OH)_2$	8 months / 15 months / 12 months	2/3	2/3	38 months
Nayar et al, 2009	Clinical study	Immature teeth	MTA	Multiple visits with $Ca(oH)_2$	Mean time 20 weeks	41/43	Not mentioned	10,67 months

TABLE 1D Presentation of the data collected from the clinical studies on apexification techniques.

Study	Type of study	Cause of open apex	Barrier	One or two visits	Duration of CaOH	Clinical success	Apical closure	Recall Period
Nuvvula et al, 2010	Case report	Immature tooth	MTA	Multiple visits with $Ca(OH)_2$	2 weeks	1/1	0/1	4 motnhs
Annamalai et al, 2010	Clinical study	Immature teeth	MTA	1 visit without $Ca(OH)_2$	-	30/30 100%	26/30 86,6%	12 months
Kusgoz et al, 2009	Case report	Apical resection	MTA	3 visits with $Ca(OH)_2$ (change every 2 weeks+ 3 visits with triple antibiotic paste)	6 weeks+ 3 months (antibiotic paste)	1/1	0/1	30 months
Raldi et al, 2009	Case report	Immature teeth	Mineralised tissue barrier	Multiple visits with $Ca(OH)_2$	12 months	1/1	1/1	2 years
			MTA	2 visits with $Ca(OH)_2$	2 weeks	1/1	1/1	5 years
			MTA	2 visits with $Ca(OH)_2$	4 weeks	1/1	0/1	9 months
Mente et al, 2009	RCT	Overinstrumentation / Apical resorption	MTA	2 visits with $Ca(OH)_2$	Not mentioned	47/56 (84%)	Not mentioned	30,9 months
Oktem et al, 2009	Case report	Apical resorption	Mineralized tissue barrier	Multiple visits with CHPP	6 Months	1/1	1/1	24 months
Bogen & Kuttler 2009	Case report	Immature tooth	MTA	2 visits with $Ca(OH)_2$	1 week	1/1	1/1	18 months
Kusgoz et al, 2009	Case reports	Horizontal root fracture	MTA	2 visits with Ca(OH)2	Not mentioned	3/3	0/3	24 months/ 12months
Ma et al, 2009	Case report	Immature tooth	MTA	2 visits with Ca(OH)2	2 weeks	Not ment.	1/1	Not mentioned
Demartis et al, 2009	Case report	Immature tooth	MTA	2 visits with Ca(OH)2	10 days	1/1	1/1	12 months
Marcos Jacobovitz et al, 2009	Case report	Immature tooth	Mineralised tissue barrier	Multiple visits with Ca(OH)2	18 months	1/1	1/1	7 years
Oliveira et al, 2008	Case report	Immature teeth	MTA	Multiple visits with Ca(OH)2	6 months	2/2	0/2	15 months
Park & Lee 2008	Case report	Immature tooth	MTA	2 visits with Ca(OH)2	1 week	1/1	1/1	24 months
Witherspoon et al, 2008	RCT	Not mentioned	MTA	1 visit with MTA	-	46/47	Not mentioned	19,4 months
				2 visit with Ca(OH)2	3 weeks	26/31		
Holden et al, 2008	RCT	Not mentioned	MTA	2 visits with Ca(OH)2	1 week	17/20 healed 1/20 healing	Not mentioned	1 year
Deepti et al, 2008	Case report	Immature tooth	Mineralised tissue barrier	3 visits with Ca(OH)2	13 months	1/1	1/1	Not mentioned
Fregnani et al, 2008	Case report	Immature tooth	IRM surgically	Multiple visits with Ca(OH)2	12 months	1/1	0/1	4 years
Zhu et al, 2008	Case report	Immature tooth	MTA	2 visits with Ca(OH)2	2 weeks	1/1	0/1	30 months
Erdem & Sepet 2008	Case report	Immature teeth	MTA	2 visits with Ca(OH)2	1-6 weeks	4/5	4/5	24 months
Soares et al, 2008	Case report	Immature tooth	Mineralised tissue barrier	5 visits with Ca(OH)2	8 months	1/1	1/1	36 months
Kristoffersen et al, 2008	Case report	Immature tooth	MTA	2 visits with Ca(OH)2	2 months	1/1	0/1	15 months
Ghaziani et al, 2007	Case report	Immature teeth	MTA	2 visits with Ca(OH)2	2 weeks	1/2	0/2	24 months
Sarris et al, 2008	Pilot study	Immature tooth	MTA	3 visits without Ca(OH)2	Not mentioned	13/17	Not mentioned	12,53 months

TABLE 1E Presentation of the data collected from the clinical studies on apexification techniques.

Study	Type of study	Cause of open apex	Barrier	One or two visits	Duration of CaOH	Clinical success	Apical closure	Recall Period
De-Deus & Coutinho-Filho, 2007	Case report	Immature tooth	WPC (White Portland Cement) + resorbable collagen sponge	1 visit	-	1/1	1/1	12 months
D'Arcangelo & D'Amario 2007	Case report	Immature teeth	MTA + Absorbable gelatin sponge	2 visits with Ca(OH)2	2 weeks	2/2	0/2	12 months
Gaitonde & Bishop 2007	Case report	Immature tooth	MTA	2 visits with Ca(OH)2	1 week	1/1	1/1	12 months
Simon et al, 2007	Prospective study	Not mentioned	MTA	1 visit	-	35/43 (81%)	11/43	12 months
Pradhan et al, 2006	Clinical study	Immature teeth	MTA	2 visits with $Ca(OH)_2$	1 week	100% 10/10	70% 7/10	Not ment–ioned
			Mineralised tissue barrier	Multiple visits with $Ca(OH)_2$	7+/-2,5 months	100% 10/10	100% 10/10	
Sübay & Kayataş 2006	Case report	Immature tooth	MTA (after surgery, because of no hard tissue barrier)	6 visits with $Ca(OH)_2$	6 months	1/1	0/1	12 months
Karp et al, 2006	Case report	Immature tooth	MTA canal obturation	4 visits with $Ca(OH)_2$ + $Ba(OH)_2$	422 days	1/1	0/1	16 months
El-Meligy & Avery DR 2006	Comparative study	Immature teeth	Mineralised tissue barrier	Multiple visits with $Ca(OH)_2$	12 months	13/15	13/15	12 months
			MTA	2 visits with $Ca(OH)_2$	1 week	15/15	Not mentioned	
Ballesio et al, 2006	Case series	Immature tooth	Mineralised tissue barrier	2 visits with $Ca(OH)_2$	6 months	15/15	15/15	7-13 years
Ghaziani et al, 2006	Case series	Immature tooth	MTA	2 visits with $Ca(OH)_2$	1 week	38/41 92,7%	Not mentioned	6 months
Silberman et al, 2006	Case report	Immature tooth	MTA	3 visits with $Ca(OH)_2$	6 months	1/1	0/1	9 months
Dominguez Reyes et al, 2005	Retrospective study	Immature teeth	Mineralised tissue barrier	Multiple visits with $Ca(OH)_2$	12,19 months	100%	100%	Not ment–ioned
Kalaskar et al, 2004	Case report	Immature tooth	Mineralised tissue barrier	6 visitswith $Ca(OH)_2$	6 months	1/1	1/1	6 months
Pai et al, 2004	Case Report	Immature tooth	Mineralised tissue barrier	Multiple visits with $Ca(OH)_2$	14 months	1/1	1/1	25 months
Jung 2004	Case report	Immature tooth	Mineralised tissue barrier	Multiple visits with $Ca(OH)_2$	6 months	1/1	1/1	12 months
Hayashi et al, 2004	Case report	Root- end resection	MTA	2 visits with $Ca(OH)_2$	2 weeks	2/2	0/2	24 months
Sedgley & Wagner 2003	Case report	Apicectomy	Mineralised tissue barrier	3 visits with $Ca(OH)_2$	12 months	1/1	1/1	5 years
Linsuwanont 2003	Case report	Immature teeth	MTA	2 visits with $Ca(OH)_2$	8 months	2/2	1/2	12 months
Maroto et al, 2003	Case report	Immature teeth	Mineralised tissue barrier	Multiple visits with $Ca(OH)_2$	2 years	1/1	1/1	12 months
			MTA			1/1	0/1	
Giuliani et al, 2002	Case report	Immature teeth	MTA	2 visits with $Ca(OH)_2$	1 week	3/3	0/3	12 months
Gupta S 1998	Case report	Immature tooth	Mineralised tissue barrier	2 visits with $Ca(OH)_2$	Not mentioned	3/3	3/3	Not ment–ioned
Selden 2002	Case report	Immature tooth	Mineralised tissue barrier	3 visits with Ca(OH)2	2 years	1/1	1/1	30 months
Kinirons et al, 2001	Retrospective study	Immature teeth	Mineralised tissue barrier	Multiple visits with Ca(OH)2	26-52 weeks	107/107	107/107	Not ment–ioned
Fava 2001	Case report	Apicoectomy	Mineralised tissue barrier	3 visits with Ca(OH)2	5 months	1/1	1/1	27 months

TABLE 1F Presentation of the data collected from the clinical studies on apexification techniques.

Study	Type of study	Cause of open apex	Barrier	One or two visits	Duration of CaOH	Clinical success	Apical closure	Recall Period
Kim 1999	Case report	Not mentioned	Mineralised tissue barrier	6 visits with $Ca(OH)_2$	18 months	1/1	1/1	6 months
Gentner 1999	Case report	Immature tooth	Mineralised tissue barrier	3 visits with Ca(OH)2	10 months	1/1	1/1	Not mentioned
Walia et al, 2000	Retrospective study	Immature tooth	Mineralised tissue barrier	Multiple visits with Ca(OH)2	Not mentioned	15/15	15/15	24 months
Gupta et al, 1999	Case report	Immature tooth	Mineralised tissue barrier	4 visits with Ca(OH)2	7 months	1/1	1/1	Not mentioned
Tarján & Rózsa 1999	Case report	Immature tooth	Mineralised tissue barrier	Multiple visits with Ca(OH)2	Not mentioned	1/1	1/1	24 months
Yeh et al, 1999	Case report	Immature tooth	Mineralised tissue barrier	3 visits with Ca(OH)2	6 months	1/1	1/1	10 months
Cotti et al, 1998	Case report	Root resorption	Mineralised tissue barrier	Multiple visits with Ca(OH)2	24 months	1/1	1/1	24 months
Calişkan & Türkün 1997	Case report	Immature tooth	Mineralised tissue barrier	4 visits with Ca(OH)2	9 months	1/1	1/1	15 months
Parashos 1997	Case report	Apicectomy	Mineralised tissue barrier	2 visits with Ca(OH)2	9 months	1/1	1/1	14 months
Harbert 1996	Case report	Immature tooth	Tricalcium phosphate as an apical plug	1 visit without Ca(OH)2	-	1/1	1/1	7 years
Holtzman & Lezion 1996	Case report	Immature tooth	Mineralised tissue barrier	3 visits with Ca(OH)2	3 months	1/1	1/1	6 months
Gupta & Sharma 1996	Case report	Immature tooth	Mineralised tissue barrier	2 visits with Ca(OH)2	18 months	1/1	1/1	Not mentioned
Schumacher & Rutledge 1993	Case report	Immature tooth	Ca(OH)2 apical plug	1 visit with compensation of Ca(OH)2 and gutta-percha obturation	-	1/1	0/1	1 year
Ohara & Torabinejad 1992	Case report	Immature tooth	Mineralised tissue barrier	3 visits with Ca(OH)2	11 months	1/1	1/1	Not mentioned
Su 1992	Case report	Immature tooth	Mineralised tissue barrier	4 visits with Ca(OH)2	15 months	1/1	1/1	4 years
Morfis & Siskos 1991	Clinical study	Immature teeth	Mineralised tissue barrier	Multiple visits with Ca(OH)2	12-24 months	31/34	30/34	Not mentioned
Yang et al, 1990	Case report	Immature tooth	Mineralised tissue barrier	4 visits with Ca(OH)2	12 months	1/1	1/1	18 months
Bal et al, 1989	Comparative study	Not mentioned	Mineralised tissue barrier	4 visits with Ca(OH)2	6 months	12/12	9/12	6 months
Morfis & Lentzari, 1989	Case report	Immature tooth	Mineralised tissue barrier	4 visits with Ca(OH)2	22 months	1/1	1/1	4 years
Thäter & Maréchaux 1988	Follow up study	Immature teeth	Mineralised tissue barrier	Multiple visits with Ca(OH)2	1-24 months	25/34	25/34	1-63 months
Ghose et al, 1987	Clinical study	Immature teeth	Mineralised tissue barrier	Multiple visits with Ca(OH)2 (Calasept)	3-10 months	49/51	49/51	Not mentioned
Ferguson et al, 1980	Case report	Immature tooth	Mineralised tissue barrier	3 visits with Ca(OH)2	12 months	1/1	1/1	5 months
Piekoff & Trott 1976	Case report	Immature tooth	Mineralised tissue barrier	Multiple visits with Ca(OH)2 mixed with CPC	4 years	0/1 (fracture during post cementation)	1/1	Not mentioned

TABLE 1 G Presentation of the data collected from the clinical studies on apexification techniques.

were used as artificial barriers [Nosrat et al., 2011; Nayak and Hasan, 2014]. In CH apexification treatment, CH is left into the root canal for several months in order to induce a hard-tissue apical barrier that facilitates proper obturation of root canal and prevents the passage of toxins and bacteria into the periapical tissues [Rafter, 2005]. Histological analysis showed that this calcified tissue barrier consists of distinct layers. The outer layer seems to be composed of a dense acellular cementum-like tissue, which surrounds a central mix of irregular dense fibrocollagenous connective tissue [Baldassari-Cruz, 1998]. Laboratory observations that detected a decrease in fracture resistance of the root

in which CH remained for a long period [Andreasen et al., 2002;Andreasen et al., 2006] as well as the long duration of CH treatment and the difficulty to monitor patients for several months, might be the reasons that brought about the need for alternative approaches [Torabinejad, 1999]. It is noteworthy that in 59% of the relevant clinical studies, CH remained in the root canal for up to 12 months. Also, in 10% of the studies it remained for more than 24 months.

The frequency, as well as the number of changes of the CH appear to be controversial topics. One placement of the intracanal medicament appeared to be enough for the induction of a hard-tissue apical barrier, [Chawla, 1986; Chosack et al., 1997], whereas other studies claim that there is more to gain from multiple changes of CH, such as quicker induction of the apical bridge [Abbot, 1998; Kinirons et al., 2001]. According to the findings of the present study, 85% of the studies reported two or more replacements of that intracanal medicament. So, it is clear that clinicians preferred changing CH at least two times in order to obtain the desired outcome.

As opposed to long-term CH apexification procedures, apical plug technique with use of artificial barriers could be completed even in one visit. A biomaterial, such as MTA, Biodentine or CEM is placed apically in order to create an artificial seal that facilitates the compaction of gutta-percha on it. Although creation of hard tissue at the apex after the placement of this material is well-documented [Nosrat et al., 2011; Umashetty et al., 2015], the primary goal of this technique is not to create a biological closure of the apex [Rafter, 2005]. This is the reason for the short time that this treatment requires in order to be completed. The treatment can be finished in one visit without the use of an intracanal medicament [Simon et al., 2007; Mente et al., 2009] or in two or more visits with the use of medication [Mente et al., 2009; Alobaid et al., 2014]. About 13% of the studies reported that the treatment was completed in one visit, 75% in two visits and 20% in more than two visits.

In orthograde apical plug technique, CH is used as intracanal medicament for intracanal disinfection. Until now, the available evidence is not sufficient to determine the impact of the use of intracanal medicaments on the clinical outcome of this treatment. Certainly, there are quite a few clinical studies that reported that there is no difference in clinical outcome between one-visit and two-visit root canal treatment of teeth with pulp necrosis and periapical lesion [Weiger et al., 2000; Peters and Wesselink, 2002]. CH was used as intracanal medicament in 95% of the clinical studies related to apical plug apexification procedures; in the majority of them CH was left in the root canal for up to 3 weeks. Longer periods were avoided possibly due to fact that delay of placement of the permanent coronal restoration increases the risk of microleakage and the risk of tooth fracture and prolonged contact of CH with the root dentine possibly affects its biomechanical properties [Heling et al., 2002; Rosenberg et al., 2007].

The main goals of apexification are the resolution of clinical signs and symptoms of periapical disease, radiographic resolution of periapical lesion and induction of a calcified tissue barrier at the apex. Both apexification procedures present high percentages of clinical success. However, looking at the findings of the present study, CH seems to be correlated with higher percentages of apical closure. This could be considered as an advantage of the long-term apexification as the formation of this apical seal is a biological procedure, which enables the preservation and rehabilitation of the treated teeth. Regarding the lower percentages of apical closure that artificial apical barriers presented in the clinical studies compared with CH apexification, it could be assumed that the follow-up time in some cases of apical plug technique was possibly not enough for the hard tissue to be visible in radiographs. Moreover, there are no studies stating that non-formation of a calcified apical barrier tissue constitutes a problem for the prognosis of the treatment.

Conclusions

Apexification treatment procedures are changed over time and probably are influenced by observations of relevant laboratory, preclinical and clinical studies. There is a strong tendency towards one-visit apexification with the use of various artificial apical plugs. Both apexification treatments lead to favorable treatment outcomes. The limited follow-up time, could not make explicit the effectiveness of artificial apical plugs regarding the induction of apical closure.

Acknowledgements

The authors deny any conflicts of interest related to this study.

References

› Abbot P. Apexification with calcium hydroxide – when should the dressing be changed? The case for regular dressing changes. Aust Endod J 1998; 24: 27–32.
› Aggarwal V, Miglani S, Singla M. Conventional apexification and revascularization induced maturogenesis of two non-vital, immature teeth in same patient: 24 months follow up of a case. J Conserv Dent 2012; 15:68.
› Ajwani P, Saini N. Non-surgical management of a mutilated maxillary central incisor with open apex and large periapical lesion. Indian J Dent Res 2011; 22:475.
› Albadri S, Chau YS, Jarad F. The use of mineral trioxide aggregate to achieve root end closure: three case reports. Dent Traumatol 2013; 29:469-73.
› Alobaid AS, Cortes LM, Lo J, Nguyen TT, Albert J, Abu-Melha AS, Lin LM, Gibbs JL. Radiographic and clinical outcomes of the treatment of immature permanent teeth by revascularization or apexification: a pilot retrospective cohort study. J Endod 2014; 40:1063-70.
› Andreasen JO, Farik B, Munksgaard EC. Long-term calcium hydroxide as a root canal dressing may increase risk of root fracture. Dent Traumatol 2002; 18:134-7.
› Andreasen JO, Munksgaard EC, Bakland LK. Comparison of fracture resistance in root canals of immature sheep teeth after filling with calcium hydroxide or MTA. Dent Traumatol 2006; 22:154-6.
› Annamalai S, Mungara J. Efficacy of mineral trioxide aggregate as an apical plug in non-vital young permanent teeth: preliminary results. J Clin Pediatr Dent 2010; 35:149-55.
› Araújo RA, Silveira CF, Cunha RS, Martin AS, Fontana CE, Bueno CE. Single-session use of mineral trioxide aggregate as an apical barrier in a case of external root resorption. J Oral Sci 2010; 52:325-8.
› Asgary S, Ehsani S. MTA resorption and periradicular healing in an open-apex incisor: a case report. Saudi Dent J 2012; 24:55-9.
› Asgary S, Fazlyab M. Nonsurgical management of an extensive endodontic lesion in an orthodontic patient by calcium-enriched mixture apical plug. Contemp Clin Dent 2014; 5:278.
› Asgary S, Nosrat A, Seifi A. Management of inflammatory external root resorption by

using calcium-enriched mixture cement: a case report. J Endod 2011; 37:411-3.
› Badole GP, Warhadpande MM, Bahadure RN, Badole SG. Nonsurgical endodontic treatment of permanent maxillary incisors with immature apex and a large periapical lesion: a case report. Gen Dent 2014; 63:58-60.
› Bal CS, Padda B, Puri P. Comparative study to evaluate the efficacy of surgical and conservative techniques for apexification in young permanent teeth with open apices. Indian J Dent Res 1988; 1:102-8.
› Baldassari-Cruz LA, Walton RE, Johnson WT. Scanning electron microscopy and histologic analysis of an apexification "cap": A case report. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 1998; 86:465-8.
› Ballesio I, Marchetti E, Mummolo S, Marzo G. Radiographic appearance of apical closure in apexification: follow-up after 7–13 years. Eur J Paediatr Dent.2006; 7:29-34.
› Beslot-Neveu A, Bonte E, Baune B, Serreau R, Aissat F, Quinquis L, Grabar S, Lasfargues JJ. Mineral trioxyde aggregate versus calcium hydroxide in apexification of non vital immature teeth: Study protocol for a randomized controlled trial. Trials 2011; 12:174.
› Bezgin T, Sönmez H, Orhan K, Özalp N. Comparative evaluation of Ca (OH) 2 plus points and Ca (OH) 2 paste in apexification. Dent Traumatol 2012; 28:488-95.
› Bogen G, Kuttler S. Mineral trioxide aggregate obturation: a review and case series. J Endod 2009; 35:777-90.
› Bonte E, Beslot A, Boukpessi T, Lasfargues JJ. MTA versus Ca (OH) 2 in apexification of non-vital immature permanent teeth: a randomized clinical trial comparison. Clin Oral Investig 2014; 19:1381-8.
› Çalışkan MK, Türkün M. Periapical repair and apical closure of a pulpless tooth using calcium hydroxide. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1997; 84:683-7.
› Camp JH. Diagnosis Dilemmas in Vital Pulp Therapy: Treatment for the Toothache Is Changing, Especially in Young, Immature Teeth. Pediatr Dent. 2008; 30: 197-205.
› Cehreli ZC, Sara S, Uysal S, Turgut MD. MTA apical plugs in the treatment of traumatized immature teeth with large periapical lesions. Dent Traumatol 2011; 27:59-62.
› Četenović B, Marković D, Petrović B, Perić T, Jokanović V. Use of mineral trioxide aggregate in the treatment of traumatized teeth in children: Two case reports. Vojnosanit Pregl 2013; 70:781-4.
› Chacko V, Pradhan M. Management of traumatically intruded young permanent tooth with 40-month follow-up. Aust Dent J 2014; 59:240-4.
› Chala S, Abouqal R, Rida S. Apexification of immature teeth with calcium hydroxide or mineral trioxide aggregate: systematic review and meta-analysis. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2011; 112:e36-42.
› Chalakkal P, Akkara F, De Ataide ID, Pavaskar R. Apicoectomy Versus Apexification. J Clin Diagn Res 2015; 9:ZD01.
› Chang SW, Oh TS, Lee W, Cheung GS, Kim HC. Long-term observation of the mineral trioxide aggregate extrusion into the periapical lesion: a case series. Int J Oral Sci. 2013; 5:54-7
› Chawla HS. Apical closure in a non-vital permanent tooth using one calcium hydroxide dressing. J Dent Child 1986; 53:44–7.
› Chhabra N, Singbal KP, Kamat S. Successful apexification with resolution of the periapical lesion using mineral trioxide aggregate and demineralized freeze-dried bone allograft. J Conserv Dent 2010; 13:106.
› Chosack A, Sela J, Cleaton-Jones P. A histological and quantitative histomorphometric study of apexification of nonvital permanent incisors of vervet monkeys after repeated root filling with a calcium hydroxide paste. Endod Dent Traumatol 1997; 13:211–7.
› Costa GM, Soares SM, Marques LS, Gloria JC, Soares JA. Strategy for apexification of wide-open apex associated with extensive periapical lesion in a weakened root. Gen Dent. 2012; 61:e2-4.
› Cotti E, Lusso D, Dettori C. Management of apical inflammatory root resorption: report of a case. Int Endod J. 1998; 31:301-4.
› D'Arcangelo C, D'Amario M. Use of MTA for orthograde obturation of nonvital teeth with open apices: report of two cases. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2007; 104:e98-101.
› de Jesus Soares A, Nagata JY, Casarin RC, de Almeida JF, de Almeida Gomes BP, Zaia AA, Ferraz CC, de Souza-Filho FJ. Apexification with a new intra-canal medicament: a multidisciplinary case report. Iran Endod J 2012; 7:165.
› De-Deus G, Coutinho-Filho T. The use of white Portland cement as an apical plug in a tooth with a necrotic pulp and wide-open apex: a case report. Int Endod J 2007; 40:653-60.
› Deepti A, Shifa S, Muthu MS, Rathna Prabhu V. Apical Closure of Immature Molar Roots: A Rare Case Report. Int J Clin Pediatr Dent 2008; 1:54.
› Demartis P, Dessì C, Cotti M, Cotti E. Endodontic treatment and hypotheses on an unusual case of dens invaginatus. J Endod 2009; 35:417-21.
› Dixit S, Dixit A, Kumar P, Arora S. Root end generation: an unsung characteristic Property of MTA-A Case Report. J Clin Diagn Res 2014; 8:291.
› Dominguez Reyes A, Munoz Munoz L, Aznar Martin T. Study of calcium hydroxide apexification in 26 young permanent incisors. Dent Traumatol 2005; 21:141-5.
› El Meligy OA, Avery DR. Comparison of apexification with mineral trioxide aggregate and calcium hydroxide. Pediatr Dent 2006; 28:248-53.
› Fava LR. Calcium hydroxide in endodontic retreatment after two nonsurgical and two surgical failures: report of a case. Int Endod J 2001; 34:72-80.
› Fayazi S, Bayat-Movahed S, White SN. Rapid endodontic management of type II dens invaginatus using an MTA plug: a case report. Spec Care Dentist 2013; 33:96-100.
› Ferguson FS, Friedman S, Frazzetto V. Successful apexification technique in an immature tooth with dens in dente. Oral Surg Oral Med Oral Pathol 1980; 49:356-9.
› Finucane D, Kinirons MJ. Non-vital immature permanent incisors: factors that may influence treatment outcome. Dent Traumatol 1999; 15:273-7.
› Floratos SG, Tsatsoulis IN, Kontakiotis EG. Apical barrier formation after incomplete orthograde MTA apical plug placement in teeth with open apex-report of two cases. Braz Dent J 2013; 24:163-6.
› Fregnani ER, Spinola LF, Sônego JR, Bueno CE, De Martin AS. Complex endodontic treatment of an immature type III dens invaginatus. A case report. Int Endod J.; 41:913-9.
› Gaitonde P, Bishop K. Apexification with mineral trioxide aggregate: an overview of the material and technique. Eur J Prosthodont Restor Dent 2007; 15:41-5.
› Galhotra V, Singla A, Jindal S, Sofat A. Effect of Unintentional Periapical Extrusion of Metapex in Immature Teeth-A Case Report. J Clin Diagn Res 2015; 9:ZD01.
› Gawthaman M, Vinodh S, Mathian VM, Vijayaraghavan R, Karunakaran R. Apexification with calcium hydroxide and mineral trioxide aggregate: Report of two cases. J Pharm Bioallied Sci 2013; 5:S131.
› Gentner MR. Apexification Following Gross Overfilling Of Gutta-Percha. Aust Endod J 1999; 25:133-5.
› Ghaziani P, Aghasizadeh N, Sheikh-Nezami M. Endodontic treatment with MTA apical plugs: a case report. J Oral Sci 2007; 49:325-9.
› Ghaziani P, Rastegar AF, Bidar M, Sadeghi G, Chegin P. Clinical and radiographic evaluation of success rate with MTA plug in open apices. Iran Endod J 2006; 1:15.
› Ghose LJ, Baghdady VS, Hikmat BY. Apexification of immature apices of pulpless permanent anterior teeth with calcium hydroxide. J Endod 1987; 13:285-90.
› Ghosh S, Mazumdar D, Ray PK, Bhattacharya B. Comparative evaluation of different forms of calcium hydroxide in apexification. Contemp Clin Dent 2014; 5:6.
› Giuliani V, Baccetti T, Pace R, Pagavino G. The use of MTA in teeth with necrotic pulps and open apices1. Dent Traumatol 2002; 18:217-21.
› Güneş B, Aydinbelge HA. Mineral trioxide aggregate apical plug method for the treatment of nonvital immature permanent maxillary incisors: Three case reports. J Conserv Dent 2012; 15:73.
› Gupta S, Sharma A, Dang N, Aggarwal S. Management of teeth with open apices and necrotic pulps with single visit apexification: 3 representative cases. J Indian Soc Pedod Prev Dent 1998; 16:52-5.
› Gupta S, Sharma A, Dang N. Apical bridging in association with regular root formation following single-visit apexification: a case report. Quintessence Int 1999; 30:560-2.
› Gupta S, Sharma A. Unmonitored apexification of wide open apex in nonvital, immature incisor: a case report. J Clin Pediatr Dent 1995; 20:145-7.
› Harbert H. One-step apexification without calcium hydroxide. J Endod. 1996; 22:690-2.
› Hayashi M, Shimizu A, Ebisu S. MTA for obturation of mandibular central incisors with open apices: case report. J Endod 2004; 30:120-2.
› Heling I, Gorfil C, Slutzky H, Kopolovic K, Zalkind M, Slutzky-Goldberg I. Endodontic failure caused by inadequate restorative procedures: review and treatment recommendations. J Prosthet Dent 2002; 87:674-8.
› Holden DT, Schwartz SA, Kirkpatrick TC, Schindler WG. Clinical outcomes of artificial root-end barriers with mineral trioxide aggregate in teeth with immature apices. J Endod 2008; 34:812-7.
› Holtzman L. Endodontic treatment of maxillary canine with dens invaginatus and immature root. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1996; 82:452-5.
› Jacobovitz M, De Pontes Lima RK. The use of calcium hydroxide and mineral trioxide aggregate on apexification of a replanted tooth: a case report. Dent Traumatol 2009; 25:e32-6.
› Jeeruphan T, Jantarat J, Yanpiset K, Suwannapan L, Khewsawai P, Hargreaves KM. Mahidol study 1: comparison of radiographic and survival outcomes of immature teeth treated with either regenerative endodontic or apexification methods: a retrospective study. J Endod 2012; 38:1330-6.
› Jung M. Endodontic treatment of dens invaginatus type III with three root canals and open apical foramen. Int Endod J 2004; 37:205-13.
› Kahler B. Endodontic retreatment of maxillary incisors previously treated with a conventional apexification protocol: a case report. Aust Endod J 2011; 37:31-5.
› Kalaskar R, Tiku A, Damle SG. Periapical repair and apical closure of a pulpless tooth using calcium hydroxide--a case report. J Indian Soc Pedod Prev Dent 2004; 22:158-61.
› Karp J, Bryk J, Menke E, McTigue D. The complete endodontic obturation of an avulsed immature permanent incisor with mineral trioxide aggregate: a case report. Pediatr Dent 2006; 28:273-8.
› Khatavkar RA, Hegde VS. Use of a matrix for apexification procedure with mineral trioxide aggregate. J Conserv Dent 2010; 13:54.
› Khetarpal A, Chaudhary S, Talwar S, Verma M. Endodontic management of open apex using Biodentine as a novel apical matrix. Indian J Dent Res 2014; 25:513.
› Khetarpal A, Chaudhry S, Talwar S, Verma M. Endodontic management of open apex using MTA and platelet–rich fibrin membrane barrier: A newer matrix concept. J Clin Exp Dent 2013; 5:e291.
› Kim ST. Successful Apexification In The Presence Of A Periapical Cyst-A Case Report. Aust Endod J 1999; 25:143-6.
› Kinirons MJ, Srinivasan V, Welbury RR, Finucane D. A study in two centres of variations in the time of apical barrier detection and barrier position in nonvital immature permanent incisors. Int J Paediatr Dent 2001; 11:447-51.
› Kleier DJ, Barr ES. A study of endodontically apexified teeth. Dent Traumatol 1991; 7:112-7.
› Kontakiotis EG, Filippatos CG, Agrafioti A. Levels of evidence for the outcome of regenerative endodontic therapy. J Endod 2014; 40:1045-53.
› Kontakiotis EG, Filippatos CG, Tzanetakis GN, Agrafioti A. Regenerative endodontic therapy: a data analysis of clinical protocols. J Endod. 2015; 41:146-54.
› Kristoffersen Ø, Nag OH, Fristad I. Dens invaginatus and treatment options based on a classification system: report of a type II invagination. Int Endod J 2008; 41:702-9.
› Kumar A, Yadav A, Shetty N. One-step apexification using platelet rich fibrin matrix and mineral trioxide aggregate apical barrier. Indian J Dent Res 2014; 25:809.
› Kumar H, Al-Ali M, Parashos P, Manton DJ. Management of 2 teeth diagnosed with dens invaginatus with regenerative endodontics and apexification in the same patient: a case report and review. J Endod 2014; 40:725-31.
› Kumar R, Patil S, Hoshing U, Medha A, Mahaparale R. MTA apical plug and clinical application of anatomic post and core for coronal restoration: A case report. Iran Endod J 2011; 6:90.
› Kumar V, Zameer M, Prasad V, Mahantesha T. Boon of MTA Apexification in Young Permanent Posterior Teeth. Case Rep Dent 2014.
› Kusgoz A, Yıldırım T, Er K, Arslan I. Retreatment of a resected tooth associated with a large periradicular lesion by using a triple antibiotic paste and mineral trioxide aggregate: a case report with a thirty-month follow-up. J Endod 2009; 35:1603-6.
› Kusgoz A, Yildirim T, Tanriver M, Yesilyurt C. Treatment of horizontal root fractures using MTA as apical plug: report of 3 cases. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2009; 107:e68-72.
› Lee LW, Hsiao SH, Chang CC, Chen LK. Duration for apical barrier formation in necrotic immature permanent incisors treated with calcium hydroxide apexification

using ultrasonic or hand filing. J Formos Med Assoc 2010; 109:596-602.
› Linsuwanont P. MTA apexification combined with conventional root canal retreatment. Aust Endod J 2003; 29:45-9.
› Ma R, Kaiwar A, Meena N, Kumari A, Shetty A, Naveen DN, Shubhashini N. Nonsurgical endodontic treatment of type II dens invaginatus. J Conserv Dent 2009; 12:73.
› Mackie IC, Bentley EM, Worthington HV. The closure of open apices in non-vital immature incisor teeth. Br Dent J 1988; 165:169-73.
› Maroto M, Barbería E, Planells P, Vera V. Treatment of a non-vital immature incisor with mineral trioxide aggregate (MTA). Dent Traumatol. 2003; 19:165-9.
› Mendoza AM, Reina ES, García-Godoy F. Evolution of apical formation on immature necrotic permanent teeth. Am J Dent. 2010; 23:269-74.
› Mente J, Hage N, Pfefferle T, Koch MJ, Dreyhaupt J, Staehle HJ, Friedman S. Mineral trioxide aggregate apical plugs in teeth with open apical foramina: a retrospective analysis of treatment outcome. J Endod. 2009; 35:1354-8.
› Mente J, Leo M, Michel A, Gehrig H, Saure D, Pfefferle T. Outcome of Orthograde Retreatment after Failed Apicoectomy: Use of a Mineral Trioxide Aggregate Apical Plug. J Endod 2015; 41:613-20.
› Mente J, Leo M, Panagidis D, Ohle M, Schneider S, Bermejo JL, Pfefferle T. Treatment outcome of mineral trioxide aggregate in open apex teeth. J Endod 2013; 39:20-6.
› Mohammadi Z, Yazdizadeh M. Obturation of immature non-vital tooth using MTA. Case report. N Y State Dent J 2011; 77:33-5.
› Moore A, Howley MF, O'Connell AC. Treatment of open apex teeth using two types of white mineral trioxide aggregate after initial dressing with calcium hydroxide in children. Dent Traumatol. 2011; 27:166-73.
› Morfis AS, Lentzari A. Dens invaginatus with an open apex: a case report. Int Endod J. 1989; 22:190-2.
› Morfis AS, Siskos G. Apexification with the use of calcium hydroxide: a clinical study. J Clin Pediatr Dent 1990; 16:13-9.
› Nagy MM, Tawfik HE, Hashem AA, Abu-Seida AM. Regenerative potential of immature permanent teeth with necrotic pulps after different regenerative protocols. J Endod. 2014; 40:192-8.
› Narang I, Mittal N, Mishra N. A comparative evaluation of the blood clot, platelet-rich plasma, and platelet-rich fibrin in regeneration of necrotic immature permanent teeth: A clinical study. Contemp Clin Dent. 2015; 6:63.
› Nayak G, Hasan MF. Biodentine-a novel dentinal substitute for single visit apexification. Restor Dent Endod 2014; 39:120-5.
› Nayar S, Bishop K, Alani A. A report on the clinical and radiographic outcomes of 38 cases of apexification with mineral trioxide aggregate. Eur J Prosthodont Restor Dent 2009; 17:150-6.
› Nosrat A, Asgary S, Eghbal MJ, Ghoddusi J, Bayat-Movahed S. Calcium-enriched mixture cement as artificial apical barrier: A case series. J Conserv Dent 2011; 14:427.
› Nuvvula S, Melkote TH, Mohapatra A, Nirmala SV. Management of immature teeth with apical infections using mineral trioxide aggregate. Contemp Clin Dent. 2010; 1:51.
› Ohara PK, Torabinejad M. Apical closure of an immature root subsequent to apical curettage. Endod Dent Traumatol 1992; 8:134-7.
› Öktem ZB, Çetinbaş T, Özer L, Sönmez H. Treatment of aggressive external root resorption with calcium hydroxide medicaments: a case report. Dent Traumatol 2009; 25:527-31.
› Oliveira TM, Sakai VT, Silva TC, Santos CF, Abdo RC, Machado MA. Mineral trioxide aggregate as an alternative treatment for intruded permanent teeth with root resorption and incomplete apex formation. Dent Traumatol 2008; 24:565-8.
› Pace R, Giuliani V, Nieri M, Di Nasso L, Pagavino G. Mineral trioxide aggregate as apical plug in teeth with necrotic pulp and immature apices: a 10-year case series. J Endod 2014; 40:1250-4.
› Pai SF, Yang SF, Lin LM. Nonsurgical endodontic treatment of dens invaginatus with large periradicular lesion: a case report. J Endod 2004; 30:597-600.
› Parashos P. Apexification: case report. Aust Dent J 1997; 42:43-6.
› Park JB, Lee JH. Use of mineral trioxide aggregate in the open apex of a maxillary first premolar. J Oral Sci 2008; 50:355-8.
› Paul ML, Mazumdar D, Vyavahare NK, Baranwal AK. Healing of the periapical lesion in posterior teeth with mineral trioxide aggregate using orthograde technique-Two case reports. Contemp Clin Dent 2012; 3:S264.
› Paula-Silva FW, Rocha CT, Flores DS, Nelson-Filho P, Silva LA, de Queiroz AM. Root canal treatment of an immature dens invaginatus with apical periodontitis: a case report. J Dent Child (Chic) 2011; 78:66-70.
› Peters LB, Wesselink PR. Periapical healing of endodontically treated teeth in one and two visits obturated in the presence or absence of detectable microorganisms. Int Endod J. 2002; 35:660-7.
› Piekoff MD, Trott JR. Apexification: report of case. J Endod 1976; 2:182-5.
› Pinar Erdem A, Sepet E. Mineral trioxide aggregate for obturation of maxillary central incisors with necrotic pulp and open apices. Dent Traumatol 2008; 24:e38-41.
› Pradhan DP, Chawla HS, Gauba K, Goyal A. Comparative evaluation of endodontic management of teeth with unformed apices with mineral trioxide aggregate and calcium hydroxide. J Dent Child (Chic) 2006; 73:79-85.
› Rafter M. Apexification: a review. Dent Traumatol 2005; 21:1-8.
› Raldi DP, Mello I, Habitante SM, Lage-Marques JL, Coil J. Treatment options for teeth with open apices and apical periodontitis. J Can Dent Assoc 2009; 75:591-6.
› Rosenberg B, Murray PE, Namerow K. The effect of calcium hydroxide root filling on dentin fracture strength. Dent Traumatol 2007; 23:26-9.
› Rudagi KB, Rudagi BM. One-step apexification in immature tooth using grey mineral trioxide aggregate as an apical barrier and autologus platelet rich fibrin membrane as an internal matrix. J Conserv Dent 2012; 15:196.
› Sarris S, Tahmassebi JF, Duggal MS, Cross IA. A clinical evaluation of mineral trioxide aggregate for root-end closure of non-vital immature permanent incisors in children-a pilot study. Dent Traumatol 2008; 24:79-85.
› Schmitz MS, Montagner F, Flores CB, Morari VH, Quesada GA, Gomes BP. Management of dens invaginatus type I and open apex: report of 3 cases. J Endod 2010;36:1079-85.
› Schumacher JW, Rutledge RE. An alternative to apexification. J Endod 1993; 19:529-31.
› Sedgley CM, Wagner R. Orthograde retreatment and apexification after unsuccessful endodontic treatment, retreatment and apicectomy. Int Endod J 2003; 36:780-6.
› Selden HS. Apexification: an interesting case. J Endod 2002; 28(1):44-5.
› Seltzer S. The root apex. In: Seltzer S, Krasner P, eds. Endodontology: Biologic Considerations in Endodontic Procedures. Malvern, PA: Lea & Febiger; 1988:1–30.
› Shabahang S, Torabinejad M, Boyne PP, Abedi H, McMillan P. A comparative study of root-end induction using osteogenic protein-1, calcium hydroxide, and mineral trioxide aggregate in dogs. J Endod 1999; 25:1-5.
› Shadmehr E, Farhad AR. Clinical management of dens invaginatus type 3: a case report. Iran Endod J 2011; 6:129.
› Sheehy EC, Roberts GJ. Use of calcium hydroxide for apical barrier formation and healing in non-vital immature permanent teeth: a review. Br Dent J 1997; 183:241-6.
› Shekhar V, Arora R, Roy M. Role of Cone Beam Computed Tomography and White Mineral Trioxide Aggregate in the Successful Management of a Permanent Anterior Tooth with Open Apex. J Int Oral Health 2014; 6:68.
› Shekhar V, Shashikala K. Cone Beam Computed Tomography evaluation of the periapical status of nonvital tooth with open apex obturated with mineral trioxide aggregate: a case report. Case Rep Dent 2013.
› Silberman A, Cohenca N, Simon JH. Anatomical redesign for the treatment of dens invaginatus type III with open apexes: a literature review and case presentation. J Am Dent Assoc 2006; 137:180-5.
› Silva EJ, Zaia AA. Open apex type III dens invaginatus: a rare case report of an endodontic retreatment with an anatomical redesign. Gen Dent 2011; 60:e389-92.
› Silva RV, Silveira FF, Nunes E. Apexification in non-vital teeth with immature roots: report of two cases. Iran Endod J 2015; 10:79.
› Simon S, Rilliard F, Berdal A, Machtou P. The use of mineral trioxide aggregate in one-visit apexification treatment: a prospective study. Int Endod J 2007; 40:186-97.
› Sinha N, Singh B, Patil S. Cone beam-computed topographic evaluation of a central incisor with an open apex and a failed root canal treatment using one-step apexification with Biodentine™: A case report. J Conserv Dent 2014; 17:285.
› Soares J, Santos S, César C, Silva P, Sá M, Silveira F, Nunes E. Calcium hydroxide induced apexification with apical root development: a clinical case report. Int Endod J 2008; 41:710-9.
› Souza RA, Silva-Sousa YT, Colombo S, Lago M, Duarte MA, Pécora JD. Healing of a tooth with an overinstrumented apex, extensive transportation and periapical lesion using a 5 mm calcium hydroxide apical plug: an 8-year follow-up report. Braz Dent J 2012; 23: 608-11.
› Sridhar N, Tandon S. Continued root-growth and apexification using a calcium hydroxide and iodoform paste (metapex®): 3 case reports. J Contemp Dent Pract 2010; 11:063-70.
› Stefopoulos S, Tzanetakis GN, Kontakiotis EG. Non-surgical retreatment of a failed apicoectomy without retrofilling using white mineral trioxide aggregate as an apical barrier. Braz Dent J 2012:167-71.
› Su HL. Dens evaginatus: report of case of continued root development after Ca (OH) 2 apexification. ASDC J Dent Child 1991; 59:285-8.
› Sübay RK, Kayataş M. Dens invaginatus in an immature maxillary lateral incisor: a case report of complex endodontic treatment. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2006; 102:e37-41.
› Tarjan I, Rozsa N. Endodontic treatment of immature tooth with dens invaginatus: a case report. Int J Paediatr Dent 1999; 9:53-6.
› Thäter M, Marechaux SC. Induced root apexification following traumatic injuries of the pulp in children: follow-up study. ASDC J Dent Child 1987; 55:190-5.
› Torabinejad M, Chivian N. Clinical applications of mineral trioxide aggregate. J Endod 1999; 25:197-205.
› Torabinejad M, Hong CU, Lee SJ. Investigation of mineral trioxide aggregate for root end filling in dogs. J Endod 1995; 21:603–8.
› Trope M. Treatment of immature teeth with non-vital pulps and apical periodontitis. Endodontic topics 2006; 14:51-9.
› Umashetty G, Patil B, Rao N, Ajgaonkar N. Apical Closure of Nonvital Permanent Teeth: 15 Months Follow-up Study of Four Cases. J Int Oral Health 2015; 7:1-3.
› Vanka A, Ravi K, Shashikiran N. Apexification with MTA using internal matrix: report of 2 cases. J Clin Pediatr Dent 2010; 34:197-200.
› Vellore KG. Calcium hydroxide induced apical barrier in fractured nonvital immature permanent incisors. J Indian Soc Pedod Prev Dent 2010; 28:110.
› Vijayran M, Chaudhary S, Manuja N, Kulkarni AU. Mineral trioxide aggregate (MTA) apexification: a novel approach for traumatised young immature permanent teeth. BMJ Case Rep 2013:bcr2012008094.
› Walia T, Singh Chawla H, Gauba K. Management of wide open apices in non-vital permanent teeth with Ca (OH) 2 paste. J Clin Pediatr Dent 2001; 25:51-6.
› Wang SH, Chung MP, Su WS, Cheng JC, Shieh YS. Continued root formation after replantation and root canal treatment in an avulsed immature permanent tooth: a case report. Dent Traumatol 2010; 26:182-5.
› Warner JJ, Al-Salehi SK. Management of open apex in a central incisor using mineral trioxide aggregate. Dent update 2010; 38:50-2.
› Weiger R, Rosendahl R, Löst C. Influence of calcium hydroxide intracanal dressings on the prognosis of teeth with endodontically induced periapical lesions. Int Endod J 2000; 33:219-26.
› Witherspoon DE, Small JC, Regan JD, Nunn M. Retrospective analysis of open apex teeth obturated with mineral trioxide aggregate. J Endod 2008; 34:1171-6.
› Yadav P, Pruthi PJ, Naval RR, Talwar S, Verma M. Novel use of platelet-rich fibrin matrix and MTA as an apical barrier in the management of a failed revascularization case. Dent Traumatol 2015; (4):328-31.
› Yang SF, Yang ZP, Chang KW. Continuing root formation following apexification treatment. Endod Dent Traumatol 1990; 6:232-5.
› Yassen GH, Chin J, Mohammedsharif AG, Alsoufy SS, Othman SS, Eckert G. The effect of frequency of calcium hydroxide dressing change and various pre-and inter-operative factors on the endodontic treatment of traumatized immature permanent incisors. Dent Traumatol 2012; 28:296-301.
› Yeh SC, Lin YT, Lu SY. Dens invaginatus in the maxillary lateral incisorTreatment of 3 cases. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1999; 87:628-31.
› Zhu WH, Pan J, Yong W, Zhao XY, Wang SM. Endodontic treatment with MTA of a mandibular first premolar with open apex: case report. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2008; 106:e73-5.