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Interventions for treating traumatized necrotic immature permanent anterior teeth: inducing a calcific barrier & root strengthening **REVIEW ARTICLE**

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Abstract – Background: Apical barrier formation and root strengthening procedures have been extensively described in the literature. This systematic review attempts to establish where the effects of interventions using multi-visit apexification, single visit apical plug techniques and root strengthening procedures are consistent and where they may vary significantly. *Objectives*: To evaluate the relative effectiveness of apexification and apical plug techniques as well as root strengthening procedures for treating traumatized necrotic immature permanent anterior teeth through a systematic review of randomized controlled trials. Reported immediate and/or long-term adverse events and effects of the materials and techniques are also evaluated. Search strategy & selection criteria: Structured electronic and hand search was performed with no restriction on the language of publication. Only randomized controlled trials comparing different apical barrier formation techniques and root strengthening procedures in traumatized necrotic immature anterior teeth were assessed. Results: Two hundred studies were identified but only two were suitable for inclusion. Included studies investigated multi-visit apexification techniques using calcium hydroxide and tricalcium phosphate. There were no eligible studies investigating root strengthening procedures or any other intervention for apical barrier formation in necrotic immature anterior teeth. No reliable information was available on long-term adverse effects of the reported interventions or cost implications. Conclusions: Based on two included studies, there is weak evidence supporting the use of either calcium hydroxide or tricalcium phosphate for apical barrier formation in necrotic immature anterior teeth employing multivisit apexification techniques. The evidence is insufficient to provide guidelines for practice. There was no reliable evidence on adverse events or long-term effects after the use of calcium hydroxide or tricalcium phosphate justifying caution in their use in apical barrier formation techniques.

Background

In immature teeth where there is loss of vitality clinicians face a challenge. The root has thin dentine walls liable to fracture under physiological forces and a wide, open apex which is time consuming and technically difficult to treat. The treatment first requires the elimination of bacterial infection from the root canal and the prevention of re-infection of this space. Disinfection of the root canal space is straight forward for most cases; however, there is no natural apical constriction or stop against which a suitable root filling material can be placed to prevent re-infection of this space. Therefore one of the aims of treatment is to produce a barrier, against which a root canal filling material can be placed thereby preventing the extrusion of material into the surrounding tissues as well as providing a restoration that reinforces or strengthens the weak immature dentinal

root walls in an attempt to improve aesthetics and function.

Apexification

The technique involves cleaning and filling the root canal with a temporary paste to stimulate the formation of calcified tissue at the apex. This paste is later removed after radiographic and clinical evidence of apical closure and a permanent filling of gutta-percha is placed in the canal. Apexification techniques have been widely used since it was described by Frank (1). Several techniques have been described, that involve the removal of necrotic pulp tissue followed by cleaning of the canal with or without the placement of a medicament as described by Chawla (2) in a case series study, as well as in other case reports (3, 4). Another technique has been described using an antiseptic paste or solution left in the root canal following root canal cleaning (3). Several reports suggested that apical closure can be induced by control of infection alone (3–9) as well as following treatment with tetracycline (10). Over-instrumentation of the root canals to induce periapical tissue bleeding has been reported in the literature (11–14). This was thought to stimulate the formation of new healthy vascularized tissue in the root canal which will organize and induce an apical barrier.

Apical plug techniques

These describe packing of a material into the apical 2–4 mm of an immature canal to act as a barrier against which gutta-percha is condensed. Many materials have been used to form apical barriers such as:

- 1 Calcium hydroxide paste (15).
- **2** Calcium hydroxide powder; mixed with CMCP (camphorated-mono-chlorophenol), metacresyl acetate, cresenol, saline, Ringer's solution, distilled water or anaesthetic solution (16–19).
- 3 Tricalcium phosphate (13, 14, 20).
- 4 Collagen calcium phosphate (21).
- 5 Osteogenic protein-1 (22).
- 6 Bone growth factor (23).
- 7 Mineral trioxide aggregate (MTA) (24).
- 8 Oxidized cellulose (Surgicel) use has been also reported (25).
- **9** Proplast, a poly-tetrafluor-ethylene and carbon feltlike porous material (26).
- **10** Decalcified allogenic bone matrix & Barium hydroxide (27).
- 11 True bovine bone ceramics and dentine chips as plugs (28).
- 12 Antibacterials such as camphorated-mono-chlorophenol (29) or metronidazole (30) were used as intracanal medications to stimulate apexification. Some reports suggested that apical closure can be induced by control of infection alone. This was achieved with minimal mechanical intervention and dressing of the root canal with an antiseptic or antibiotic paste, or a mixture of those (3, 4, 6–10).

Root strengthening

The risk of root fracture during apexification is a concern. It was reported that 60% of all endodontically treated teeth with immature root formation have had cervical fractures due to minor impacts and sometimes even spontaneous fractures have occurred (31). The risk of root fracture was quantified by maturity of root formation (32). A figure of 32% of teeth suffered cervical root fracture following apexification was reported (33). This was due to minor traumatic episode or due to spontaneous fractures in the rest of their cases. This late stage failure of apexification has lead researchers to start looking at whether the root can be strengthened in addition to inducing a barrier. Root strengthening interventions can be divided into the following three categories.

Adhesive resins as a root strengthening material

Adhesive dental materials may offer an opportunity to reinforce the endodontically treated tooth through the use of adhesive sealers in the root canal system. The bonding of endodontic sealers to intra radicular dentin might possibly enhance resistance to fracture of endodontically treated teeth especially in cases where there are thin weak dentinal walls as in immature permanent teeth. The use of a root canal sealer with the additional quality of strengthening the root against fracture would then be of value (34, 35).

Glass ionomer cements as a root strengthening material

The use of glass ionomer cements in endodontics has been suggested by several investigators (36, 37). Its use has been shown to have long-term adhesive effects by bonding to the hydroxyapatite component of dentine (38, 39). Glass ionomer based endodontic sealers have been suggested for the potential increase in resistance to root fracture and thus root reinforcement (36). On the other hand, it was reported in an *in vitro* study (40) that the reinforcement of glass ionomer sealer in the root canals was not demonstrated.

Fibre glass posts

Fibre posts were introduced in 1990 (41). The biomechanical properties of fibre-reinforced composites (FRC) posts have been reported to be close to those of dentin (42) with a modulus of elasticity similar to that of dentine (43). This seems to reduce stress transmission to the root canal walls by the post, thus avoiding possible root fractures (44). The combination of a fibre post and bisphenol A glycerolate dimethacrylate (Bis-GMA)-based resin cement has been described as a homogeneous structure that may reinforce weak dentinal walls of an immature root canal by replacing dentine mechanically thus contributing to stress absorption (45). Recently introduced, FRC posts are made of a material having silanated glass fibres impregnated with an interpenetrating polymer network resin matrix (46). This system has been described as being able to chemically bond to luting root canal cement (47).

Objectives of this systematic review

- To evaluate the relative effectiveness of the following interventions for treating traumatized necrotic immature permanent anterior teeth:

 (a) apexification techniques;
 - a) apexilication techniques,
 - (b) apical plug techniques and;
 - (c) root strengthening procedures.
- **2** To evaluate any immediate and/or long-term side effects and limitations for the materials and techniques used.

Null hypotheses

1 There is no difference between apexification and apical plug techniques as an intervention for inducing an apical barrier in traumatized necrotic immature permanent anterior teeth.

- **2** There is no difference in the proportion of teeth exhibiting clinical and/or radiological signs of failure following various types of treatment for inducing an apical barrier.
- **3** There is no difference in the proportion of treated teeth showing root fractures whether root strengthening procedures are used or not used.

Methods of the review

Electronic search

OVID[®] (Ovid Technologies, New York, NY, USA) electronic bibliographic databases were searched for relevant reports from 1966 till the end of this study in October 2006 using a structured search strategy. This was done to determine an article's relevance to this review based on the title and abstract. The subject search strategy for Medline via Ovid[®] used a combination of controlled vocabulary and free text terms. Databases searched via OVID gateway are shown in Table 1. There was no restriction for the language of publication.

Hand searching

Hand searching was undertaken to identify key articles, using citation databases to search for any paper that cites a seminal article, to identify authors or institutions working in this particular topic area and to search for papers originating from these sources. Additional hand searching was done for the volumes and issues of the identified key journals to manually search through indexes, bibliographies or issues of these journals.

Personal contact

Personal communication via e-mail with the author(s) and journals of the identified potentially relevant clinical trials was performed to obtain further full text information on their published studies and to identify ongoing, unpublished or unlisted studies that may be eligible for inclusion in this review.

The manufacturers of dental materials were contacted to obtain information on relevant published or unpublished clinical studies. Communication was

Table 1. Database se	arch via OVID
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ACP Journal Club (ACP)			
Cochrane Central Register of Controlled Trials (CENTRAL)			
Cochrane Database of Systematic Reviews (CDSR)			
Cochrane Oral Health Group Trials Register			
Database of Abstracts of Reviews of Effects (DARE)			
EMBASE databases; the Excerpta Medica Database (EMBASE), EMBASE			
Drugs and Pharmacology (EMDP), and EMBASE Psychiatry (EMPS)			
Index to Scientific and Technical Proceedings			
National Library of Medicine – Toxnet (http://toxnet.nlm.nih.gov)			
Ovid MEDLINE(R) (1966 to date)			
Ovid MEDLINE(R) (daily update)			
Ovid MEDLINE(R) in-process, other non-indexed citations			
Science Citation Index Expanded			
Social Science Citation Index			
System for Information on Grey Literature in Europe			

established with only one company (Stick Tech Ltd., Turku, Finland) via e-mail. They provided further information on four studies (47–49). None of these reports was a randomized controlled clinical trial fulfilling the inclusion criteria of this review.

Attempts to contact authors of reports in languages other than English were unsuccessful. However, we were able to locate some of these studies with the help of the Cochrane Oral Health Group and the British Library through the University of Leeds Health Sciences Library. These studies were obtained in full text and were translated into English, but none of the reports was a randomized controlled trial fulfilling the inclusion criteria of this review.

Description of studies

Completed searches from all sources identified 200 reports. Following to scanning of the titles and abstracts of these reports; 33 electronically identified reports were non-relevant to the review topic and were rejected; leaving 167 reports of different study designs to be assessed. Abstracts and full text were obtained whenever there was a doubt that the article could not be definitely rejected. Where the article is accepted, information from it was then formally extracted and analysed. A diagrammatic representation of the assessment process is shown in Fig. 1. All studies other than prospective clinical trials (i.e. planned experimental interventional studies designed to evaluate the effect of a treatment on a clinical outcome in humans) were excluded leaving 11 studies for further assessment. There was no prospective controlled clinical trial looking at root strengthening interventions for necrotic immature permanent anterior teeth that were detected by all the methods of searching applied.

Examination of full text reports was performed and the data abstraction form was pilot tested by two reviewers independently and in duplicate. Pilot testing gave 100% agreement on the study eligibility for inclusion and 80% agreement on deciding the risk of bias according the review criteria. Further discussions resulted in 100% agreement on the assessment of methodological quality of the pilot sample.

The methodological quality assessment of evaluated studies was based on the criteria described by Higgins & Green (50). Accordingly, two studies were eligible to be included in this review. Studies included were: Roberts and Brilliant (13) and Mackie et al. (54). Both studies investigated multi-visit apexification techniques and two different materials:

- 1 Calcium hydroxide vs tricalcium phosphate as multivisit apexification agent (13).
- 2 Two types of calcium hydroxide paste; Reogan Rapid[®] (Reogan Rapid, Vivadent, Liechtenstein) vs Hypo-cal[®] (Ellman Int'l Inc., New York, NY, USA) as multi-visit apexification agents (54).

Four studies: Coviello and Brilliant (14), Yates (51), Merglova (52) and Dominguez Reyes et al. (53) were fully analysed before being excluded. Reasons for their exclusion are shown in Table 2. These studies had problems in their study design severely affecting their validity as shown in Table 3.



Assessment process for identified studies

Fig. 1. Assessment process for identified studies.

Characteristics of included studies

One study was conducted in the United States of America (13), and one in the United Kingdom (54). Both studies were conducted in a university teaching hospital environment.

Characteristics of the participants in included studies

Roberts and Brilliant (13) reported the age and sex of each patient included in their study with an age range of 8–23 years. Mackie et al. (54) fully reported the age of their patients and divided them into two age groups of 6–10 year olds and 11 years and above group.

Both studies included patients with necrotic immature permanent anterior teeth due to a traumatic injury as an initial diagnosis. Some patients were symptom free at the initial examination but showed arrested root development and a wide open apex compared to contra-lateral teeth whereas most of the patients presented with clinical signs and symptoms related to these teeth with necrotic pulps (pain, intra-oral swellings and sinuses) as well as radiographic signs of periapical pathology related to these teeth.

Characteristics of the interventions described by included studies

Materials used for apexification or apical barrier formation

Roberts and Brilliant (13) compared tricalcium phosphate to Calcium hydroxide as multi-visits apexification powders. Mackie et al. (54) compared two different

Table 2. Description of excluded studies

Study	Reason for exclusion
Coviello & Brilliant 1979 (14)	Control group (apexification) participants were randomly selected without reporting the method of randomization. There was no information reported on selection of the experimental group participants (apical plug group). Age and sex of participants were not reported. Clear inclusion criteria were not stated. Patients were excluded from the final analysis after the treatment had started due to either inadequate follow-up (less than 6 months) or if the treatment was not completed by root canal obturation. Drop-outs & excluded cases were not included in the analysis. Barrier detection technique (apexification group) was not reported
Dominguez Reyes et al. 2005 (53)	Control group were healthy contra-laterals (incomparable groups & cannot be considered a control group as no intervention was provided to this group Selective reporting of study results as well as follow-up tests done (e.g. Performing vitality testing and not reporting the results due to 'un-reliability' of the test raise more concern regarding the possibility of bias
Merglova 2001 (52)	Control group was treated with periapical surgical method (Kominek & Rozkovcova 1968). Teeth in this group had been necrotic due to several kinds of injury. The control group was not followed-up, no further information was available on this group
Yates 1988 (51)	Control group allocation is not clear. This group was formed from patients who received treatment that deviated from the treatment protocol. This cannot be considered as 'control'. Also this group has many confounding variables as well as being not a homogenous group

Table 3. Methodological quality assessment of excluded studies

	Excluded studies			
Quality assessment	Coviello & Brilliant 1979 (14)	Yates 1988 (51)	Merglova 2001 (52)	Dominguez Reyes et al. 2005 (53)
Randomization & allocation concealment	Unmet: Inadequate randomization & no concealment	Unmet	Unmet	Unmet
Exclusion & inclusion criteria	Unclear	Met	Unclear	Unclear
Control & treatment groups comparability	Unmet: large potential for confounding	Unmet: large potential for confounding	Unmet	Unmet
Protection against performance bias (blindness of the study)	Partially met	Unmet: no blinding	Blinding not possible	Unmet: no blinding
Follow-up of participants	Met: more than 80% are included in analysis	Unclear: no reported	Unmet	Unclear: not reported
Success & failure criteria	Unclear	Met	Unclear	Met
Intention-to-treat	Partially met: withdrawals stated, analysis unmodified	Unmet: not mentioned	Partially met: withdrawals stated, analysis unmodified	Unmet: not mentioned
The global validity of the study	High risk of bias: two unmet criteria	High risk of bias: four unmet criteria	High risk of bias: three unmet criteria	High risk of bias: four unmet criteria

commercial brands of calcium hydroxide pastes. Both were used as multi-visits apexification agents.

Intra canal medicaments other than apexification agents and solutions used for root canal irrigation

- 1 Roberts and Brilliant (13) used in their initial visit a 5.25% sodium hypochlorite solution for both treatment groups followed by a sterile cotton pledget moistened with formocresol and plotted dry was left inside pulp chamber for 7–10 days. In the second visit the same concentration of sodium hypochlorite solution was used before the apical plug of the tested materials were packed into the root canal apical 4 mm.
- **2** Mackie et al. (54) used normal saline irrigation throughout treatment and in cases with infection and pus presence in the root canal a poly-antibiotic paste was used on a weekly intervals as indicated till the infection was controlled and then calcium hydroxide apexification was started.

Technique for apical barrier detection

The clinical method used to detect apical barrier formation and apical closures was almost the same in both studies and was based on the tactile sensation felt by the operator to detect an apical stop. Radiographs were used as an adjunct to the clinical technique in both studies, with variable degree of reliability. Roberts and Brilliant (13) used a curved endodontic file of the same size of that used in their working length determination. Mackie et al. (54) used paper points to feel the apical stop and to detect any intracanal haemorrhage or exudate.

Materials used as an intermediate restoration between visits

Both studies (13, 54) used reinforced Zinc Oxide and Eugenol as an intermediate restoration for coronal seal of the root canal till apexification has occurred.

Materials & techniques used for final root canal obturation following to barrier formation

Final obturation was done using gutta-percha in both studies but with different techniques. Roberts and Brilliant (13) used the chemically plasticised gutta-percha-chlororosin technique, where gutta-percha master cone and accessory cones were dipped individually in chlororosin for 20–25 and 5 s respectively prior to packing and lateral condensation into the root canal using spreaders. Mackie et al. (54) used multiple gutta-percha points with a non setting Zinc Oxide and Eugenol sealer employing a lateral condensation technique.

Other interventions

Both studies reported the use of rubber dam for isolating teeth during the provision of treatment. Roberts and Brilliant (13) reported deliberate over-instrumentation of root canal to establish bleeding before the use of their apical plug test materials.

Characteristics of the outcome measures reported in included studies

Success rate of the medicament used in apical barrier formation and the time required were the main outcomes assessed by studies included. In addition to these outcomes, individual studies assessed other specific outcomes:

- **1** Roberts and Brilliant (13) assessed the presence & solubility of tricalcium phosphate and calcium hydroxide powder in the root canals clinically and radiographically as well as progression or healing of the original pathology radiographically (periapical rarefaction, and internal or external root resorption) at the recall visits.
- **2** Mackie et al. (54) assessed the number of dressings (visits) required for both calcium hydroxide preparations under investigation.

Methodological quality assessment of included studies

Included studies (13, 54) were rated according to the review's methodological quality assessment criteria as described by Higgins & Green (50). Both studies were rated as having 'High risk of bias' as they had one or more of the assessment criteria 'unmet' and there was plausible bias that seriously weakens the confidence in the results. Table 4 describes the methodological quality assessment criteria applied to included studies.

Method of allocation concealment

Neither study has reported allocation concealment of participants to either group.

In the study by Mackie et al. (54), allocation was done using toss-coin followed by alternation. Patients were stratified according to their age and apical width of studied teeth into four groups. The allocation of the first tooth to each stratum was done by toss-coin, then if the patient had another tooth to be included; it was allocated to the other group by alternation. Allocation procedure for patients to each group in the study by Roberts and Brilliant (13) was stated clearly in their paper and was done by alternation. There was no further information regarding how the sample was selected.

Definition of exclusion & inclusion criteria in included studies

Roberts and Brilliant (13) included necrotic immature teeth in their study [15 incisors and one premolar]. Criteria used for the diagnosis of loss of vitality were clearly reported in tables for each tooth. This was based on radiographic identification of periapical rarefaction and clinical signs & symptoms of tenderness to percussion, pain on palpation, presence of sinus tracts, tooth discolouration, presence or absence of tooth fracture, mobility and finally the presence or absence of pain.

Mackie et al. (54) included necrotic immature incisors in their study, but without defining the criteria for this diagnosis. Further communication with the first author clarified that inclusion was based on clinical signs, pain history, ethyl chloride cold test and radiographic evidence of periapical pathology. Exclusion criteria were also clear, as replanted teeth following to avulsion injuries or teeth showing radiographic evidence of external root resorption were excluded. These exclusion criteria were justified by being reasons for increased failure rates of apical barrier formation based on previous case report (55) and a retrospective study (56).

Control and treatment groups' comparability in included studies

Differences between comparison groups in numbers of patients allocated to each group, age, root developmental stage, initial diagnosis, type of original injury, type of coronal seal used with the possibility of re-infection of the canal space and many other unknown confounding factors can affect apical barrier formation. Confounding factors can distort the apparent magnitude of treatment

Table 4. Methodological quality assessment of included studies

Criteria of assessment	Roberts and Brilliant 1975 (13)	Mackie et al. 1994 (54)
Randomization & allocation concealment Exclusion & inclusion criteria	Unmet: inadequate randomization & no concealment Unclear	Partially met: adequate randomization & no concealment Met
Control & treatment groups comparability Protection against performance bias (blindness of the study)	Confounding small Partially met	Good comparability & confounding adjusted for Unmet: no blinding
Follow-up of participants Success & failure criteria Intention-to-treat analysis The global validity of the study	Met: more than 80% are included in analysis Unclear Partially met: withdrawals stated, analysis unmodified High risk of bias: one unmet criterion	Met: more than 80% are included in analysis Unclear Partially met: withdrawals stated, analysis unmodified High risk of bias: one unmet criterion

effects if not controlled or adjusted for. Randomization is the only means of allocation that controls for unknown and unmeasured confounders as well as those that are known and measured (57). Roberts and Brilliant (13) had healthy patients with 16 necrotic open apex teeth. Participants were divided into two groups using alternation. Both groups had the same number of teeth and both groups were matched for age, periapical and pulp conditions. The stage of root development and the type of trauma inflicted are examples of such confounders that were not described or accounted for. Five out of eight teeth from the group treated with calcium hydroxide had concomitant crown fractures of different severity compared to only two teeth in the tricalcium phosphate group. The difference in the severity of original trauma inflicted in both groups may have affected the outcome (success or failure), also the use of an inadequate randomization with no allocation concealment, and the small numbers in each group may denote a large potential for the study results to be affected by any of these factors.

Mackie et al. (54) dealt with confounders (factors that may affect the outcomes) by creating sub-groups and stratifying the data set by the levels of the confounding variables (e.g. age or apical width) and then perform analysis separately in each sub-group. In this study, participants were stratified according to their age and the apical teeth width and divided into four groups; 6-10 years old with apical width 2 mm or less, 6–10 years old with apical width >2 mm, 11 years & older with apical width 2 mm or less and finally 11 years & older with apical width >2 mm. This sub-grouping was based on previous studies (55, 56) that showed that the time and number of calcium hydroxide dressings needed to achieve apical closure might be influenced by the age of the patient and the width of the apical foramen. Whilst this approach is simple and recommended when there are few confounders, e.g. age and apical width, the subgroups might become small and the analysis will have reduced power to detect a significant effect. In this study sub-group analyses were not performed but both comparison groups (Reogan Rapid[®] & Hypo-Cal[®]) were matched for age and apical width and the final analysis was done based on these two main groups.

Protection against performance bias (blindness of the studies included)

Performance bias refers to systematic differences in the care provided to participants other than the intervention under investigation. To protect against unintended differences in care and placebo effects, those providing and receiving care can be 'blinded' so that they do not know the group to which the recipients of care have been allocated. Some research suggests that such blinding is important in protecting against bias (58, 59).

Roberts and Brilliant (13) clearly reported that operators were blinded to both tested medicaments (calcium hydroxide & tricalcium phosphate). Both powders were placed in identical, sealed, and coded glass vials. The identity of the canal dressing was not available to the clinician when the powder was placed into the root canal. Blinding was not reported during re-application of the medicaments or during follow-up assessment visits. Mackie et al. (54) did not report any blinding attempt at any stage of their study. This was confirmed by further communication with the first author.

Follow-up of participants in included studies

Follow-up of participants can be considered adequate if not less than 80% of the total patients included in the trial were included in the final analysis (50). Roberts and Brilliant (13) reported one drop-out which was from the control group (n = 8). Teeth that were available at the end of the study were 15 out of 16 recruited teeth (93.8%). There was no statistical analysis performed and no further follow-up for patients after root canal obturation has been completed. Mackie et al. (54) reported one drop-out (one patient with one tooth) and two exclusions (two patients with one tooth each). At the end of the study, there were 33 children with 38 teeth (out of 41) available for final analysis (86.8%).

Definition of success and failure criteria described by included studies

Roberts and Brilliant (13) had three failed cases in their study that were described clearly. Apical closure did not occur in two teeth during the study period (one treated with calcium hydroxide and one tricalcium phosphate) and in one tooth (previously avulsed and replanted) internal & external root resorption occurred after 6 months of tricalcium phosphate treatment. Although this study aimed to assess the progression or healing of the original pathology present in these teeth (periapical rarefaction and internal or external root resorption) these criteria were not considered in the success or failure of treatment provided. Treatment was considered successful if an apical barrier was felt clinically using a small size file and teeth were obturated with gutta-percha.

Mackie et al. (54) study's objective was to compare the success rate of two brands of calcium hydroxide pastes regarding the time needed and number of visits required for apical barrier formation. There was no follow-up after apical barrier formation and root canal obturation.

Intention-to-treat analysis

Intention-to-treat (ITT) analysis aims to include all participants randomized into a trial irrespective of what happened subsequently. An estimated treatment effect may be biased if some randomized participants are excluded from the analysis (60, 61). It is widely agreed that trial participants should be analysed in the groups to which they were randomized regardless of which (or how much) treatment they actually received, and regardless of other protocol irregularities, such as ineligibility (62).

Roberts and Brilliant (13) had three failed cases in their study and the group they belonged to were reported. Although there was no statistical analysis performed, the results were fully described in tables. Mackie et al. (54) based their final analysis on successful cases only (33 teeth out of 41). The reported drop-out case failed to keep treatment appointments and self discharged, while the two other excluded participants had treatment with both calcium hydroxide brands under investigation.

Results

As there is no 'gold standard' for the measurement of 'true' validity of a trial (59, 63); this systematic review used a simple approach for assessing the validity of studies that can be fully reported and based on how each trial scored on each criterion.

Included studies (13, 54) addressed one techniques and two material used to induce apical barrier formation. Studies showed clear clinical diversity (clinical heterogeneity) between them due to the variability in the characteristics of participants and treatment provided. This diversity was also evident in the included trials design and quality (methodological diversity or methodological heterogeneity). A test of heterogeneity between trials and sub-group analyses were not possible because of the limited number of included studies and their small samples size. The following comparisons should be interpreted with caution.

Success of apical barrier formation using different materials and techniques

Calcium hydroxide compared to tricalcium phosphate in multi-visit apexification

The results reported by Roberts and Brilliant (13) showed 87.5% (seven out of eight teeth) had a successful apical barrier formed using calcium hydroxide powder compared to 75% (six out of eight teeth) treated with tricalcium phosphate. Small numbers of participants in both groups did not allow any difference between materials to be identified. One drop-out was reported (calcium hydroxide group). ITT analysis reduced the success rate to 75% in this group Fig. 2.

Reogan Rapid[®] and Hypo-cal[®] as multi-visits agents inducing apical barrier

Mackie et al. (54) compared two calcium hydroxide paste preparations. The success for both brands was 100% based on available patients at the time of final analysis (33 children with 38 teeth out of 36 children with 41 teeth). Drop-outs (one patient with one tooth) and excluded cases (two patients with two teeth) were not included in the final analysis. ITT analysis if done; would change the total success into 92.7%, which is still a favourable per cent of success. It should be noted that both comparison groups were calcium hydroxide preparations and the results should be interpreted based on comparing Reogan Rapid[®] to Hypo-cal[®]. This should not to be interpreted as a general success rate for calcium hydroxide material in multi-visit apexification due to the lack of comparison with other materials. The success of calcium hydroxide when used in multi-visit apexification in included studies (13, 54) is presented in Fig. 2.

Time required & number of visits for apical barrier formation using different materials and techniques

Time required to achieving an apical barrier was reported by both studies whereas the number of visits was reported by only one as shown in Fig. 3. There was no information provided on cost implications for the use of different treatment interventions.

Roberts and Brilliant (13) reported the number of months needed to complete the apexification treatment for every patient in each group. The calcium hydroxide group needed 6.71 months whereas the tricalcium phosphate group needed 6.75 months to complete the treatment. Number of visits was not reported.

Mackie et al. (54) compared two calcium hydroxide paste preparations regarding the time required to achieve an apical closure and the number of dressings (visits) needed. The mean time to achieve an apical barrier in the Reogan Rapid[®] group was 6.8 months with an average of 3.1 visits and for the Hypo-cal[®] group the mean time



Fig. 2. Apexification using both materials in included studies.



Fig. 3. Mean time & number of visits to obtain an apical barrier using calcium hydroxide multi-visit apexification.

to achieve closure was 5.1 months with an average of 2.1 visits. There was no statistically significant difference between the two medications in both the time needed to obtaining apical closure and the number of visits required (54).

Discussion

Reporting of randomized controlled trials

The Consolidated Standards of Reporting Trials (CON-SORT) statement (64) is an important checklist for those designing and reporting clinical trials. The intention of this checklist is to make the experimental process clearer so that users of the data can more appropriately evaluate its validity (64). In general, none of the identified studies were adequately reported when compared to the CON-SORT checklist. However, studies that were done in the seventies were better reported than many more recent studies. Significant information were missing from almost all of the clinical trials that were identified e.g. no stated hypotheses, no sample size determination, no clear inclusion or exclusion criteria for participants, and no information whether or not participants, clinicians, and assessors were blinded to group assignment or treatment. The flow of participants through each stage was very difficult to follow in almost all identified clinical trials.

Methodological appraisal

Mackie et al. (54) reported an acceptable randomization process (although not concealed) by toss of a coin, which allocated patients into each stratum as they grouped their patients according to their age and apical width. If the patient had another tooth to be included, it was allocated to the other group by alternation (a less acceptable method of randomization). Inadequate allocation concealment leads to exaggerated estimates of treatment effect, on average, but with scope for bias in either direction (65). Achieving good comparability between groups was clear in the study by Mackie et al. (54) regarding age of the participants and teeth's apical width. This is a simple way to control for known confounding factors. Some trial participants may legitimately be excluded (i.e. without introducing bias) if their reason for exclusion was specified in the protocol and relates only to information collected before randomization e.g. excluding replanted teeth following to an avulsion injury or teeth showing radiographic evidence of external root resorption.

Diagnosis of loss of vitality in immature teeth

The importance of careful case assessment and accurate pulpal diagnosis in the treatment of traumatized immature teeth cannot be overemphasized (66). It was not clear from some studies whether pulp necrosis had occurred or whether some vital pulp tissue was still present in the apical part of the root canal. It was suggested that further root growth and lengthening should raise a possibility that vital parts of the pulp or functioning epithelial root sheath of Hertwig are still present (67). The diagnosis of teeth with necrotic pulps should be based on clinical assessment, which requires a thorough history of symptoms, careful clinical and radiographic examination and performance of diagnostic tests hoping by combining the results, an accurate clinical diagnosis of pulp vitality can be made.

Long-term success and freedom of symptoms after treatment

The main outcome measures concerning the patient and parents are the long-term success (aesthetics and function) and freedom from symptoms (pain and discomfort). This outcome was not reported adequately in included studies. Neither studies followed-up their patients adequately to asses any long-term success or failure following obturation and restoration of these teeth. A follow-up period of 12 months or longer was chosen in this review as we considered that it was not possible to make valid conclusions regarding effectiveness of treatments with shorter follow-up times.

In a review of 10 studies on calcium hydroxide apexification (67); it was pointed out that follow-up is necessary and information regarding long-term outcomes is limited. Problems such as re-infection and cervical root fracture may occur.

Yates (51) suggested that the criteria of success should include disappearance of all signs and symptoms; bony healing, preferably complete or at least progressing; barrier formation; and no long-term deterioration. Many complications were reported in this study, these included persistent sinuses, deterioration in the apical condition, no apical healing, and finally crown-root or root fractures.

Coviello and Brilliant (14) reported an average followup time of 43 months for some participants. Their follow-up showed a decrease in reported success rate. This highlights the fact that success rates may change dramatically with time and studies on apexification should include an adequate follow-up time and shouldn't end up with obtaining an apical barrier and root canal obturation.

One of these long-term failures that have been reported in the literature was root fractures of immature teeth after apical barrier formation and obturation. This has been attributed to the prolonged use of calcium hydroxide as an apexification agent (32, 33, 68, 69). The hypothesis was that long-term exposure to calcium hydroxide might weaken dentine and thus making the roots more susceptible to fracture.

Cvek (32) reported a 40% of cervical root fracture after4 years of follow-up in a retrospective study of 885 luxated necrotic immature incisors treated with calcium hydroxide and obturated with gutta-percha. The majority of these fractures (60%) occurred during the first 3 years after treatment and were due to chewing or biting forces. It is worth mentioning that, most fractured teeth in this study had a healed cervical resorptive defect and only 34% of teeth without a healed cervical resorptive defect had fractured. This shows a possible relation between cervical defects and fracture in these teeth. Al-Jundi (33) performed an analysis of the outcomes of a previously reported retrospective study (70) regarding complications arising from late presentation of dental trauma. Among the outcomes assessed in this study were root fractures as a long-term complication following apexification. It was reported that in 83 patients who had apexification treatment; 32% (about 26 teeth) had root fractures, 85% of these fractured teeth (around 22 teeth) occurred spontaneously. The technique of apexification and type of restorations provided were among key confounding factors that were not reported in the study.

Andreasen (68) in an *in vitro* study on sheep's immature teeth; concluded that a marked decrease in fracture strength occurs with increasing storage time (in saline) for teeth treated with calcium hydroxide dressing. It was also concluded that the fracture strength of calcium hydroxide-filled immature teeth will be halved in about a year due to the root filling and this may explain their frequent reported fractures with long-term use of calcium hydroxide. In a second study with similar experimental conditions, Andreasen (69) compared the fracture resistance of immature sheep incisors after using calcium hydroxide or mineral trioxide aggregate. It was concluded that calcium hydroxide if kept in the canals of immature sheep teeth for only 30 days followed by root filling with MTA there was no significant decrease in strength of the root within an observation period of 100 days. In both studies, teeth were embedded in plaster blocks that were carved to end at the cervical margins of teeth and tested for fracture strength using a testing machine.

One of the problems of the interpretation of results from *in vitro* studies occurs when these results are applied to a real-life situation, i.e. human teeth that are functioning in the oral environment within a unique system of highly specialized periodontium. The behaviour of these teeth under the experimental conditions when stored in saline for prolonged periods then subjected to mechanical forces while embedded in plaster maybe very different from teeth that are subjected to physiologic forces, and surrounded by the periodontium. Other factors may play more important role in the increased fracture susceptibility (if present) in these teeth, e.g. thin week dentine walls of immature teeth as suggested by Trope (71).

A decision regarding the effect of any medicament placed into these root canals should take into account all the possible known confounding factors that may affect root fracture in immature teeth. It is possible to control or adjust for confounders that are known and measured such as type of final restorations, root reinforcement attempts, further tooth weakening by preparation for post retained restorations, size of coronal access cavity and the amount of remaining coronal tooth structure etc. On the other hand, it is not possible to adjust for those factors that are not known to be confounders or that cannot be measured. Unfortunately, it can rarely if ever, be assumed that all the important factors relevant to prognosis and responsiveness to apexification or root strengthening or any other treatment are known (57).

Frequency of replacing calcium hydroxide

Roberts and Brilliant (13) evaluated the solubility of both calcium hydroxide and tricalcium phosphate clinically and radiographically at each recall visit and they found that the initial radio-opacity of both materials was about equal. At the 3 months recall visits; calcium hydroxide appeared less radiopaque and clinically it appeared as a soft fluid mixture through the canal, whereas tricalcium phosphate remained in the coronal third of the canal as dense material. After 6 months, both materials were missing from the canals. Tricalcium phosphate was missing from the apical third and calcium hydroxide from the entire canal.

Controversy still exists as to whether or how frequent the calcium hydroxide dressing should be changed. Chawla (2) in a case series study suggested a single application of calcium hydroxide and follow-up for radiographic evidence of barrier formation. In an animal study (72) it was found that after the initial root filling with calcium hydroxide there was nothing to be gained by repeated root filling either monthly or after 3 months. It was suggested in a case series study (73) that calcium hydroxide should be replaced only when symptoms develop or the material dissolves out of the canal when assessed radiographically. Other investigators (56, 74, 75) suggested that regular replacement of the dressing has the advantage of allowing clinical assessment of the apical barrier and may increase the speed of barrier formation.

Factors affecting apical barrier formation

Studies vary in assessment of the time required for apical barrier formation in apexification using calcium hydroxide. Finucane & Kinirons (75) found that the mean time to barrier formation was 34.2 weeks (range 13-67 weeks). The strongest predictor of rapid barrier formation was the rate of change of calcium hydroxide and the narrower the initial apical width. Factors that had a significant influence on the number of visits were the severity of the trauma and the outcome of treatment provided as reported by Wong & Kolokotsa (76) in their retrospective study. Cvek (73) has reported that infection and/or the presence of a periapical radiolucency at the start of treatment increases the time required for barrier formation. However, animal studies (77-79) and a retrospective study by Mackie et. al. (56) reported no relationship between pretreatment infection and periapical radiolucency and barrier formation time. It was found that in the presence of symptoms, the time required for apical closure was extended by approximately 5 months to an average of 15.9 months (80).

Cost implications

Wong (76) retrospectively evaluated the total cost of treating children and adolescents with traumatic injuries to their incisors, including the direct costs (outpatient costs) and indirect costs (missed working day). A rough estimate of treating various traumatic injuries in children's incisors was calculated to be £856 considering the median of eight visits per patient, outpatient cost and loss of working days. This was based on the average weekly earnings of a full employed parent or carer, the time spent during travelling, and the time spent in the hospital (treatment and waiting time). The cost of transport, medicine prescribed, disturbance to home life, other dental visits outside the hospital setting and further long-term treatment after discharge were not included in this cost estimation.

Reviewers' conclusions

Based on the available evidence from eligible included studies (13, 54), there is weak unreliable evidence supporting the use of either calcium hydroxide or tricalcium phosphate in multi-visit apexification in traumatized necrotic immature anterior teeth. There was no reliable evidence found for the use of other materials or techniques described in the literature. The use of both materials for apical barrier formation in open apex teeth appears promising but the evidence is insufficient to provide clear guidelines for practice. There was no reliable evidence on adverse events or long-term effects reported after the use of calcium hydroxide or tricalcium phosphate in any clinical trial assessed (included or excluded) due to inadequate followed-up.

The validity of included studies must be viewed with caution due to limitations in their methodology as described in the previous sections. This does not imply that techniques described for apical barrier formation are ineffective, but this highlights the need for a good quality randomized controlled trials in this field.

The use of MTA or root strengthening techniques and materials, were not investigated by randomized controlled trials that could be detected by our search. The lack of randomized controlled trials in this field were less surprising than our findings on calcium hydroxide or tricalcium phosphate, as the use of MTA and root strengthening as treatment interventions for traumatized necrotic immature teeth can be considered relatively recent compared to both materials. Further research is required in this field before conclusions for practice can be drawn.

No firm conclusions can be made as to the optimum treatment or technique for apical barrier formation in immature anterior teeth due to the lack of reliable scientific research.

According to the available level of evidence, we were not able to reject the following null hypotheses:

- 1 There is no difference between apexification and apical plug techniques as an intervention for inducing an apical barrier in traumatized necrotic immature permanent anterior teeth.
- 2 There is no difference in the proportion of teeth exhibiting clinical and/or radiological signs of failure following various types of treatment for inducing an apical barrier.
- **3** There is no difference in the proportion of treated teeth showing root fractures whether root strengthening procedures are used or not used.

Implications for research

Trials on interventions for treating necrotic immature teeth should be well designed randomized controlled trials and reported according to the CONSORT guidelines. Trial design should consider the implications of unit of randomization (patient or tooth) and applying a proper method of allocation concealment. Primary outcomes should be of relevance to patients and parents or carers, e.g. pain episodes, discolouration, mobility and satisfaction with function and aesthetics. Other outcomes, e.g. clinical failure and radiological evidence of failure, if based on well-defined objective criteria can be useful indications of pathology and may have implications for the investigation of long-term adverse effects.

Trials should ideally investigate the potential longterm effects e.g. recurrence of periapical pathology, root resorption and root fractures and it should include data on the survival of the coronal restorations provided as well as radicular rehabilitation using root strengthening procedures if applicable. It is acknowledged that this may not be easy or possible in many cases.

References

- 1. Frank AL. Therapy for the divergent pulpless tooth by continued apical formation. J Am Dent Assoc 1966;72:87–93.
- 2. Chawla HS, Tewari A, Ramakrishnan E. A study of apexification without a catalyst paste. J Dent Child 1980;47:431–4.
- Das S. Apexification in a nonvital tooth by control of infection. J Am Dent Assoc 1980;100:880–1.
- Whittle M. Apexification of an infected untreated immature tooth. J Endod 2000;26:245–7.
- 5. Ball JS. Apical root formation in non-vital immature permanent incisor. Report of a case. Br Dent J 1964;116:166.
- 6. Cooke C, Rowbotham TC. Root canal therapy in non-vital teeth with open apices. Br Dent J 1980;108:147-50.
- Rule DC, Winter GB. Root growth and apical repair subsequent to pulpal necrosis in children. Br Dent J 1966;120:586–90.
- Vojinovic O. Induction of apical formation in immature teeth by different endodontic methods of treatment. Experimental patho-histological study. J Oral Rehabil 1974;1:85–97.
- Vojinovic O, Srnie E. Introduction of apical formation by the use of calcium hydroxide and iodoform – Chlumsky paste in the endodontic treatment of immature teeth. J Br Endod Soc 1975;8:16–22.
- Das S, Das AK, Murphy RA. Experimental apexigenesis in baboons. Endod Dent Traumatol 1997;13:31–5.
- 11. Nygaard-Ostby B. The role of the blood clot in endodontic therapy. Acta Odontol Scand 1961;19:324–53.
- Ham JW, Patterson SS, Michell DF. Induced apical closure of immature pulpless teeth in monkeys. Oral Surg Oral Med Oral Pathol 1972;33:438–49.
- Roberts SC, Brilliant JD. Tricalcium phosphate as an adjunct to apical closure in pulpless permanent teeth. J Endod 1975;1:263–9.
- Coviello J, Brilliant JD. A preliminary clinical study on the use of tricalcium phosphate as an apical barrier. J Endod 1979;5: 6–13.
- Kaiser HJ. Management of wide open apex canals with calcium hydroxide. Presented at the 21st Annual meeting of the American Association of Endodontics, Washington, DC, April 17, 1964.
- 16. Michanowicz JP, Michanowicz AE. A conservative approach and procedure to fill an incompletely formed root using calcium hydroxide as an adjunct. J Dent Child 1967;34:42–7.
- Pitts DL, Jones JE, Oswald RJ. A histological comparison of calcium hydroxide plugs and dentin plugs used for the control of gutta-percha root canal filling material. J Endod 1984;10:283–93.
- Schumacher JW, Rutledge RE. An alternative to apexification. J Endod 1993;19:529–31.
- Weisenseel JA Jr, Hicks ML, Pellen GB. Calcium hydroxide as an apical barrier. J Endod 1987;13:1–5.
- Koenigs JF, Heller AL, Brilliant JD, Melfi RC, Driskell TD. Induced apical closure of permanent teeth in adult primates using a resorbable form of tricalcium phosphate ceramic. J Endod 1975;1:102–6.
- Nevins A, Finkelstein F, Laporta R, Borden BG. Induction of hard tissue into pulpless open-apex teeth using collagen-calcium phosphate gel. J Endod 1978;4:76–81.
- 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.
- Tittle K, Farley J, Linkhart T, Torabinejad M. Apical closure induction using bone growth factors and mineraltrioxide aggregate. J Endod 1996;22:198.
- Lee SJ, Monsef M, Torabinejad M. Sealing ability of a mineral trioxide aggregate for repair of lateral root perforations. J Endod 1993;19:541–4.

- Dimashkieh MR. The problem of the open apex a new approach. Oxidised regenerated cellulose technique. J Br Endod Soc 1977;10:9–16.
- Eleazer PD, McDonald TW, Sinai IH, Fantasia JE, Michelich RJ, Yagiela JA. Proplast as an apical barrier in root canal therapy. J Endod 1984;10:487–90.
- Narang R, Wells H. Experimental osteogenesis in periapical areas with decalcified bone matrix. Oral Surg Oral Med Oral Pathol 1973;35:136–43.
- Yoshida T, Itoh T, Saitoh T, Sekine I. Histopathological study of the use of freeze-dried allogenic dentin powder and true bone ceramic as apical barrier materials. J Endod 1998;24:581–6.
- 29. Weine FS. Endodontic therapy, 6th edn. St Louis: Mosby; 2004.
- Nyarasdy I, Ferenczi I, Banoczy J, Herczegh B. Experience with the use of the metronidazole-containing paste (grinazole) in root canal therapy of gangrenous teeth. Fogorv Sz 1987;80:149– 52.
- Stormer K, Jacobsen I, Attramadal A. In: Hvor funkjonsdyktige blir rottfylte unge permanente incisiver? Nordisk forening for pedodonti. Bergen, Norway: Aarsmote; 1988.
- Cvek M. Prognosis of luxated non-vital maxillary incisors treated with calcium hydroxide and filled with gutta-percha. A retrospective clinical study. Endod Dent Traumatol 1992; 8:45–55.
- 33. Al-Jundi SH. Type of treatment, prognosis and estimation of time spent to manage dental trauma in late presentation cases at a dental teaching hospital: a longitudinal and retrospective study. Dent Traumatol 2004;20:1–5.
- 34. Teixeira FB, Teixeira EC, Thompson JY, Trope M. Fracture resistance of roots endodontically treated with a new resin filling material. J Am Dent Assoc 2004;135:646–52.
- Trope M, Ray HL Jr. Resistance to fracture of endodontically treated roots. Oral Surg Oral Med Oral Pathol 1992;73:99–102.
- 36. Pitt Ford T. The leakage of root fillings using glass ionomer cement and other materials. Br Dent J 1979;146:273–8.
- Zmener O, Dominguez FV. Tissue response to glass ionomer used as an endodontic cement. Oral Surg Oral Med Oral Pathol 1983;56:198–205.
- Powis DR, Folleras T, Merson SA, Wilson AD. Improved adhesion of a glass ionomer cement to dentin and enamel. J Dent Res 1982;61:1416–22.
- Weiger R, Heuchert T, Hahn R, Lost C. Adhesion of a glass ionomer cement to human radicular dentine. Endod Dent Traumatol 1995;11:214–9.
- Johnson ME, Stewart GP, Nielsen CJ, Hatton JF. Evaluation of root reinforcement of endodontically treated teeth. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2000;90:360–4.
- Duret B, Reynaud M, Duret F. New concept of coronoradicular reconstruction: the composipost (1). Chirurgie Dentaire Francaise 1990;60:131–41.
- Duret B, Duret F, Reynaud M. Long-life physical property preservation and postendodontic rehabilitation with the composipost. Compend Contin Educ Dent Suppl 1996;20:S50–6.
- 43. Asmussen E, Peutzfeldt A, Heitmann T. Stiffness, elastic limit and strength of newer types of endodontic posts. J Dent 1999;27:275–8.
- Isidor F, Odman P, Brondum K. Intermittent loading of teeth restored using prefabricated carbon fiber posts. Int J Prosthodont 1996;9:131–6.
- 45. Ferrari M, Scotti M. Fiber posts characteristics and clinical applications, 1st edn. Milan: Masson; 2002.
- Mannocci F, Sherriff M, Watson TF, Vallittu PK. Penetration of bonding resins into fibre-reinforced composite posts: a confocal microscopic study. Int Endod J. 2005;38:46–51.
- Wong F. Glass fibre reinforced composite post a novel technique for treating severly traumatised incisors. Int Assoc Paediatr Dent (IAPD) Scientific Meeting Abstract, Sydney, Australia, 2005.

- Lassila LV, Vallittu PK. The effect of fiber position and polymerization condition on the flexural properties of fiberreinforced composite. J Contemp Dent Pract 2004;15:14–26.
- Le Bell AM, Lassila LVJ, Kangasniemi I, Vallittu PK. Bonding of fibre-reinforced composite post to root canal dentin. J Dent 2005;33:533–9.
- Higgins JPT, Green S, editors. Cochrane handbook for systematic reviews of interventions 4.2.5 [updated May 2005]. http://www.cochrane.org/resources/handbook/ [accessed on 31st May 2005].
- 51. Yates JA. Barrier formation time in non-vital teeth with open apices. Int Endod J 1988;21:313–9.
- Merglova V. The treatment of non-vital permanent teeth by filling of root canals with calcium hydroxide. Eur J Paediatr Dent. 2001;1:38–44.
- 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.
- Mackie IC, Hill FJ, Worthington HV. Comparison of two calcium hydroxide pastes used for endodontic treatment of nonvital immature incisor teeth. Endod Dent Traumatol 1994;10:88–90.
- Thater M, Marechaux SC. Induced root apexification following traumatic injuries of the pulp in children: follow-up study. J Dent Child 1988;55:190–5.
- Mackie IC, Bentley EM, Worthington HV. The closure of open apices in non vital immature incisor teeth. Br Dent J 1988; 156:169–73.
- 57. Kunz R, Oxman AD. The unpredictability paradox: review of empirical comparisons of randomised and non-randomised trials. BMJ 1998;317:1185–90.
- Colditz GA, Miller JN, Mosteller F. How study design affects outcomes in comparisons of therapy. I: medical. Stat Med 1989;8:441–54.
- Schulz KF, Chalmers I, Hayes RJ, Altman DG. Empirical evidence of bias: dimensions of methodological quality associated with estimates of treatment effects in controlled trials. JAMA 1995;273:408–12.
- Lewis JA, Machin D. Intention to treat-who should use ITT? Br J Cancer 1993;63:467–650.
- Newell DJ. Intention-to-treat analysis: implications for quantitative and qualitative research. Int J Epidemiol 1992;21:837–41.
- Hollis S, Campbell F. What is meant by intention to treat analysis? BMJ 1999;319:670–4.
- 63. Emerson JD, Burdick E, Hoaglin DC, Mosteller F, Chalmers TC. An empirical study of the possible relation of treatment differences to quality scores in controlled randomized clinical trials. Controll Clin Trials 1990;11:339–52.
- Moher D, Schulz KF, Altman DG. Revised recommendations for improving the quality of reports of parallel group randomised trials. http://www.consort-statement.org, 2001 [accessed on 31st May 2005].
- Schulz KF, Grimes DA. Allocation concealment in randomised trials: defending against deciphering. Lancet 2002;359:614–8.

- 66. Rafter M. Apexification: a review. Dent Traumatol 2005;21:1-8.
- 67. Sheehy ES, 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.
- 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.
- 69. 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.
- Al-Jundi SH. Dental emergencies presenting to a dental teaching hospital due to complications from traumatic dental injuries. Dent Traumatol 2002;18:181–5.
- Trope M, Maltz DO, Tronstad L. Resistance to fracture of restored endodontieally treated teeth. Endod Dent Traumatol 1985;1:108–11.
- 72. 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.
- Cvek M. Treatment of non-vital permanent incisors with calcium hydroxide. I. Follow-up of periapical repair and apical closure of immature roots. Odontologisk Revy 1972; 23:27–44.
- 74. Kinirons MJ, Srivasan 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.
- Finucane D, Kinirons MJ. Non-vital immature permanent incisors: factors that may influence treatment outcome. Endod Dent Traumatol 1999;15:273–7.
- Wong FSL, Kolokotsa K. The cost of treating children and adolescents with injuries to their permanent incisors at a dental hospital in the United Kingdom. Dent Traumatol 2004;20:327– 33.
- 77. Torneck CD, Smith JS, Grindall P. Biologic effects of endodontic procedures on developing incisor teeth. II. Effect of pulp injury and oral contamination. Oral Surg Oral Med Oral Pathol 1973a;35:378–88.
- Torneck CD, Smith JS, Grindall P. Biologic effects of endodontic procedures on developing incisor teeth. III. Effect of debridement and disinfection procedures in the treatment of experimentally induced pulp and periapical disease. Oral Surg Oral Med Oral Pathol 1973b;35:532–40.
- 79. Torneck CD, Smith JS, Grindall P. Biologic effects of endodontic procedures on developing incisor teeth. IV. Effect of debridement procedures and calcium hydroxide-camphorated parachlorophenol paste in the treatment of experimentally induced pulp and periapical disease. Oral Surg Oral Med Oral Pathol 1973c;35:541–54.
- Kleier DJ, Barr ES. A study of endodontically apexified teeth. Endod Dent Traumatol 1991;7:112–7.

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