International Journal of Science and Research (IJSR)
ISSN: 2319-7064
Index Copernicus Value (2016): 79.57 | Impact Factor (2017): 7.296

Efficacy of Calcium Hydroxide versus Chlorhexidine in Reducing Endodontic Post Operative Pain: A Systematic Review

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Abstract: ***Introduction: Postoperative pain is one of the primary problems in endodontic treatment. Chlorhexidine (CHX) and calcium hydroxide (CH) are the major two intracanal medications used in apical periodontitis. Objective: to compare through a systematic review of the literature, the efficacy of calcium hydroxide versus chlorhexidine used as intracanal medicaments in the management of postoprerative pain in permanent teeth with apical periodontitis. Material and methods: The working group included 4 reviewers. The research was conducted in November; 2018 on Medline (PubMed), and the Cochrane Library databases. Using the following keywords: "periapical periodontitis", "calcium hydroxide" and, "chlorhexidine". After selection of articles, data were extracted and analyzed. Results: Fourty two articles were retrieved from databases and one article from hand-searching. Four articles were considered as relevant. The selected items found some clinical evidence that Even though calcium hydroxide is one of the most widely used intra-canal medicament due to its anti-microbial properties, it is not very effective in reducing post-treatment pain when it is used alone, but its effectiveness can be increased when used in combination with other medicaments like chlorhexidine and camphorated monochlorophenol (CMCP). Conclusion: Chlorhexidine (2%) has a superior effect on pain relief than calcium hydroxide.***

Keywords: apical periodontitis, calcium hydroxide, chlorhexidine, postoperative pain

1. Introduction

Pain of endodontic origin has been a major concern to the patients and the clinicians for many years. Postoperative pain is one of the primary problems in endodontic treatment, even when proper anesthesia is provided. The success of endodontic treatment is highly related to the elimination or reduction of post-endodontic pain [1, 2]. Interappointment pain is almost exclusively due to the development of acute inflammation at the periradicular tissues in response to an increase in the intensity of injury arising from the root canal system. Mechanical and chemical injuries are often associated with iatrogenic factors, but microbial injury is arguably the major and the most common cause of inter appointment pain in apical periodontitis [3, 4].

Chlorhexidine (CHX) and calcium hydroxide (CH) are the major two intracanal medication used in apical periodontitis. Chlorhexidine is a cationic bisguanide that seems to act by adsorbing into the cell wall of the microorganism and causing leakage of intracellular components. At low concentration, CHX has a bacteriostatic effect and at high concentration it has a bactericidal effect because of precipitation and/ or coagulation of intracellular constituents. Its optimal antimicrobial activity is at pH 5.5-7.0. CHX has a broad-spectrum antimicrobial activity, targeting both gram-positive and gram-negative microbes [5]. After instrumentation with CHX, there was complete elimination of E. coli and C. albicans, except for E. faecalis, which was significantly reduced[6].

Calcium hydroxide has been used in dentistry for almost a century (Siqueira& Lopes 1999). Its use in root canal treatment as an intracanal medication has been associated with periradicular healing (Sjo¨gren et al. 1990) Calcium hydroxide has limited effectiveness in eliminating bacteria from human root canal when assessed by culture techniques [7]. It can be suggested that any intracanal medication with good antimicrobial properties could be useful to reduce post-operative pain[8].

When different studies report inconsistent results, a systematic review and meta-analysis technique can clarify conflicting research data and the current state of knowledge regarding specific issues. This study was conducted to find out the effectiveness of chlorhexidine versus calcium hydroxide as intracanal medication in controlling post operative pain after endodontic treatment in permanent teeth with apical periodontitis.

2. Material and Methods

The working group included 4 reviewers. The study required a commitment from the working group members for a critical reading of articles, extracting and synthesizing data independently. Conclusions were confirmed under a well coordinated predefined grid. In case of disagreement, a discussion between the group members was necessary.

1) Review question

The following (well-defined) review question was developed by using the population, intervention, comparison, and outcome (PICO) criteria: does CHX alone or combined with CH (I), compared to CH aloneor combined with another medicament (C), result in higher efficacy in postoperative pain relief (O) in permanent teeth with apical periodontitis

(P)? Therefore, the key words for search strategy were "apical periodontitis" as Population, "chlorhexidine" as Intervention, "calcium hydroxide" as Comparison.

2) Search strategy

The research for articles was conducted on Medline (PubMed), and the Cochrane Library databases. Indexing language based on Medical Subject Headings (MeSH) terms was used. The following keywords were used: "periapical periodontitis" [Mesh], "calcium hydroxide" [Mesh] and, "chlorhexidine" [Mesh]. Using the Boolean operator "AND", the following Boolean equation was formulated: (("Periapical Periodontitis"[Mesh] OR "Periapical Abscess"[Mesh]) AND ("Calcium Hydroxide"[Mesh] OR "barium sulfate, calcium hydroxide drug combination" [Supplementary Concept] OR "calcium hydroxide, iodoform, silicone oil drug combination" [Supplementary Concept])) AND ("Chlorhexidine"[Mesh] OR "chlorhexidine gluconate" [Supplementary Concept]). The search for this equation was stopped on November; 2018.Hand searching was also performed on Pubmed.

3) Study Selection and data extraction

Article search was limited to the ones published between 2008 and 2018 only. Human species were considered in this study (but not animal). The articles that were not published in French or English were excluded from the study. For the first screening, all papers were read in abstract except one item which has no abstract.Two independent reviewers screened the titles and abstracts of all the identified studies to determine relevant studies which met predetermined inclusion criteria. If there were insufficient data to make a clear decision, the full text was considered.Articles that had cited these studies were also identified through google scholar (http://www.scholar.google.com)to identify potentially relevant subsequent primary research.Two independent reviewers assessed the full texts of the relevant studies finally meeting the inclusion criteria proposed by the working group. Any disagreements were discussed and resolved by consulting a third reviewer.

Inclusion criteria were as follows :*Types of article: Randomized controlled trial ; Controlled clinical trial; Comparative study ; Clinical trial ; Clinical study; Guidelines; Systematic review ; Meta-analysis.*Language : English, french.*Studies comparing calcium hydroxide versus chlorhexidine effectiveness on postoperative pain. In other words, it must be a comparison between CHX group and CH group in pain relief efficacy.*These medicaments should be used as intracanal medication. *CHX alone or in combination with CH in the CHX group.*CH alone or in combination with another product (not CHX) in the CH group.*Population: patients presenting Apical periodontitis.

Exclusion criteria were as follows: The following studies were excluded :Case reports/case series, animal studies, in vitro studies, review article, studies in which CHX and/or CH were used as irrigant and not intracanal medicament, patients presenting other pathology.

The relevant informations found in the articles included in this study were extracted according to a predefined reading grid. This grid was developed by the working group including details concerning: the article, the study design, the population, the intracanal medicament, the Endodontic protocol.

3. Results

Description of studies

The search, arrested on November 2018, identified fourtytwo publications, out of which thirteen were excluded after application of date limitation.Twenty six publications were excluded after reviewing the title and abstract [9-34]. Within these articles, one was excluded after reading the full text because it has no abstract. Details of the excluded articles are given in (Table I). So, a total of 3 articles fulfilled the inclusion criteria[35, 36, 37]. One additional study[8] was considered relevant whenhand-searching articles. Therefore, a total of 4 publications[8, 35, 36, 37]fulfilled all criteria for inclusion. Figure 1 shows the search flowchart.Three papers[8, 36,37]were controlled trials. One item was a cross sectional study[35]. The extracted data from selected articles were presented in a summary table for a better analysis (Table II).

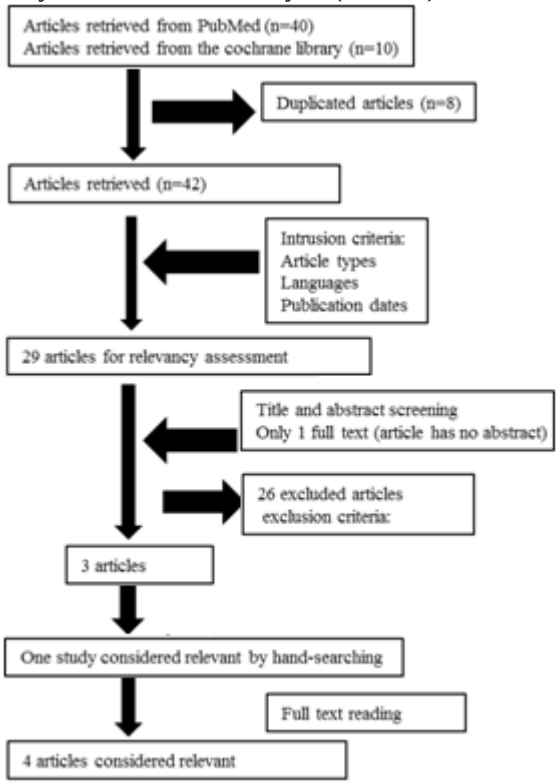

Figure 1: Flow chart of the search strategy

Quality assessment

The quality assessment of included trials was undertaken independently as a part of data extraction process. A JADAD score was attributed to each paper (see table III). Other methodological criteria were examined. Sample size calculation was found for the studies of Menakaya et al. andSingh et al.Clear inclusion/ exclusion criteria was obtained for the three papers.

4. Interpretation of results

According to Singh et al. 2013 [37], the study was performed on 64 patients consulting with acute apical

periodontitis. The teeth were randomized into four groups (n = 16). In Gr1: Calcium hydroxide paste mixed with 2% chlorhexidine gel, Gr2: 2% chlorhexidine gel, Gr3: Calcium hydroxide paste, and Gr4 : received no dressing (control). Pain experienced by the patients was then evaluated at 4 h after treatment and daily for a further 24, 48, 72, and 96 for the post-treatment pain. They have concluded that chlorhexidine alone and calcium hydroxide plus chlorhexidine gave rise to less pain than that experienced by patients who had a calcium hydroxide dressing alone or no dressing at all. According to Gama et al. 2008 [35], 138 asymptomatic teeth were included in this study. Seventy nine of these presenting periradicular bone destruction. These 138 teeth were equally divided into two groups (n = 69). Gr1: 0.12% chlorhexidine gel and Gr2: Calcium hydroxide/CPMC. Comparison of inter-appointment pain incidence between groups after one week was not significant. According to Menakaya et al. 2015 [36], 70 teeth were randomly divided into two equal groups (n = 35). Gr1: Calcium hydroxide mixed with 0.2 % Chlorhexidine digluconate and Gr2: Calcium hydroxide mixed with normal saline. The incidence of postoperative pain was lower in the normal saline treatment group, but the difference was not statistically significant. A comparison of the pain score (intensity) between the two groups at both 1-day and 1-week post-operative reviews showed that the difference was not statistically significant ($p > 0.05$). According to Quadir et al. 2015 [8],465 single rooted teeth were included in the study, and were equally divided into three groups (n = 155). Gr A : calcium hydroxide paste, Gr B : chlorhexidine gel, and Gr C : Cotton pellets for placebo. There was a significant difference between post-operative pains in the three different groups. Group B (chlorhexidine) proved to be most effective against pain (22.58%) followed by group A (calcium hydroxide) (9.68%) and group C (cotton pellets) (1.29%) respectively.This study showed that Chlorhexidine has better analgesic effects as an intracanal medicament than Calcium hydroxide or no medication.The selected items found some clinical evidence that calcium hydroxide is not very effective in reducing post-treatment pain when it is used alone, but its effectiveness can be increased when used in combination with other medicaments like chlorhexidine and camphorated monochlorophenol (CMCP).Chlorhexidine has a superior effect on pain relief than calcium hydroxide.

Table 1: Rejected articles

Articles	*Reasons for exclusion*
Martinho et al., 2018	This clinical study compared the effectiveness of intracanal medications in the reduction of bacteria/endotoxins from primarily infected root canals with determination of levels of cytokines.
Silva et al., 2017	This study evaluated in vivo the antibacterial effect of calcium hydroxide dressings, with or without chlorhexidine on human primary teeth.
Neskovic et al., 2016	No comparison between calcium hydroxide (CH) and chlorhexidine (CHX)
Ferreira et al., 2015	This clinical study aimed to determine the microbiological profile resistant to different intracanal medications in primary endodontic infections by using both microbiological culture and the checkerboard DNA-DNA hybridization technique.
Provenzano et al., 2015	This study evaluated the occurrence of bacterial metabolic end products in infected root canals before and after treatment.
Sousa et al., 2014	No comparison between (CH) and (CHX)
Stojanović et al., 2014	This studyevaluatedthe prevalence of Enterococcus faecalis and Porphyromonasgingivalis in infected root canals and the effect of endodontic therapy.
Lin et al., 2014	Case report and No comparison between (CH) and (CHX)
Sousa et al., 2014	No comparison between (CH) and (CHX)
Teles et al., 2014	Comparison of antimicrobialeffectwith count of anaerobicmicroorganisms
Herrera et al., 2014	A case report of a repair of apical rootresorption
Jolly et al., 2013	Primarymolars
Chen et al., 2013	Case report and No comparison between (CH) and (CHX)
Paiva et al., 2012	No comparison between (CH) and (CHX)
Oliveira et al., 2012	CHX and CH used as irrigants
Vera et al., 2012	No comparison between (CH) and (CHX) and CHX used as irrigant
Beus et al., 2012	No comparison between (CH) and (CHX) and CHX used as irrigant
Ito et al., 2011	No comparison between (CH) and (CHX) and primary teeth
Pannkuk , 2011	Case series
Mohammadi, 2010	Review and diagnosis not mentioned
Trope and Debelian, 2009	No comparison between (CH) and (CHX) and Full text not available
Mente et al., 2009	No comparison between (CH) and (CHX)
Tervit et al., 2009	No comparison between (CH) and (CHX)
Blome et al., 2008	No comparison between (CH) and (CHX)
Vianna et al., 2008	Comparison of antimicrobialeffect
Penesis et al., 2008	No comparison between (CH) and (CHX)

Table 2: Details of selected articles

Articles	Singh et al., 2013	Gama et al., 2008	Menakaya et al., 2015	Quadir et al., 2015
Study design	double-blind randomized clinical trial	cross-sectionalstudy	Randomizedcontrolledclinical trial	Controlledclinical trial
Population/ Sample size	64 mandibularmolars 64 patients (age 20-40)	138 teeth, 69 in each group (age 9-72)	70 teeth, 35 in each group 55 patients (age 17–60)	465 single rooted teeth, 155 on each group (age: 15-50)

Diagnosis	Pulp necrosis and acute apical periodontitis	Asymptomatic (80 Necrotic pulp/treament and 58 Previously treated/ Retreatment) 69 CHX group: 48 with periradicular bone destruction and 21 without 69 CH/CPMC group : 31 with periradicular bone destruction and 38 without	Apical periodontitis None or minimal (2X2mm) periapical radiolucency	necrotic pulp and radiographic evidence of radiolucent lesions at the apex
Type and concentration of the product	Gr 1 : calcium hydroxidepaste (Calcipulpe, Septodont, France) + 2% chlorhexidine gel (Endogel, Itapetininga, SP, Brazil) in equal parts Gr 2 : 2% chlorhexidine gel	Gr1 : 0.12% chlorhexidine in natrosol gel (Dermage, Rio de Janeiro, RJ, Brazil)	Gr1 : calcium hydroxide + 0.2% chlorhexidinedigluconate (Corsodyl^{R})	Chlorhexidine gel
Comparison	Gr 3 : calcium hydroxidepaste	Gr2 : calcium hydroxide/camphorated paramonochlorophenol (CPMC)/glycerin paste	Gr2 : calcium hydroxide + normal saline	Calcium Hydroxidepaste
Control group	Gr 4 : no dressing	None	none	cotton pellets
anaesthesia	inferior alveolar nerve block injections by using 1.8 mL of 2% lignocaine with 1:200000 epinephrine (Xylocaine; Astra Zeneca Pharmaceutical Products, London, UK).	2% lidocaine chloridrate with 1:100,000 adrenaline	local anaesthesia	Not precised
Endodontic protocol	a single endodontist Working length was determined with apex locator and then confirmed radiograhically patency of canal with No. 10 K file of 0.02 taper (DentsplyMaillefer, Ballaigues, Switzerland). stepback technique using K files (DentsplyMaillefer) and Gates-Glidden drills (DentsplyMaillefer). Master apical preparation : 25-30 in narrow canals and 35-40 in wide canals. Irrigation : 1% sodium hypochlorite alternating with 17% EDTA. Last irrigation : normal saline canals were dried	Not precised Working length was established 1 mm short of the root apex, and the patency length coincided with the radiographic root edge. alternated rotation motion technique and Gates–Glidden burs: coronal two thirds of the root canals. Apical preparation : hand nickel–titanium files (Nitiflex, Dentsply-Maillefer, Ballaigues, Switzerland). step-back Master apical preparation : 35 or larger. Retreatment cases : hand files and eucalyptol (Biodinâmica, São Paulo, SP, Brazil). Irrigation : 2.5% sodium hypochlorite Last irrigation : 17% EDTA in the canal for 3 min followed by 5 ml of 2.5% NaOCl. Canals were dried with paper points	the same endodontist Working length was estimated at 0.5 mm short of the radiographic apex. Stepback biomechanical preparation technique using manually operated files. Master apical preparation : not precised Irrigation : 2% sodium hypochlorite (Milton) last irrigation : normal saline. Canals dried with paper point	Not precised Not precised crown-down tech-nique : coronal part of the root is prepared before the apical part. Irrigation : 5.2% sodium hypochlorite solution. Final irrigation : sterile saline solution. Canals dried with sterile paper points.
Occlusal reduction	Done	Not done	Not done	Not done
Intracanalmedication application	lentulospirals (DentsplyMaillefer)	Lentulo spiral fillers and packed with a cotton pellet at the level of canal entrance.	lentulo spiral fillers (Henry Schein) A sterile cotton wool pellet	lentulo spiral
Dressing period	4 days	Approximately1 week	1 week	72 hours
Pain assessment times	4h, 24h, 48h, 72h, 96h	1 week	1 day, 1 week,	During 72 hours
Provisionalrestoration	Cavit (ESPE Dental AG, Seefeld, Germany).	temporary cement (Coltosol, Coltène/ Whaledent, Cuyahoga Falls, OH, USA).	zinc phosphate cement	Glass-ionomerce-ment

Pain Scale	Visual analog pain scale (0-100) 0-25 No pain to mild pain requiring no analgesics 26-50 Moderate pain requiring analgesics 51-75 Severe pain not relived by analgesics 76-100 Extreme pain not relieved by any medicine	Level of discomfort : • no pain, • mild pain, which was recognizable, but not discomforting. • moderate pain, which was discomforting, but bearable (analgesics, if used, were effective in relieving pain) • severe pain, which was difficult to bear (analgesics, if used, were ineffective in relieving pain).	Universal pain assessment tool validated by Wong et al., 2001, a verbal descriptor pain scale : • None • mild (can be ignored) • moderate (interferes with tasks or interferes with concentration) • severe (interferes with basic needs) • worst (bed rest required). • also whether or not analgesic was used	questionnaire

Table 3: Quality Assessment

	Menakaya et al., 2015	Singh et al., 2013	Quadir et al., 2015
Randomization	Yes	Yes	yes
Method of randomization	Balloting	Computer generated random number table	Not mentioned
Double blinding	Yes	Yes	no
Method of blinding	Not precised	Appropriate	no
Dropouts /withdrawals	None	None	none
Jadad score	4	5	2

5. Discussion

No systematic review has been done on this subject so far. Two databases were searched for articles. Certainly, more interfaces may be useful to obtain information. Nevertheless, Pubmed and cochrane library remain the major databases.

Torabinejad et al. [38] found that many factors play a significant role in the incidence of endodontic inter appointment emergencies. Pain can be present before the dental treatment starts and can be present or absent during or after the treatment. Most common causes of pain after dental treatment are the result of certain pre-existing factors relating to tooth or can attributed to certain iatrogenic factors during treatment phase. Apprehensive patients are more sensitive to pain in general, than those who are relaxed. Micro organisms are allegedly the major cause of flareups [39]. Some investigators have suggested that the use of antimicrobial intracanal protocols involving application of an interappointment medication can reduce the risks of flare-ups during the treatment of infected canals [40, 41]. Genet et al.[42] reported a positive correlation between the incidence of postoperative pain and a non-vital pulp or the presence of a radiolucency larger than 5mm in diameter.

Measuring the subjective experience of pain is a continuing challenge in medicine. A variety of measurement tools have been developed from unidimensional rating scales to complex questionnaires, each with its specific strengths and limitations. The aim of the researcher is to capture as accurately as possible a measure of the intangible pain, to make appropriate clinical assessments which guide the decision-making process and evidence based practice. The Visual Analogue Scale (VAS) has been in use for the measurement of intangible quantities such as pain, quality of life and anxiety since the 1920s [43]. Visual analogue scale is one of the most commonly used method to determine the amount of pain in many studies [44, 45].

Two clinical trials included in this systematic review, compared the combination of calcium hydroxide plus chlorhexidine with calcium hydroxide alone [36, 37].Singh et al. concluded that pain reduction in Chlorhexidine plus Calcium hydroxide group was significantly higher than Calcium hydroxide group. Whereas, Menakayaetal. concluded that there is no difference between the two intracanal medications. This limited action of chlorhexidine in the second study could be because of its lower concentration (0.2%) [36]. In addition, the type of the product was not the same (solution, gel).

The effectiveness of chlorhexidine as intra-canal medication in controlling the post-operative pain might be because of its ability to reduce or eliminate the endotoxins associated with the development of spontaneous pain [37]. V. Ballal et al. [46]in their study proved that 2% chlorhexidine gel may be a more effective intracanal medicament than calcium hydroxide paste or their combination against Candida albicans and Enterococcus faecalis. Chlorhexidine gel provided 100% inhibition of microorganisms at the depth of 200 µm as well as 400 µm from the day one and thus demonstrating its high diffusibility.When comparing chlorhexidine and CPMC plus calcium hydroxide combination, no significant difference between the two medications with regard to the incidence of postoperative pain was observed. Walton and colleagues showed that the use of calcium hydroxide as an intracanal medicament was unrelated to the incidence and/or severity of postoperative endodontic treatment [47]. In several studies, chlorhexidine as an irrigant has been shown to lower the number of positive bacterial cultures after irrigation, as well as the number of colony-forming units remaining in positive cultures [48].Owing to its cationic properties, chlorhexidine can bind to surfaces covered with acidic proteins, such as the hydroxyapatite component of dentin, and be released at therapeutic levels, a phenomenon known as substantivity. This can occur in 48 hours to 72 hours after instrumentation [49].An important factor that may influence postoperative pain is the amount of excluded apical debris after root canal

treatment. The crown down technique associated with step back technique in the apical third of the root canal have been shown to result in significantly less apically extruded debris [50]. Rotary preparation with continuous irrigation has not been more effective than the standard preparation method for reducing pain [51].

The occlusal reduction in teeth with irreversible pulpitis and mild tenderness to percussion had no significant influence on postoperative pain after root canal preparation [52].Occlusal reduction does not have an effect on postoperative pain in teeth with symptomatic apical periodontitis [53]. Generally,differences in frequency levels of flare-ups in studies could bedue to various study populations and different treatment protocols [54].

6. Conclusion

From this systematic review, it can be concluded that Chlorhexidine (2%) has a superior effect on pain relief than calcium hydroxide. Calcium hydroxide is not very effective in reducing the incidence and severity of post-treatment pain when it is used alone, but its effectiveness can be increased when used in combination with other medicaments like chlorhexidine and camphorated monochlorophenol (CMCP).

7. Future Scope

1) Studies with longer duration and larger sample size are recommended with longer follow-up period to assess long term impact.
2) More double blind randomized clinical trials are necessary.

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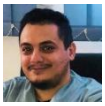

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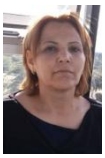

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