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Comparison of the Effects of Different Natural and Synthetic Intracanal Medicaments on the Healing of Periapical Lesion in Retreatment Cases (A Randomized Clinical Trial)

A Protocol Submitted to
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Presented by

Rawda Mohammad Abd El-Rahman Baghdady

Assistant lecturer of endodontics- Faculty of dentistry Assiut university

B.D.S 2009, M.Sc 2017 (Cairo University)

Supervisors

Prof. Dr. Karim Mostafa El Batouty

Professor of Endodontics

Vice Dean for Education and Student Affairs

Faculty of Dentistry Ain Shams University

Dr. Sarah Hossam Fahmy

Lecturer of Endodontics

Faculty of Dentistry Ain Shams University

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Introduction/ Background

Apical periodontitis is an inflammatory disease mostly of microbial etiology. There are many factors that may contribute to a persistent periapical radiolucency after treatment, intraradicular infection; extraradicular infection; foreign body reaction; cysts, and fibrous scar tissue healing following conventional treatment. Bacterial injury is probably the major and the most common cause of endodontic failure. This occurs when endodontic treatment is carried out inadequately. While in most cases, procedural errors (broken instruments, perforations, overfilling, underfilling, ledges and so on) do not jeopardize the outcome of endodontic treatment unless a concomitant infection is present.

Root canal infections have a polymicrobial nature; hence, anaerobic and facultative anaerobic microorganisms are usually found together in endodontic flare-ups and cases with post-treatment disease. *Enterococcus faecalis (E. faecalis)* and *Candida albicans (C. albicans)* are most commonly found in secondary apical periodontitis. *E. faecalis* can withstand the ecologically amenable conditions within the root canal makes it challenging to eliminate. As this pathogen can grow and survive in a hypotonic, hypertonic medium, at a pH ranging from 2 to 10, in acid and alkaline environments and those lacking nutrients[(1)].

Although biomechanical preparation and shaping of root canal effectively decrease the number of microorganisms in the root canal system. However, these procedures are unable to completely remove bacteria from lateral canals, isthmuses and apical deltas. Therefore, in order to achieve more decrease in the number of intracanal bacteria, intracanal medicaments between appointments is recommended. The most important properties of intracanal medicaments are their biocompatibility, stability and bactericidal effects.

Calcium hydroxide is the most commonly used intracanal medication. As it has high pH (12.5-12.8), it disturbs outer wall of bacteria, destructs potent toxins of bacteria, a lipopolysaccharide and it induces hard tissue formation. But calcium hydroxide as a root canal medicament has limitations as it does not eliminate the whole spectrum of microorganisms. The antimicrobial ability of calcium hydroxide was dependent upon direct contact with bacteria. So, it is not very effective in eliminating bacteria from the dentinal tubules. *E. faecalis* is small enough to

proficiently invade and live within dentinal tubules So, calcium hydroxide needs long time to provide its antimicrobial effect Therefore, different intracanal medicaments have been used inside the root canal to overcome disadvantages of calcium hydroxide.

Systemic antibiotic therapy may be useful in dental surgical and non-surgical procedures, but it has many limitations such as allergic reactions or toxicities and the development of resistant strains of microbes. Moreover, it needs absorption of systemic drugs by the gastrointestinal system, transportation via the blood stream to the infected area which require a proper blood supply which is no longer available in an infected root-filled tooth. As a result, topical application of antibiotics within the canal may be a more effective method for the drug delivering

Ciprofloxacin is a second-generation fluoroquinolone antibiotic with few side effects. Its range of effect includes most strains of bacterial pathogens as *Enterococcus faecalis*, and *Streptococcus pyogenes*. Ciprofloxacin has antimicrobial activity with wide broad spectrum of activities, excellent tissue penetration and excellent pharmacokinetic properties. So, it was used as intracanal medication either with calcium hydroxide or other locally delivered antibiotics[(2)].

Nonsteroidal anti-inflammatory drugs e.g. brufen as a component of inter-appointment dressing possess potential beneficial effects due to anti-inflammatory action as it decrease inflammatory mediators and local analgesia consequently it is effective in the relief of posttreatment pain and possible anti-bacterial action (E. faecalis). Especially, placing the drug directly at the site of tissue injury may be more effective in controlling pain and inflammation than waiting for absorption through the gastrointestinal tract. Antibiotics (ciprofloxacin) in conjunction with NSAIDs (ibuprofen) may be used as intracanal medication to prevent secondary infection.

To remove drawbacks of the current intracanal medications, extracts of herbal plant can be used. Recent trends in endodontics prefers natural plant medication due to it has more properties antimicrobials, less expensive, better patient tolerance and renewable in nature

Curcuma longa (turmeric) belongs to the Zingiberaceae family. It is a native of south-east Asia and is cultivated mainly in India. It is a natural polyphenolic

flavonoid. The main yellow bioactive component of *C. longa* is curcumin (diferuloylmethane). It possesses a wide spectrum of action, including anti-inflammatory, antioxidant, antibacterial, antifungal, antiprotozoal, antiviral, antispasmodic and anticancer activities and many other properties which may be a gift to dentistry and to be used as intracanal medication. But its clinical applications are still restricted due to the poor aqueous solubility, rapid degradation and low oral bioavailability[(3)].

Endodontics main goal is long lasting sterilization of the root canal. So, antibacterial effect of various intracanal medications is of high concern. Since nanotechnology has been infiltrating the field of medicine with its high antibacterial potential, its use in endodontics is highly prompted.

The solubility of curcumin can be increased by reducing it to nanoform which increases bioavailability, specificity and pharmacological activity. In addition to large surface area, controlled particle size, site specific targeting, stability, biodegradable and controlled release of drugs

Data from clinical trials showed that curcumin nano formulations can enhance curcumin bioavailability and are systemically safe. On the other hand, testing of these nano formulations as therapeutic modalities is highly desirable and is vital for upcoming clinical trials and for human use[(4)]. Therefore, the aim of the present study is to compare curcumin in its regular and nanoforms versus ibuprofen and ciprofloxacin intracanal medicaments

Review of literature

Fava[5] studied 60 necrotic upper central incisors from 48 patients with acute apical periodontitis & evaluated the incidence of post-operative pain after biomechanical preparation and dressing with a calcium-hydroxide paste (group 1) and a corticosteroid - antibiotic solution (group 2) on the first visit. All patients asked to report post-operative pain in 48 h after treatment and then teeth reevaluated clinically after 7 days. He concluded that no difference was observed in the incidence of post-operative pain between the two groups.

Sundqvist et al.[6] evaluated which types of organisms in teeth after failure of endodontic treatment was present . 54 root-filled teeth with persisting periapical lesions were selected for retreatment. After removal of the root filling, initial bacteriologic sample was taken from the root canal after instrumentation, second samples was taken at second visit after 7 days before placement of intracanal medicament and finally post medication samples after removal of intracanal medicament at a third appointment 7 to 14 days later. They found the microbial flora was mainly gram-positive organisms, bacteria of the species *Enterococcus faecalis*. They concluded that after endodontic treatment failure, the canals ' microbial flora were markedly different from that of primary endodontic treatment. Also, three of four endodontic failures were successfully managed by retreatment.

Filho et al.[7] evaluated effects of irrigating solution and CH intracanal medicament on healing of periapical tissue of necrotic teeth with apical lesion in dogs. 72 root canals from four mongrel dogs were prepared, using 5.25% NaOCL or 2% CHX irrigating solutions. Either obturation was done immediately or an application of intracanal medication for 15 days before obturation. Two hundred and ten days later, animals were anesthetized, killed, and sections were taken for histological examination of periapical healing. They concluded that even with the use of concentrated sodium hypochlorite and chlorhexidine as bactericidal irrigation, the use of a root canal dressing was important in the root canal treatment of dog teeth with chronic apical diseases.

Shuping et al.[8]evaluated the extent of bacterial reduction with nickel-titanium rotary instrumentation and 1.25% NaOCl irrigation. Also, the additional antibacterial effect of calcium hydroxide for >1 week was tested in 42 patients with

chronic apical periodontitis. The canals were sampled before treatment, during and after instrumentation, and after treatment with calcium hydroxide and the samples incubated for 7 days. They found that the initial sample confirmed infection of the canals. There was a significantly greater reduction of bacteria after instrumentation and irrigation with NaOCl (61.9%) than sterile saline. Also, CH dressing for seven days led to sterilization of 92.5% of the canals. They concluded that rotary instrumentation in conjunction with sodium hypochlorite irrigation is necessary for disinfection of canal, but not completely. Therefore, Ca $(OH)_2$ intracanal medication must be added.

Ehrmann et al. [9] investigated the relationship of postoperative pain to three different medicaments placed in the root canal of 223 teeth in 221 patients with non-vital pulp and acute apical periodontitis presenting for emergency relieve of pain. Canals were medicated Group 1: ledermix paste, Group 2: CH paste and Group 3: no medicament. Pain was recorded 4 h after root canal therapy and daily for 4 days. They found that preoperative pain mean was 44.4% for all groups and declined by 22.1% after 24h. After four days the pain score for CH group was ten, for no dressing group was seven and for ledermix group was four. They concluded that ledermix paste led to more effective decrease of pain level than with Ca $(OH)_2$ or no dressing at all.

Yoldas et al. [10] determined single or double visit endodontic treatment effect on the post endodontic pain in 218 failed endodontic treatment cases. Cases divided according to presence of pre endodontic pain or not. Nearly half of each group was treated in single visit and those in double appointment group were used calcium hydroxide- chlorhexidine combination as intracanal medication. They found that after seven days, eight cases from the single appointment group and two cases from the double visit group had flare-ups. They concluded that double visit with intracanal medication remove pain completely than single visit in teeth with preoperative pain, decreased flare-ups in all failed endodontic cases.

Rôças et al.[11] studied the association of different periradicular diseases with presence of Enterococcus faecalis. Bacterial samples from studied cases were taken. PCR was used to identify E. faecalis. They found that E. faecalis present in 1/19 pus samples aspirated from acute periradicular abscesses, in 1/10 root canals with acute apical periodontitis and in 7/ 21 root canals with asymptomatic chronic

periradicular lesions. Moreover, it was found in 20/ 30 cases of persistent endodontic infections associated with endodontically treated teeth. They concluded that E. faecalis was markedly present, in asymptomatic primary endodontic cases than symptomatic ones and in failed endodontic treated teeth than in primary ones.

Zerella et al.[12]evaluated the efficacy of CH mixed with 2% CHX solution versus CH on pulp space sterilization of 40 single rooted failed endodontically treated teeth with periradicular lesions during nonsurgical endodontic retreatment. Determination at the initial visit for presence of enterococci in the root canals was done. Application of either medication in root canals over 3 treatment visits (with 7-10-day intervals) was done. Root canal cultures collection and bacterial growth assessment were done daily for 1 week, then weekly for another 3 weeks. They found that bacteria present in twelve/40 (30%) before obturation. Aqueous CH disinfected 12/20 (60%) teeth and CH mixed in aqueous 2% CHX disinfected 16/20 (80%) teeth. They concluded that experimental medicament was slightly more effective on the disinfection of failed endodontically treated teeth than control one.

Ercan et al.[13]assessed the effect of CH and 1% CHX mixture as intracanal medicaments in failed endodontically treated cases with apical lesions. 70 patients were included. [59 had received root canal treatment and 11 had been subjected to previous apical surgery]. Mechanical preparation, 2% CHX irrigation, CH powder mixed with 1% CHX solution as intracanal medication was applied for 6-week, medicament was periodically changed till teeth became asymptomatic. Radiographic and clinical examination was done after 3-months. They found that complete healing of retreatment cases 64%, incomplete healing 14% and failure 22%. They concluded that CH with 1% CHX intracanal medication more effectively disinfect teeth with periapical lesions in endodontic retreatment

Gama et al.[14]assessed post-endodontic pain incidence in 138 asymptomatic teeth after application of intracanal medicaments (0.12% CHX gel or CH / CPMC /glycerin pastes). Incidence of interappointment pain was recorded. They found that eighty four percent of cases showed absence of any level of pain regardless the type of medicament. There were no significant differences in treatment/retreatment cases with/without apical lesions between the two medicaments. They concluded that both medications were effective as regards antimicrobial, postoperative pain

Therefore, it was advised to used either one or both medications in routine treatment/retreatment.

Rocas and Siqueira [15] assessed antimicrobial effect of chemo-mechanical preparation supplemented by intracanal medication during treatment of teeth with apical periodontitis by molecular microbiologic techniques and samples from twenty four nonvital canals were taken at the baseline (S1), after mechanical preparation with irrigation by 2.5% sodium hypochlorite (S2), and after intracanal medication for one week with (CHG) or (CHPG) (S3). Identification of bacteria by PCR was done. They found that all S1 samples were positive for bacteria. Treatment procedures were highly effective in reducing the bacterial levels. Overall, S2 and S3 samples were bacteria free by 46%, 62.5% respectively. Specifically, in the CHG group: S2 and S3 samples were bacterial free in 50% and 58% of the canals and in the CHPG group: 42% and 67%. But several bacteria were still present in S2 and S3 samples. They concluded that bacterial levels were decreased after preparation and medication. Moreover, another antimicrobial strategies and materials must be used to overcome all types of microbes which may deteriorate the outcome.

Paredes-Vieyra and Enriquez[16] evaluated one and double visits endodontic treatment effects on success rate of 300 maxillary and mandibular nonvital teeth with apical periodontitis for 2 years follow up postoperatively. Radiographically, all teeth showed small and irregular periapical radiolucencies before treatment. In one visit group: master apical file for anterior and premolars were #60 and for molars were #45 to #55. Irrigation of canals using EndoVac system then obturation. For the 2visit group, dryness and application of CH for 7 days then temporary restoration. At the second appointment (7 days after first visit), removal of CH with (hand instruments, irrigation with 5.25% NaOCL - 2.5 mL 17% EDTA – finally; 5.0 mL 5.25% sodium hypochlorite using the EndoVac). Canals were dried with sterile paper points, and obturated. They concluded that no significant difference in periapical healing between single and double visit endodontic treatments radiographically. This may be due to the ability to obtain infection control.

Singh et al.[17]compared between 3 different intracanal medications and the placebo, evaluated the postoperative pain level after endodontic treatment. Sixty-

four lower necrotic molars with acute apical periodontitis were included. 1st group(n=16): CH paste+2% CHX gel, 2nd group(n=16): 2% CHX gel, 3rd group (n=16): CH paste and 4th group(n=16): no dressing. Pain level was recorded 4, 24, 48, 72 and 96 h after treatment. They found that the post-operative pain level was significantly decreased at each time period for 1st and 2nd groups than 3rd and 4th groups. They concluded the efficacy of CHX alone or CH - CHX mixture on reducing the postoperative pain level for non-vital teeth with acute apical periodontitis than Ca $(OH)_2$ dressing alone or no dressing at all.

Gondim et al.[18]evaluated the success of root canal treatment in deciduous necrotic teeth which has or not furcal or periapical lesion detected radiographically. This evaluation was done clinically and radiographically, after using medication with (CH) pastes prepared with polyethylene glycol (PEG) and chlorhexidine (CHX) intracanal dressing. It was included 32 necrotic primary teeth (twelve without and twenty with lesion). Preparation and medication of the canals with (Ca $(OH)_2$/ polyethylene glycol) or gel 2% chlorhexidine gel with CH. Teeth in each group equal sixteen. Teeth filled with final restoration after 1 month. Examination of teeth in twelve months for determination of the endodontic therapy success (clinically and radiographically). They found that no significant difference in the success rate in the studied groups (with and without lesion). They concluded that there no difference between both medications clinically and radiographically on the success rate.

Pai et al.[19] evaluated and compared antibacterial intracanal medication effect on pain between visits in diabetic patients. 50 diabetic cases were divided into three groups. 1st group (no dressing), 2nd group (CH) and 3rd group (TAP). Recording Pain between visits by verbal rating scale at 1, 2, 3 days, one week and after 2 weeks. They found that overall incidence of pain between visits was 16%. 50% in 1st group, 15% in 2nd group had pain between visits while no one in 3rd group. They concluded that between visits TAP prevented pain than CH in diabetic patients.

Marickar et al.[20] compared antibacterial effect of propolis, curcumin, 2% (CHX), 2% metronidazole gel and 2% of both on E. faecalis. CH as (Control group). Agar diffusion and tube dilution tests evaluated MIC effects of medications. Time-kill assay analyzed bactericidal activity. They concluded that

curcumin and 2% CHX had highest antibacterial effect against *E. faecalis,* 2% (MZ), propolis, 2% (CHX- MZ) and finally CH. Therefore, they reported curcumin may considered as an alternative to most commonly available intracanal medications.

Raslan et al.[21] compared clinical and radiographic success rates of an antibiotic mix consisting of metronidazole, minocycline and ciprofloxacin (3Mix-MP) and another mix where minocycline was replaced with clindamycin (3Mix-MP-R) in deciduous necrotic molars without mechanical preparation and determined the effect of root resorption on the success of the treatment. 42 necrotic mandibular primary molars from 22 healthy children were randomly assigned to either mixture. Clinical evaluation was conducted after 1, 3, 6 and 12 months and radiographic evaluation was conducted at 6 and 12 months follow ups. They found overall success rates of 3Mix-MP and 3Mix- MP-R were 80.96% and 76.20% respectively. They concluded that the primary teeth with necrotic pulp can be treated with 3Mix-MP or 3Mix-MP-R irrespective of the degree of root resorption.

de Freitas et al.[22] studied the antibiofilm activity and pH of (CH) when mixed with NSAIDs and antibiotics. The studied groups included; 1st group (CH) paste+ propylene glycol, 2nd group (CH) paste + propylene glycol + 5% diclofenac sodium, 3rd group, (CH) paste + propylene glycol + 5% ibuprofen, 4th group (CH) paste + propylene glycol +5% ciprofloxacin and finally, positive control group (no dressing). For pH analysis, pH was measured at 3h,1,3,7 days with a calibrated pH meter for each paste. For microbial analysis, each paste was placed for 7 days on the 30 bovine dentin blocks induced with biofilm for three weeks. Then medication washed by sterile water and analyzing specimens. They concluded that the combination of NSAIDs or antibiotic did not interfere with the pH of calcium hydroxide paste and increased the antimicrobial action of calcium hydroxide paste against Enterococcus faecalis biofilm formation.

Ferreira et al.[23]determined antimicrobial effect of different intracanal medications in primary root canal infections. Selection of 20 infected canals were done then instrumented and divided randomly according to the intracanal dressing into two groups: CH or CH/ CHX. Before and after endodontic treatment, samples were collected, analyzed by culture, total bacterial load and checkerboard DNA-DNA hybridization technique. They found no differences in the reduction of

cultivable bacteria between (CH)group and CH/ CHX group [(99.98%), (99.76%) respectively]. In initial samples, bacteria present were F. nucleatum ssp. vincentii (70%) and Capnocytophaga ochracea (70%). Enterococcus faecalis after instrumentation was (60%). F. nucleatum ssp. vincentii (90%) and E. faecalis (40%), after either intracanal medications. Significant reduction of bacterial number by both medications than the initial sample. But, CH/CHX group had highest bacterial number reduction than CH. They concluded that CH /CHX had greater antibacterial effect on gram positive and gram-negative species. But its antibacterial effect on enterococcus species need further studies.

Marinho et al.[24]studied teeth with apical periodontitis for the presence of bacterial species and their endotoxins level. Also, determination of inflammatory mediator levels (IL-1$_\beta$ and TNF-$_\alpha$) after root canal treatment with different irrigation. 30 infected root canals were divided randomly into: group I (n =10); 2.5% NaOCL, group II (n =10); 2% CHX and group III (n =10; saline (control). 5 Samples were taken by sterile paper points from root canal: S1; at baseline, S2; after mechanical preparation, S3; after irrigation by 17% EDTA, S4; after medication (CH mixed with saline) for 1 month and S5; before obturation. Bacterial detection (PCR) and endotoxin detection (limulus amebocyte lysate assay). IL-1$_\beta$ /TNF-$_\alpha$ measured by (ELIZA) after macrophages stimulation by contents of root canals. They found that S1; bacterial endotoxins=100% + reasonable amounts IL-1$_\beta$ and TNF-$_\alpha$), S2; (bacterial endotoxin levels were significantly decreased in all groups, with greatest reduction in group I). Reduction of bacterial endotoxins levels at S3, S4 and S5with no difference between groups. Also, release of IL-1$_\beta$ and TNF-$_\alpha$ were reduced directly proportional to residual endotoxin levels. They concluded that the greatest reduction after instrumentation of bacterial endotoxin levels irrespect of the type of irrigant used. Moreover, application of intracanal dressing enhances reduction of endotoxins which lead to marked inhibition of macrophages.

Das et al.[25] compared antimicrobial effect of different intracanal medications. Forty-eight necrotic deciduous teeth were included. Samples were taken by sterile paper point as follow; S1: after access opening, S2: after canals instrumentation. Studied teeth were classified into; 1st group; CH+ distilled water, 2nd group; CH + 2% CHX, 3rd group: TAP mixed with distilled water, 4th group: TAP + 2% CHX. S3: 7 days post medication. Finally, GIC was used for cavity

restoration. They found that in S3 of all studied groups: significant decrease in *Enterococcus faecalis* count compared with S2. TAP + 2% CHX intracanal dressing showed a maximum bacterial reduction compared to minimum reduction in CH group. They concluded that antimicrobial efficacy markedly increased by mixing different medications with each other than single one.

Arruda et al.[26] demonstrated antibacterial effect in infected canals of teeth with primary apical periodontitis when using different intracanal dressing. Forty-eight patients (23 females and 25 males) with single rooted teeth were included. After mechanical instrumentation by a reciprocating technique, irrigation with 2.5% NaOCL. Medication with either TAP (minocycline, metronidazole, and ciprofloxacin) at 1 mg/mL or CH +2% CHX. Samples were collected from the canal as follow: S1; at baseline, S2; after chemo-mechanical preparation and S3 after dressing. Microbiological analysis was made by quantitative polymerase chain reaction assay. They found that in S1 bacteria was present. In comparing S2 with S3, in TAP group: reduction was 97% and in CH/ CHX: 39%. In S3 quantitative PCR showed negative results in TAP group than in CH group. They concluded that TAP (1mg/ml) provide better disinfection of canal than CH/CHX paste. Easy application and better antibacterial effect of TAP allowing use of it as routine intracanal dressing for conventional nonsurgical root canal treatment and possibly regenerative endodontics.

Chockattu et al.[27] compared anti-bacterial efficiency of ibuprofen, diclofenac, and calcium hydroxide against *Enterococcus faecalis* in an endodontic model. 76 single-rooted mandibular premolar teeth were instrumented to F4-ProTaper rotary. All teeth subjected to protocol to make them completely sterilized and microbially free then contaminated with *E. faecalis* for 14 days. Samples were taken before and after intracanal medication by paper point for microbiological analysis by colony-forming unit counts. The 76 teeth were randomly allocated into 4 groups (n = 19), depending on medicament used: Group I; Ibuprofen + distilled water, Group II; Diclofenac sodium salt+ distilled water Group III; $Ca(OH)_2$ powder + distilled water and all in (1:1 w/v) ratio control group; no medicament. They concluded the anti-inflammatory nonantibiotics (ibuprofen, diclofenac) had antibacterial effect against *E. faecalis*. Since nonsteroidal anti-inflammatory drugs had an anti-bacterial effect, it is possible to replace Ca $(OH)_2$ with NSAIDs, or

even combine them to form a cocktail of local disinfectants to optimize canal disinfection.

Ahirwar et al.[28] evaluated the antimicrobial efficacy (both aerobic and anaerobic) of *Ocimum Sanctum* essential oil and compared it with that of TAP for deciduous molars. 40 children were selected and assigned randomly into: TAP group(n=20) and *O. sanctum* group (basil) (n=20). Two intracanal samples from each patient were collected (after access opening, irrigation and three days after medicament placement). The samples were cultured (in aerobic and anaerobic media) and CFUs were used for counting. They found that saline + TAP had significant antibacterial reduction (with more effect on anaerobic) than saline + O**.** sanctum essential oil. They concluded that to overcome the antibiotic resistance due to its abuse, *O. sanctum* can be used as an alternative intracanal medicament in deciduous teeth in long- lasting infection as it has antimicrobial and anti-inflammatory efficacy.

Riaz et al.[29] compared the healing of apical lesion by radiograph after using two types of intracanal medicament(CH and CH /2% CHX) for 2 weeks. 60 patients with maxillary and mandibular teeth till first molar and lesion size was 2‑4 mm. Studied groups were randomly assigned into 1st group (CH, n=30) and 2nd group (CH / 2% CHX gel, n=30). After 2 weeks the teeth were obturated and final restoration were placed. At the end of 3 months of obturation, final outcome was assessed radiographically. They found that at end of twelve weeks in 1st group apical lesion size reduced (91.03%) while for 2nd group (97.26%). So, CH/2% CHX more preferrable than CH alone as intracanal dressing on healing. They concluded that CH/2% CHX leads to better apical healing (percentage)

Samir Abouelenien et al.[30]evaluated the effect of DAP and CH medications in infected root canals on postoperative pain. Thirty-six single rooted nonvital premolars with apical periodontitis were divided randomly: 1st group (CH) and 2nd group (DAP). NRS was used for recording preoperative pain. After endodontic treatment steps and placement of intra-canal dressings. NRS was used for recording postoperative pain at 6, 12 hours, 1 day and 2 days. They concluded that in non-vital teeth with apical periodontitis using any type of intracanal dressings were effective in decreasing post-operative pain

Barbosa-Ribeiro et al.[31] investigated antibacterial effect of CH intracanal dressing, its effects on pro-inflammatory cytokines and matrix metalloproteinases effects(in canals & periradicular tissues) of failed endodontically treated teeth with apical periodontitis. 20 single-rooted teeth with infected canals were divided randomly into: 1st group; 2% CHX gel and 2nd group; 6% NaOCL. S1: samples before chemo-mechanical preparation and S2: after 1 month of CH based intracanal dressing. CFU count for calculation of bacterial reduction, ELISA for measuring of PICs and MMPs. They concluded that there was a significant decrease in PICs and MMPs levels and consequently bacterial level reduction by CH intracanal dressing. Also, on using 2% CHX or 6% NaOCl, there no difference between the two types of irrigant on CH intracanal dressing. Using CH intracanal dressing for 1 month in failed endodontically treated teeth with apical periodontitis (with high levels of bacteria, PIC and MMP) showed excellent prognosis

Özdemir et al.[32] evaluated in periapical lesions the effect of CH and (CHX) gel on matrix metalloproteinase-9 (MMP-9) and vasoactive intestinal peptide (VIP) secretion. Sixty cases were assigned randomly into: 1st group; (CH, n=30) and 2nd group; (CHX gel, n=30). Sterile paper points were used for taking pre-and post-treatment samples from the interstitial fluid of periapical lesions. ELISA used for determination of VIP and MMP-9 levels. They found that in the 1st group, VIP level was significantly increase in the post-treatment than in the pre-treatment one. In 2nd group, MMP-9 level was significantly increase in the post-treatment than the pre-treatment one. They concluded that the amount of periapical VIP andMMP-9 secretion affected by the type of intracanal dressing. VIP (a neuropeptide that promotes new bone formation), its secretion increased by CH dressing. Therefore, using CH dressing may enhance the process of bone tissue repair.

da Silva et al.[33] evaluated the effect of association of non-steroidal anti-inflammatory and antibiotic agents with calcium hydroxide pastes on their biocompatibility and cytotoxicity. In 30 rats was used CH pastes with drugs tubes and empty tubes by implanting it in subcutaneous tissue. Removing these tubes after 1 week and 1 month and analyzed histologically. Pre-osteoblast-like cells were cultivated, the cytotoxicity of the paste was determined by MTT test after 1, 2, 3 days and 1 week. They concluded that tubes contained CH pastes with drugs were biocompatible and not cytotoxic. So, pastes of CH with anti-inflammatory or

antibiotic may be clinically used as replacement for conventional intracanal dressing to decrease microorganism resistance in root canal system.

Karataş et al.[34] evaluated antimicrobial effectiveness of CH paste with ibuprofen or ciprofloxacin in teeth with infected root canal and asymptomatic apical periodontitis. 45 patients (23 males and 22 females) were randomly assigned into: 1st group; 1 g CH powder + 1 mL propylene glycol, 2nd group ; 950 mg CH powder + 50 mg of ibuprofen +1 mL propylene glycol, 3rd group; 950 mg CH powder + 50 mg of Ciprofloxacin + 1 mL propylene glycol. Then taken three samples from canals; first sample (S1) at baseline, second one (S2) after intracanal preparation and final sample (S3); after removal of intracanal medication (7 days from their placement). Samples were subjected to microbiological analysis. They concluded that calcium hydroxide and ciprofloxacin intracanal medication combination produced more antibacterial effectiveness in vivo during endodontic treatment of necrotic teeth.

Neelakantan et al.[35]evaluated different irrigant (curcumin, NaOCl and CHX) antimicrobial effect on E. faecalis biofilm formed on tooth substrate in vitro. 96 instrumented extracted human teeth which *E. faecalis* biofilms were formed on it. In 48 hours, 2weeks and 2months biofilms, CFUs was calculated after thirty-minute application of test solutions or saline on studied specimens. They found that complete removal of bacteria at all time periods only by sodium hypochlorite. Also, curcumin and sodium hypochlorite caused significantly complete reduction in CFU than chlorhexidine and saline groups in 48 hours and 2 weeks. But sodium hypochlorite significantly lower CFU/ml in 2 months biofilms than curcumin treated samples which showed significantly lower CFU/ml than chlorhexidine and saline control group. They concluded that NaOCL (3%) had greatest antibacterial effect on biofilms of Enterococcus faecalis formed on the tooth substrate, then curcumin and chlorhexidine. Due to sodium hypochlorite side effects, curcumin herbal alternative might be promoted to be used in endodontic treatment.

Kumar[36]compared the effects of different intracanal dressing[(10%, 20%) *C. longa*, (10%, 20%) *Tachyspermum ammi*; (1%)chlorhexidine gel; and (10%) calcium hydroxide] on E. faecalis cultures. it was cultivated at 37°C on BHI broth, inoculated at 37°C for 72 h. Microbial zone of inhibition was calculated by well

diffusion method. He found that *C. longa* (20%) and CHX gluconate gel (1%) had highest degree of microbial zones inhibition than *C. longa* (10%) that were highly significant when compared to *T. ammi* (10%, 20%) and calcium hydroxide. He concluded that in failed endodontically treated teeth *C. longa* can be used as intracanal dressing.

Taur et al.[37]compared and evaluated the effect of curcumin and another different intracanal dressings on Enterococcus faecalis and its effect on the microhardness of root dentin. seventy extracted human single-rooted teeth were used for Preparation of 140 dentin blocks. One hundred-twenty blocks were infected with *E. faecalis* (for 21 days) for antibacterial analysis. Then it was treated according to type of dressing as: 1st group (CH), 2nd group (CHX gel; 2%), 3rd group (curcumin), 4th group (saline) and 5th group (negative control). At depth of 400 μm, dentin powder was obtained, cultivated in broth media and CFUs counted at 1, 3 days and 1 week. Four dentin blocks were used for microhardness analysis by preparation of 8 samples each 2 mm thickness. At 400μm from canal lumen microhardness test (by Vickers hardness indentation machine) was performed after dressings application and this test was done at 1, 3 days and 1 week. They found that chlorhexidine group showed total eradication of *Enterococcus faecalis,* CH group (64%) and curcumin group (54%). Chlorhexidine group showed greatest effect on microhardness of root dentin, CH group, finally no effect on microhardness in curcumin group. They concluded that curcumin has proper antibacterial effect with no microhardness effect on root dentine. So, it was promoted for its use as intracanal dressing alternative if its antibacterial effect accelerated.

Chamele and Bhat[38]evaluated in vitro the antimicrobial effect of curcumin (intracanal dressing) on *E. faecalis* in primary teeth. 60 single canalled deciduous teeth infected with *E. faecalis* were included. They were treated with a paste made of either turmeric extract, calcium hydroxide and saline for one week. Dentinal shavings were collected from within the canal. Digital colony counter was used for counting CFU. The pH of the medicaments used was measured with the help of pH meter. They showed that untreated Group III was significantly different from Group I & Group II, indicating that Group I and Group II were effective against the species *E. faecalis*. They concluded that turmeric extract (curcumin) is effective against *E. faecalis*. Calcium hydroxide and Curcumin showed better

antibacterial effect. There is 50% reduction in colony count was observed when treated with curcumin. Curcumin is effective against *Enterococcus faecalis*. Hence use of CH which can be substituted with curcumin as an intracanal dressing.

Dhariwal et al.[39]evaluated clinically the effect of different irrigation (NaOCL, *C. longa* and green tea) on anaerobic bacteria from canals of infected deciduous teeth. 30 children were included. After preoperative radiographs, isolation and determination of W.L., collection of 30 samples from canals by sterile paper points and placing it in thioglycolate transport medium tubes. Microbiological analysis was done by bacterial isolation and antibiotic sensitivity testing using 3 irrigating solutions. They reported that the most commonly bacteria isolated; (*Porphyromonas* sp., *Bacteroides fragilis*, *Peptostreptococcus*, and *S. aureus*). Also, the antibacterial effectiveness of 3 studied irrigating solutions was statistically significant (the highest NaOCL and *C. longa* and the lowest was green tea). They concluded that there was almost a polymicrobial infection in infected deciduous teeth. Eradication of predominant infection by endodontic preparation (instrumentation and irrigation) considered an important step for disinfection of infected deciduous teeth. Also, new herbal extract (*C. longa*) considered as natural alternative for NaOCL due to its adverse effects.

Vasudeva et al.[40]evaluated the effect of different intracanal dressings(2% CHX gel, Honey, Aloe vera gel, C. longa, Propolis gel and CH) on E. faecalis present in D.T. 210 lower 1st premolars were infected with E. faecalis for 21days. Studied samples were: 1st group (Saline; negative control), 2nd group(2%CHX gel) , 3rd group (honey), 4th group(Aloe vera gel), 5th group (20% C. longa gel), 6th group (Propolis gel) and 7th group(CH). Microbiological analysis for studied intracanal dressings on E. faecalis at 200 mm and 400 mm depth was done at 24, 72 hours and 5 days. They found the greatest antimicrobial efficacy was by 2% CHX gel then Propolis and C. longa. They concluded that (2% CHX gel) was the best antimicrobial intracanal dressing. While herbal extracts (Propolis and C. longa) considered the future natural alternative intracanal dressings but they need further long-term investigation in vivo

Xiao et al.[41]investigated the anti-inflammatory effects of curcumin in rat gingival fibroblasts both in vitro and in vivo by (the lipopolysaccharide induced inflammatory response and ligation-induced experimental periodontitis). In the

absence or presence of LPS, incubation of gingival fibroblasts by curcumin (by oral gavage every 48 hours) at different concentrations. ELISA was used for determination of (IL-1$_\beta$, TNF-α, OPG and soluble RANKL) in culture supernatants of rat gingival fibroblasts. After extraction of nuclear fraction of gingival fibroblasts, determination of NF-κB activation. Histological analysis was done by taking sections from between the first and second molars and observation for gingival inflammation. Micro-CT analysis assessed alveolar bone loss at the same area. They reported that curcumin decreased production of (IL-1β and TNF-α, OPG/sRANKL ratio and NF-κB activation) in rat gingival fibroblasts. They concluded that in vivo (gingival inflammation, modulated collagen fiber and alveolar bone loss) was reduced significantly by curcumin. Also, inflammatory activity in rat periodontitis improved by curcumin through its inhibitory effects of NF-κB activation and lowering the OPG/sRANKL ratio induced by lipopolysaccharides.

Lone et al.[42] studied C. Longa healing benefits and its therapeutic effect. One hundred seventy-eight cases with dry socket were diagnosed clinically and divided into group I [Turmeric dressing (C. Longa) with mustard oil] and group II (ZOE dressing). They found that both studied dressings significantly reduced pain, inflammation and discomfort. But faster wound healing with group I than group II. Also, C. Longa has no side effect. They concluded that local application of C. Longa accentuates wound healing at injury site. Therefore, different forms of the turmeric (C. Longa) is effective in treatment of different diseases e.g. surgical wounds.

Meizarini et al.[43]determined the healing effect of wound by ZO + C. Longa dressing as an anti-inflammatory through the expression of macrophages by means of immunohistochemistry examination, MAC387 and COX-2. 40 studied experimental wistar rats [4 control and 4 treatment groups (n=5)]. From all rat excision of part of skin (6 mm × 6 mm) at 24 hours was done. Then dressing wound of treatment groups was done by a mixture of ZO + turmeric extract (C. Longa), but the control groups (undressed). Sequential scarification of experimental rats and excision of subepithelial samples were taken on 72 hours, five days, 1 week and 2 weeks was done. Evaluation of the healing of the wound in the samples through anti-inflammatory action of dressing. They reported that in the treatment groups: MAC387 was showed the highest expression on the fifth day

then reduce slowly on 1 week and 2 weeks. While in the undressed groups: it reached the peak after 2 weeks. As regard to COX-2 expression; it started high on 3rd day, then decreased gradually on 5th and seven days, finally reached to minimum at the end of two weeks and this in treatment groups. While in undressed groups; it showed higher expression at third day, elevated at fifth day, started to reduce after 1 week and finally reduced after 2 weeks. They concluded that the wound dressing consisting of (ZO + C. Longa mixture) had an anti-inflammatory effect for excised wounds healing.

Neelakantan et al.[44] tested different irrigants (NaOCL and light or ultrasonic activated curcumin) effect in vitro on E. faecalis biofilms. One hundred and seventy-five root canals infected with E. faecalis and divided into: 1st group; (saline; n= 25), 2nd group; (3% NaOCL; n= 25), 3rd group; (3% ultrasonically activated NaOCL; n= 25), 4th group; (3% NaOCL irradiated with blue light; n=25), 5th group; [curcumin (2.5mg/mL); n=25], 6th group; [ultrasonically activated curcumin (2.5mg/mL); n=25], 7th group; [curcumin (2.5mg/mL) irradiated with blue light; n=25]. SEM examination of ultrastructure of biofilms was done. Confocal microscopy was measured bacterial viability. They found that the dead bacteria percentage were significantly lower in control group (saline) than in all treatment groups. Light activated curcumin had significantly higher percentage of dead bacteria, moreover, no growth of bacteria at depths (200 and 400 microns). They concluded that significantly higher antibacterial effect produced by light activation than ultrasonic one, the maximum elimination of bacterial biofilms (within the root canal lumen and D.T.) caused by light activated curcumin.

Gera et al.[45]evaluated the anti-microbial effect of nanocurcumin coated surgical bandages in-vitro on (E. coli, S. aureus and S. pyogenes). Tetracycline was added to surgical bandages. Then comparing between nanocurcumin coated surgical bandages native curcumin coated one. It was found that nanocurcumin coated bandages showed antimicrobial activity more than 99%, remarkable wound healing and controlled drug delivery in comparison to native curcumin coated bandages. They concluded that the preparation of nano particles of curcumin and nanocurcumin coated bandages are the novel method. The developed nanocurcumin coated bandages exhibited superior antimicrobial properties compared to other bandages. Curcumin nanoparticles were more effective at both accelerating wound closure and clearing infection with microbes as compared to

curcumin in its bulk size. They considered as promising method to combine normal bandages with nano product of natural compound curcumin and antimicrobial drug. Moreover, it will not contain any synthetic nano material which can lead to toxicity. This will provide a way to use this type of bandages in future also for controlled release of drugs at the target site of injury especially with respect to cancer treatment.

Devaraj et al.[46] demonstrated the effect of different intracanal medications (photoactivated curcumin, TAP ,DAP, 2% CHX and CH) and untreated teeth as control) on E. faecalis biofilms. Microbiological analysis for biofilm mass and percentage of live/dead bacteria within the root canal as well as dentinal tubules was made by confocal microscopy. Also, colony forming units count was made for dentinal shavings obtained from the root canal walls (at 200 and 400 microns depth). They concluded that light activated curcumin had maximum activity on bacteria and biofilms of *E. faecalis* followed by TAP. However, 2% CHX more effective than CH on killing *E.* faecalis cells at 200 microns depth in dentinal tubules, but both dressings had no effect on its biofilm structure. So, Curcumin, TAP and DAP were significantly reduced the Colony forming units at 200 and 400microns depths when compared to other dressings and untreated group.

Gopal et al.[47]evaluated bactericidal efficacy of macro-, micro- and nanocurcumin on four predominant pathogenic bacteria including *E. coli, S. enteritidis, S. aureus* and *S. mutans*. They demonstrated a five-fold enhancement in bactericidal activity by nanocurcumin. They concluded that the higher penetration as shown by the confocal laser scanning microscope imaging and the enhanced solubility of the nanocurcumin are speculated to be reasons for the observed superior bactericidal property of nanocurcumin

Gomes-Filho et al.[48]evaluated the effects of different irrigating solutions (light activated curcumin, 5% NaOCl and saline) on viability of cell and production of cytokine (IL-1β and IL-6) of mouse fibroblasts. 500mg/L curcumin pre-irradiated for 60 seconds with Led wavelength (λ) (480 nm) & for 300 seconds for photodynamic therapy with 72 Jcm^2. Mouse fibroblasts L-929 were cultured in 24-well cell culture plates containing studied diluted solutions plus culture medium. While, control group was culture medium only. After 6, 24 and 48 hours, the cell viability was calculated by (MTT) assay, while, ELISA used for evaluation

of cytokines from supernatant. They found that cytotoxic effect of PDT curcumin and saline was low as control group. But cytotoxic effect of 5% sodium hypochlorite in all time intervals was significantly higher than PDT curcumin. IL-1β and IL-6 were expressed likely by all studied irrigating solutions regardless to time intervals. They concluded that light activated curcumin neither has no effect on viability of L-929 fibroblasts and not cytotoxic nor inhibit release of cytokines IL-1β and IL-6.

Sivieri-Araujo et al.[49]evaluated antimicrobial effect, biocompatibility and production of cytokine by light activated curcumin in rats. In Wistar rats' dorsal connective tissue were implanted polyethylene tubes which containing (5% NaOCl, 500 mg /L curcumin photosensitizer and saline as control). Scarification of rats were done at 1week, 2 weeks, 1, 2 and 3 months of implantation, tubes and surrounding tissues were removed, divided into two part, one; for histological analysis, the other for estimation of production of IL-1β and IL-6 by ELISA. They reported that severe tissue reactions at 1 week in all studied specimens but reduced significantly by time. On the other hand, antimicrobial photoactivated curcumin enhanced production of IL-1β at all time intervals. Moreover, the maximum level of IL-6 at the end of three months was reached. They concluded that biocompatibility was the same in control and experimental groups. While, the production of cytokines (IL-1β and IL-6) by rat cells were enhanced by PDT curcumin

Adahoun et al.[50]evaluated the nanocurcumin effects as anti-cancer (PC3, HEK and human erythrocytes)and antimicrobial against (Micrococcus luteus, S. aureus, E. coli, P. aeruginosa). The anticancer and antibacterial effects of nanocurcumin were assessed by cell viability curve, half maximal inhibitory concentration and the minimum bactericidal concentration. They found that curcumin nanoparticles had significant anticancer effect on (PC3) in comparison of parent one and low cytotoxic effect on normal cells (HEK). Hemolytic effect of curcumin nanoparticles and its native were very low with no significant difference. Also, all different bacterial strains killed by lowest concentration of curcumin nanoparticles (MBC) when compared with parent one. Moreover, antimicrobial effect of both curcumin nanoparticles and parent one was higher in gram +ve than gram -ve bacterial strains. They concluded that curcumin nanoparticles are safe compound and has potent antimicrobial and anticancer efficacy, so, it preferred to

be use in treatment of prostatic cancer cells. Moreover, curcumin nanoparticles have remarkable antimicrobial activity than parent one. Also, low hemolytic and cytotoxic activities against eukaryotic cells were showed.

Zambrano et al.[51] assessed the biological activity of topically applicated nanocurcumin on experimental periodontal disease. 16 rats classified into: [experimental group (n=8), local microinjections of 3 μL of a 10 mg/mL LPS solution from *E. coli* strain for induction of experimental periodontal disease] and [vehicle control group (n=8); PBS]and both these materials were injected bilaterally directly into the gingival tissues adjacent to the palatal surface of both maxillary first molars 3times / 7 days for 1 month. Each group was injected by either nanocurcumin or nano vehicle of the same volume at same sites 2 times per 7 days. They reported that total inhibition of inflammatory bone resorption by topically applicated nanocurcumin (μCT analysis). Also, osteoclast counts, inflammatory infiltrate and p38 MAPK and NF-kB activation were reduced significantly. They concluded that topical application of nanocurcumin causes marked inhibition of number of osteoclastic cells so, inhibit bone resorption and inflammation associated with experimental periodontal disease.

Hashemzadeh et al.[52] evaluated the effect of recently, nanomicelle curcumin "nanocurcumin" on the symptoms relief of knee osteoarthritis patients. Studied cases were divided into thirty-six patients as experimental that treated with capsules (40 mg nanocurcumin) every twelve hours for six weeks and thirty-five patients as control treated with placebo (similar components of nanomicelle curcumin capsules yet without curcumin). The pain level was recorded by patients before treatment at 1st visit and after treatment at the end of 6 weeks. They found that pain relieved significantly with nanocurcumin group than with the placebo group. They concluded that osteoarthritis symptoms were significantly improved by nanocurcumin and can be used as alternative for NSAIDs which were usually used for the treatment of the osteoarthritis but with complications such as gastrointestinal bleeding

Ghorbanzadeh et al.[53] evaluated effect of the traditional endodontic irrigants (sodium hypochlorite) and new ones [rGOCur, rGOCur LED, rGOCur PDI]compared to control group (only bacterial suspension)on disinfection of root canal and their effect on virulence factors of *Enterococcus faecalis*(ex vivo

biofilms). Also, on production of intracellular ROS. They found that enterococcus faecalis growth inhibition by reduced graphene oxide-curcumin (250µg/ml) evaluated by MBIC. However, its anti-biofilm activity was insignificant even after application of LED for long periods (300 sec). Also, rGO-Cur LED, rGO-Cur-PDI, and NaOCl treatment cause remarkable reduction on expression levels of virulence factors in biofilms of *Enterococcus faecalis* in comparison to control. However, there was no significant change in virulence genes expression by LED. They concluded that rGO-Cur-PDI can be used clinically to control endodontic infections, due to it had double inhibitory effects on virulence activity of *E. faecalis* and biofilm formation ability

Aim and objectives of the study

The aim of the present study is to compare curcumin in its regular and nano forms versus ibuprofen and ciprofloxacin mixture as intracanal medicaments in retreatment cases with periapical lesion regarding:

(1) Inter-appointment pain
(2) Antibacterial effect
(3) Clinical and radiographic signs of healing

Social & scientific values:

Currently there are no clinical studies comparing the natural and synthetic intracanal medications in patients suffering from symptomatic root canal treatment failure. Thus, we are conducting this study to compare the efficacy of different intracanal medicaments [nanocurcumin, curcumin (natural herbs), ciprofloxacin and ibuprofen mixtures, calcium hydroxide as control] in case of posttreatment disease aiming to solve the problem of the inter appointment pain felt by these patients after nonsurgical endodontic retreatment. Given that the most common cause of pain is microbial infection, so comparing their antibacterial effects and effects of these different types of intracanal dressing on periapical lesion healing.

If natural intracanal medications in their bulk or their nanoform will become successful and evolution in future endodontics for patients and dentists would be achieved. For patients, the best treatment with natural extracts which is more applicable and more affordable without side effects would be provided. Despite of the fact that the nanoform is more expensive options for sponsorships would be available. Regarding dentists an opportunity to provide the best quality service with least expenses would be provided, which in turn would save time, effort and money. Finally, it will represent a turning point for researchers.

Study Design:

Randomized clinical trial (medications)

Materials and methods

Materials used:

- Nanocurcumin gel[#]
- Curcumin powder[$] + propylene glycol paste
- Ciprofloxacin[@] + brufen[^] + propylene glycol paste
- Calcium hydroxide paste (Metapaste)[*]

Methods:

This study is designed to be a prospective clinical study. The research proposal will be approved by the ethical committee, Faculty of Dentistry Ain shams University, Cairo, Egypt.

Sample size determination:

A power analysis was designed to have adequate power to apply a two–sided statistical test of the research hypothesis (null hypothesis) that there was no difference between the antibacterial effect of different tested intracanal medication, According to the results of **Karataş et al.**[(34)] using 0.05 α error , power of 0.8 and effect size 0.48 (difference proportion of positive culture) for four studied groups. The predicted sample size (n) is a total 80 teeth with ratio 1:1:1:1 (study group1: study group2: study group3: control) i.e. 20 teeth per group. Sample size calculation was performed using G power software version 3.1.9.4 (© 1992-2019)

Subjects of research:

Recruitment:

Patients are recruited for present clinical trial from out-patient of the clinic of endodontics at the faculty of dentistry, Ain shams University, Egypt to meet the target sample size.

[#] Nano Tech Egypt for Photo- Electronics, City of 6 October, Egypt.

[$] Aldoha company, 10th of Ramadan city, Cairo, Egypt

[@] European Egyptian Pharm. Ind., Cairo, Egypt

[^] kahira pharmaceuticals & chemical industries Company, Cairo, Egypt

*META BIOMED CO., LTD, Korea

Selection of patients:

Patients having maxillary or mandibular single rooted anterior or premolar teeth with signs &/ or symptoms of post treatment disease and referred for non-surgical root canal retreatment will be participated in this study

Participants Eligibility criteria:

Inclusion criteria:

- Medically free patients.
- Sex includes both male and female.
- Patient's age between 20-60 years.
- Patients must agree positively to share in the study.
- Patients able to sign informed consent.
- On clinical and radiographic examination, the included teeth [Maxillary or mandibular single rooted (anterior/premolar) teeth] must be suffering from failed endodontic treatment with periapical lesion.

Exclusion criteria:

- Badly broken down teeth indicated for extraction or with difficult isolation
- Teeth with former procedural errors as perforation & instrument separation, ledge, etc.
- Medically compromised patients
- Patients with history of receiving antibiotics within a month,
- Periodontally affected teeth by pocket depth > 4mm

Diagnosis:

The diagnostic data will be collected in a case report form

Diagnostic criteria:

Root canal filled single rooted teeth with post treatment disease manifest by one or more of the following criteria:

- History of recurrent acute &/ or chronic apical lesion &/ or
- Pain on percussion and /or tenderness on palpation at least after one month of primary root canal treatment, &/ or
- Radiographic evidence of bone loss (apical radiolucency)

Patient classification:

According to intracanal medicament that will be used between visits, the participants will be categorized into:

Group I: (n=20) Root canals will be medicated by nanocurcumin gel

Group II: (n=20) Root canals will be medicated by curcumin powder + propylene glycol paste

Group III: (n=20) Root canals will be medicated by 50mg ibuprofen and 50mg ciprofloxacin mixture + propylene glycol paste

Group IV: (n=20) (positive control) Root canals will be medicated by calcium hydroxide in barium sulphate base (metapaste)

Procedures:

First visit:

Treatment plan will be discussed with patients and their acceptance to share in the study will be obtained. Patient will be anesthetized by using inferior alveolar nerve block local anesthesia for mandibular premolar teeth or labial/buccal infiltration local anesthesia for mandibular or maxillary anterior or maxillary premolar teeth. Removal of any caries and previous coronal restoration will be done. Teeth will be isolated with rubber dam. Access cavity will be completely disinfected before entering the root canals using sodium hypochlorite 2.5%, then its effect will be inhibited using sodium thiosulphate 5%.

Old gutta percha will be removed with protaper rotary retreatment files in the following manner D1, (with cutting tip) will be used for first penetration into old gutta percha in the coronal third of the canal. D2, (with non-cutting tip) will be used for removal of old gutta percha from middle third of the canal. Finally, D3, (with non-cutting tip) will be used to remove old gutta percha from apical third of the canal. This system will be used without gutta percha solvent. Patency of the

filled canals will be obtained using manual k files #10, #15. Sterile saline will be used as an irrigant. Working length determination will be done by J Morita apex locator followed by intraoral periapical radiograph to confirm the length to be 0.5-1 mm shorter than radiographic apex.

Sterile paper point equivalent to the size of largest file reaching the working length will be placed for one minute in the canal and this is the first sample for bacteriological assessment (S1). Then complete cleaning and shaping of the canal will be made using 15 ml of 2.5% sodium hypochlorite as an irrigant with a side vented needle of 27 gauge placed one millimeter from working length between every subsequent instruments and M3-Pro Gold rotary endodontic files, in an endodontic motor according to the manufacturer instructions and MD-Chelcream will be used as lubricant during mechanical preparation

After complete cleaning and shaping, inhibition of action of sodium hypochlorite using 10 ml of 5% sodium thiosulphate then it will be flushed from the canal using sterile saline. Then sterile paper point equivalent to size of master apical file will be placed for 1 minute in the canal 1 mm from working length and this second sample for bacteriological assessment (S2). Then these cases will be divided into four group according to intracanal dressing which will be used:

- **Group I:**(n=20) canal will be completely dried and nanocurcumin gel will be used as intracanal medicament for 7 days
- **Group II:** (n=20) canal will be completely dried and curcumin powder 1gm + 1ml propylene glycol paste will be used as intracanal medicament for 7 days
- **Group III:** (n=20) canal will be completely dried and ibuprofen + ciprofloxacin mixture (1 g) powder + 1ml propylene glycol paste will be used as intracanal medicament for 7 days
- **Group IV:** (n=20) (positive control) canal will be completely dried and metapaste will be used as intracanal medicament for 7 days.

Finally, a cotton pellet & temporary filling (**MD-Temp)** will be applied under complete a septic condition. Patient will be given numerical rating scale (NRS) and will be asked to rate inter-appointment pain level at 6, 12, 24 & 48 hours and at 3, 6 day.

Second visit:

After one week (7 days later), placement of rubber dam , removal of the temporary fillings will be done and M pro file #20, 0.04 taper will be placed in each canal to loosen medicament and to create a space for subsequent irrigating solution, then root canal will be washed with 10 mL of sterile saline until saline will be got out clear from the canal. Sterile paper point will be placed in the canal 1mm from the working length to take the last sample (S3)**.** Dryness of the canals by paper points and master cone adjustment will be made. Obturation with cold lateral compaction technique with gutta percha #35 or #40 with 0.04 taper according to canal size and resin sealer will be done. Final restoration with composite resin will be done for all teeth**.**

The sterile paper points with three samples (S1, S2, S3) will be placed each in a sterile tube labelled according to the type of medication and the order of the sample and each tube contain broth media then all tubes will be transferred to microbiological lab within 2-3 hours from sampling procedure in an ice box with refrigerated ice bag in contact with it. Patient will be recalled at 1, 3, 6 months for follow up clinically and radiographically.

Methods of evaluation:

1- **Inter- appointment pain evaluation:**

Incidence of inter- appointment pain will be collected by the operator through NRS which is an 11-point scale consisting of numbers from 0 through 10:

0 reading represents “no pain”, 1- 3 readings represent “mild pain”, 4- 6 readings represent “moderate pain”, 7- 10 readings represent “severe pain”

2- **Microbiological evaluation:**

Counting the bacteria by colony forming unit/ml

3- **Clinical and radiographical evaluation of healing:**

The clinical and radiographic data will be collected at the initial examination and at 1, 3, 6 months postoperative follow up and will be used as a base to determine success or failure of the endodontic retreatment after four studied intracanal medications. The following criteria will be used to determine the

success or failure of the endodontic retreatment after four studied intracanal medications:

a) Complete repair (success)

• on clinical examination: no signs and symptoms of acute or chronic apical periodontitis and

• on radiographic examination: no pathological apical root resorption, normal PDL space width and complete resolution of lesion present preoperatively.

b) Incomplete repair (success)

• on clinical examination: no signs and symptoms of acute or chronic apical periodontitis and

• on radiographic examination: no pathological apical root resorption and size of periapical lesion decreased.

c) Absence of repair (failure)

• on clinical examination: signs and symptoms of acute or chronic apical periodontitis still present and/or

• on radiographic examination: presence of pathological apical root resorption, no change in the size or increase of pre-existing periapical lesion during the follow-up period.

Statistical analysis:

Data management and statistical analysis will be performed using the Statistical Package for Social Sciences (SPSS) version 21. Data will be presented as mean and standard deviation (SD) values, analysis of variance (ANOVA) will be used for comparison between groups and the changes by time in each group evaluated by T test.

Z test will be used for comparison of proportions with a significance level of 5% from clinical and radiographic data collected preoperatively and at 1,3,6 months postoperatively as regard to intracanal dressing type and its relation to the visible periapical lesion in radiograph(complete remission or not).

Risks to study participants:

No adverse effects were reported by previous studies from nanocurcumin (**Gomes-Filho et al.[48]**, **Sivieri-Araujo et al.[49], Adahoun et al.[50], Zambrano et al.[51], Hashemzadeh et al.[52].** Moreover , these studies reported its

biocompatibility and **Hashemzadeh et al.**[52]used nanocurcumin in capsules given to patients and swallowed them. They provided the patients with analgesic and anti-inflammatory effects. However, if any harm is seen in the participants in any of studied groups they will be recorded and reported at the end of the trial.

Benefits to study participants/ community:

Participants and community will receive the best treatment without side effects as these materials are biocompatible.

Privacy, Record keeping & confidentiality:

Personal information about participants will be acquired during the process of trial recruitment, eligibility screening, and data collection. Much of this information consists of private details. All study-related information will be stored securely at the study site. All participant information will be stored in locked file cabinets in areas with limited access. All records that contain names or other personal identifiers will be stored separately from study records identified by the patient's serial number. Participants' study information will not be released outside of the study without the written permission of the participant.

Informed consent materials:

Patient informed consent:

The research operator will introduce the trial to the patient and operator will obtain signed consent from patients willing to participate in the trial. However, the subject could quit at any time without penalty or loss of any benefits.

Ethics Committee will revise and modify according to their guidelines.

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الملخص العربي

المقدمة :

يوجد عوامل عديدة يرجع لها فشل علاج اللب اهمها المسببات الميكروبية التي تنقسم الي ميكروبات هوائية ولاهوائية مثل التي تتحمل اقسي الظروف المحيطة بها وتتلائم مع اقل مصادر للغذاء والنمو
ولذالك مع التحضير القناه باستخدام الأدوات اللبية وتعقيمها بالمواد المضادة للميكروبات تظل انواع من البكتريا المقاومه في الاماكن الضيقة في القناه اللبية مثل القنوات الفرعية

لهذا السبب يستخدم ادوية موضعية داخل القناه اللبية بين الجلسات ولكن الانواع التقليدية مثل هيدروكسيد الكالسيوم لاتؤثر جيدا علي البكتريا المقاومة

ولذالك استخدام انواع اخري يكون لها تاثير جيد علي انواع البكتريا المختلفة الموجودة في القناه اللبية التي فشل علاجها بالادوية التقليدية هذة الانواع مثل خليط المضاد البكتيري مع مضاد الالتهاب وقد استخدمت من قبل ولكن كل دواء بمفرده ووجد لها تاثير جيد

كما ان الاتجاه الجديد نحو الادويه الطبيعية مثل الكركم وقد وجد لها تاثير ممتاز علي البكتريا المقاومه الموجودة في القنوات اللبية التي فشل علاجها من قبل

ولكن وجد ان الكركم العادي له بعض العيوب مثل قلة الذوبان والانتشار وسرعة التحلل والتكسير لذالك الاتجاه نحواستخدام الكركم النانو اصبح له اهمية كبيره لانه لايوجد به هذة العيوب.

الغرض من الدراسة:

مقارنة كفاءه الكركم العادي والكركم النانو بخليط المضاد الحيوي ومضاد الالتهابات كادوية موضعية داخل القناه اللبية في حالات فشل علاج اللب وتقييم تاثيرهم كمضادات للبكتريا وعلي تقليل الالم وايضاعلي شفاء الاتهاب تحت جذر السن.

الطريقه:

سوف يتم تقسيم٨٠ سنه ذات قناة واحدةالي اربع مجموعات :
مجموعه ١: بعد تنظيف القناه اللبية وتنشيفها يتم وضع الكركم النانو لمدة اسبوع
مجموعه٢: بعد تنظيف القناه اللبية وتنشيفها يتم وضع الكركم العادي لمدة اسبوع
مجموعه ٣: بعد تنظيف القناه اللبية وتنشيفها يتم وضع خليط المضاد الحيوي(سيبروفلوكساسين) مع مضاد الالتهابات (بروفين) لمدة اسبوع
مجموعه٤(مجموعة ضابطه): بعد تنظيف القناه اللبية وتنشيفها يتم وضع هيدروكسيد الكالسيوم (ميتابيست)لمدة اسبوع
يتم وضع هذة الادوية الموضعية بعد ازاله حشو اللب القديم بين الجلسات ثم ازالتها بعد اسبوع من وضعها وبعد ذالك يتم حشو اللب من جديد ويتم تقييم تاثيركل دواء موضعي من الناحية الميكروبيولوجية وتاثيره علي تقليل الالم بين الجلسات ومتابعه الاسنان لمدة ٦ اشهر سريريا واشعاعيا لمقارنه ايضا تاثير كل دواء موضعي علي شفاء الاتهاب تحت جذر السن.

مقارنة تاثير الادوية الطبيعية والصناعية المختلفة المستخدمه كادوية داخل قناه اللب علي علاج التهاب تحت جذر السن في حالات فشل علاج اللب (تجربة إكلينيكية بالانتقاء العشوائي)

مشروع رسالة مقدم الي كلية طب الاسنان, جامعة عين شمس ، تمهيداً للحصول علي درجة الدكتوراه في علاج الجذور

مقدمة من

روضة محمد عبد الرحمن بغدادي

مدرس مساعد بكلية طب اسنان جامعه اسيوط

بكالوريوس طب اسنان جامعة القاهرة ٢٠٠٩

ماجستير علاج الجذور جامعة القاهرة ٢٠١٧

المشرفون

ا.د/كريم مصطفي البطوطي

استاذ بقسم علاج الجذور

ووكيل الكلية لشئون التعليم والطلاب

كلية طب اسنان-جامعة عين شمس

د./ سارة حسام فهمي

مدرس بقسم علاج الجذور

كلية طب اسنان-جامعة عين شمس

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