Chapter 102

Use Of Calcium Hydroxide Between Visits In Endodontic Treatment

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ABSTRACT
The aim of this study was to conduct a literature review on the effectiveness of endodontic treatment with calcium hydroxide between visits in intracanal medication in teeth with periradicular lesions. The methodology was descriptive, based on PUBMED databases, in English articles published in the last ten years. It was found that the treatment with calcium hydroxide as intracanal medication presents as advantages the improvement of the microbiological state of the root canal system, decreasing levels of bacteria, pro-inflammatory cytokines (PICs) and matrix metalloproteinases (MMPs), standing out as an effective anti-endotoxin agent, being also able to minimize the intensity or severity of postoperative pain after endodontic treatment. It was concluded that the use of calcium hydroxide as an intracanal medication is indicated for multi-visit endodontic treatment in teeth with periradicular lesions prior to definitive root canal obturation. However, the evidence available in the literature is considered insufficient, thus highlighting the need for further studies comparing the long-term success of the treatment.

Keywords: Calcium Hydroxide, Intracanal Medication, Apical Periodontitis.

1 INTRODUCTION

Periradicular disease is an inflammatory response in response to intraradicular bacterial infection and can be prevented (in case of pulpal inflammation) or resolved (in case of pulpal infection) by root canal treatment. Periradicular lesions are barriers that restrict microorganisms and prevent their spread to the surrounding tissues. The bone is resorbed, followed by replacement by a granulomatous tissue and a dense wall of polymorphonuclear leukocytes (PMN) (KARAMIFAR *et al.*, 2020).

Gram-negative bacteria predominate in root canals of teeth with pulp necrosis and periradicular lesions. Among the virulence factors of gram-negative bacteria, lipopolysaccharides (LPS/endotoxins) are especially important in endodontic infection because of their biological effects, which lead to a complex interaction with host factors, resulting in clinical symptomatology, inflammatory reaction and resorption of mineralized tissues. On the other hand, lipoteichoic acid (LTA), present in gram-positive bacteria, shares its pathogenic properties with lipopolysaccharides (LPS), resulting in well-known lesions in periapical tissues. In general, both LPS and LTA are capable of potently activating monocytes/macrophages, causing

rapid release of cytokines at periradicular sites related to tissue destruction (GOMES and HERRERA, 2018).

Most periradicular lesions heal after meticulous non-surgical endodontic treatment (KARAMIFAR *et al*., 2020). The selection of effective microbial controls for infected root canals requires detailed knowledge of the microorganisms responsible for pulpal and periradicular pathology associated with knowledge of the mechanism of action of the antimicrobial substance employed (ESTRELA *et al*., 2014).

Antimicrobial agents must interrupt the growth of microorganisms in order to reduce the process or eliminate the microbiota of infected root canals with periradicular lesions (ESTRELA *et al*., 2002).

Among the substances used as adjuvants in the disinfection of root canal systems, calcium hydroxide stands out. Since its introduction in dentistry by Hermann in 1920, calcium hydroxide has been widely used in endodontics. Although its general mechanisms of action are not fully understood, the choice for its use is due to its high alkalinity, in addition to its antibacterial properties and its ability to dissolve organic tissue (DE MOOR; DE WITTE, 2002).

The advantages of endodontic treatment in multiple visits using calcium hydroxide include symptom-free period before obturation of the canal, greater reduction of the microbiological load or even a complete eradication of microorganisms, greater effectiveness in reducing endotoxin levels, moreover, in cases with symptoms such as pain, exudation, it is contraindicated to obturate the root canal (IBRAHIM *et al*., 2020).

2 ADVANTAGES OF USING CALCIUM HYDROXIDE BETWEEN CONSULTATIONS

Oliveira *et al*. (2012), in a clinical study investigated the effects of endodontic treatment using different irrigants on endotoxins in root canals with pulpal necrosis and apical periodontitis and evaluated the cytotoxic effects. Thirty-six root canals were selected. Samples were collected before (S1) and after instrumentation (S2). The root canals were divided into 3 groups (n = 12) according to the irrigant combination used: CLX + LW, chlorhexidine gel 2% + calcium hydroxide (0.14%, lime water); CLX + PmB, chlorhexidine + polymyxin B; CLX (control), chlorhexidine + saline solution. The third collection (S3) was performed after ethylenediaminetetraacetic acid and S4 after intracanal medication (CLX + calcium hydroxide for 14 days). The results showed that endotoxins were detected in all root canals before instrumentation (S1). The CLX + LW group, 2% chlorhexidine gel + calcium hydroxide (0.14%, lime water) showed the highest reduction of endotoxins after instrumentation (99.18%), similar to the CLX + PmB group (96.42%, $P > 0.05$) and different from the CLX group (90.78%, $P < 0.05$). The intracanal medication promoted important neutralization of endotoxins, with a 99.2% to 100% reduction. They concluded that the combination of chlorhexidine gel 2% and calcium hydroxide 0.14% (lime water) as irrigant was the most effective in reducing endotoxins in root canals, and the use of intracanal medication (chlorhexidine gel 2% + calcium hydroxide) for 14 days was important to neutralize cytotoxic effects.

Paredes-Vieyra and Enriquez (2012) evaluated the outcome of endodontic treatment in one or two appointments of teeth with apical periodontitis after a 2-year follow-up period. Three hundred upper and lower non-vital teeth with apical periodontitis were treated in a single appointment or in 2 appointments. The main inclusion criteria were radiographic evidence of apical periodontitis (minimum size ≥ 2.0 × 2.0 mm) and diagnosis of pulp necrosis confirmed by negative response to hot and cold tests. The results demonstrate that of the 300 teeth treated, 18 were lost at follow-up, 9 in the 2 appointment group and 9 in the 1 appointment group. Of the 282 teeth studied, the randomization procedure allocated 146 teeth for 1 appointment treatment and 136 teeth for 2 appointments treatment. In the 1 appointment group, 141 of 146 teeth (96.57%) were classified as healed compared to 121 (88.97%) of 136 teeth in the 2 appointment group. Eleven cases were classified as uncertain in the 2 appointment group (8.08%) compared to 4 (2.73%) in the 1 appointment group. Two of the 10 teeth in the 2-consultation group had pain before the 2-year follow-up and were classified as unhealed. Statistical analysis of the healing results showed no significant difference between the groups. They concluded that several factors play an important role in the decision making process of 1 appointment versus 2 appointments endodontics. These include objective factors such as preoperative diagnosis, ability to achieve infection control, root canal anatomy, complications of the procedure, and subjective factors such as patient signs and symptoms. This study provided evidence that a treatment protocol with instrumentation for predefined larger apical instrumentation sizes and irrigation with a negative apical pressure system can lead to healing in cases of apical periodontitis, which is a significant finding compared to more dated studies that showed average healing in cases of apical periodontitis. With the sample size, there was no statistically significant difference between the two treatment modalities.

Taneja and Kumari (2012) reported a case of a non-surgical endodontic treatment of teeth with a large periradicular lesion. First, an intracanal calcium hydroxide dressing was administered. Since the symptoms did not subside, the treatment protocol was changed. Instead, a triple antibiotic paste was used for 3 months. At follow-up, the teeth were clinically asymptomatic and radiographically showed healing of the periradicular lesion. The outcome of the case shows that when the most commonly used medications fail to eliminate symptoms, then a triple antibiotic paste (metronidazole, ciprofloxacin and minocycline) can be used clinically to treat teeth with large periradicular lesions.

Thomas *et al.* (2012) presented a case of conservative non-surgical management of periradicular lesions. Non-surgical conservative management of larger, presumably cystic, periradicular lesions eliminates the potential complications of surgery and has greater patient compliance and acceptance. In this case, a cystic periradicular lesion associated with the upper central incisor and lateral incisor was treated conservatively with buccal aspiration decompression followed by conventional endodontic therapy employing calcium hydroxide paste and iodoform as an intracanal medication. The treatment was successful, evidenced by symptom relief and radiographic evaluation. They concluded that large periapical

cyst-like lesions can be resolved by non-surgical endodontic therapy employing calcium hydroxide intracanal medication.

Vera *et al*. (2012) analyzed the *in vivo* microbiological status of root canal systems of mesial roots of mandibular molars with primary apical periodontitis after endodontic treatment of 1 or 2 appointments. Mesial root canals were instrumented using a combination of K3 and LightSpeed instruments (mesio-vestibular canals) or the ProTaper system (mesio-lingual canals), with 5% NaOCl irrigation. The smear layer was removed and a final rinse was performed with 5 mL of 2% chlorhexidine. In the 2 appointment group (7 roots, 14 canals), the canals were medicated with calcium hydroxide for 1 week and then obturated using the continuous wave compaction technique. In the 1 appointment group (6 roots, 12 canals), the canals were immediately obturated after chemical-mechanical procedures. Teeth were extracted 1 week after root canal instrumentation and processed for histobacteriological analysis. The results showed that in the 1 appointment group, no case was completely free of bacteria; residual bacteria occurred in the main root canal (5 of 6 cases), isthmus (5 of 6), apical ramifications (4 of 6), and dentinal tubules (5 of 6). In the 2 appointment group, 2 cases were free of bacteria; residual bacteria were found in the main canal only in 2 cases (none of them with persistent dentinal tubule infection), in the isthmus (4 of 7 cases), and in ramifications (2 of 7). The 2 instrumentation techniques performed similarly. When obturating material was observed in the ramifications, it was usually mixed with necrotic tissue, debris, and bacteria. They concluded that the 2 appointment protocol using interconsultation medication with calcium hydroxide resulted in improved microbiological status of the root canal system when compared to the 1 appointment protocol. Residual bacteria were more frequent and abundant in ramifications, isthmuses, and dentinal tubules when root canals were treated without interconsultation medication. Apical ramifications and isthmuses were never completely filled. The use of an antibacterial interconsultation agent is necessary to maximize bacterial reduction prior to filling.

Marinho *et al*. (2014) monitored the efficacy of root canal procedures using different irrigants and intracanal medication on endotoxin levels found in root canals of teeth with chronic apical periodontitis. Thirty root canals from teeth with pulp necrosis associated with peri-radicular lesions were selected and randomly divided into groups according to the irrigants used: GI - NaOCl 2.5%, GII - chlorhexidine gel (CHX) 2% and GIII - saline solution (SS) (all, n=10). Samples were collected with sterile/apirogenic paper tips before (S1) and after root canal instrumentation (S2), after the use of 17% ethylenediaminetetraacetic acid (EDTA) (S3) and after 30 days of intracanal medication (Ca(OH)2+ SS) (S4). The results showed that endotoxins were detected in 100% of the investigated root canals (30/30), with a mean value of 18.70 EU/mL. After S2, a significant reduction of the median percentage was observed in all groups, regardless of the irrigant tested: NaOCl 2.5% (99.65%) (GI), CHX 2% (94.27%) (GII) and SS (96.79%) (GIII) (all $p<0.05$). Rinsing the root canal with 17% EDTA (S3) for a period of 3 minutes failed to decrease endotoxin levels in GI and a slight decrease was observed in GII (59%) and GIII (61.1%) (all $p>0.05$). Intracanal medication for 30 days was able to significantly reduce residual endotoxins: NaOCl 2.5% (90%) (GI), CHX

2% (88.8%) (GII) and SS (85.7%) (GIII, $p<0.05$). No differences in endotoxin reduction were found when comparing treatment groups s2 and s4. They concluded that the effectiveness of the mechanical action of the instruments together with the flow and ebb of instrumentation of the irrigating permanent root canal for the removal of endotoxin from the root canals of teeth with chronic apical periodontitis. In addition, the use of intracanal medication calcium hydroxide + saline solution for 30 days contributed to an improvement in the reduction of endotoxins.

Matos *et al*. (2014) reported two cases in which conventional endodontic therapy resulted in clinical success without the need for further corrective surgery. The first case was a 21-year-old patient who sought dental care for orthodontic reasons. The panoramic radiograph revealed a large radiolucent area in the periapical region of teeth 12, 11, 21, 22 and 23. Treatment was limited to endodontic therapy consisting of pulpectomy, emptying of septic content, biomechanical preparation, and dressing. Calcium hydroxide associated with 2% chlorhexidine gel was used as an intracanal dressing that provided broad spectrum. In the second session, the root canal system of all 5 teeth was obturated. Radiographic control after two and five years showed complete repair of the radiolucent area and areas of bone formation. The second case reported an 84-year-old diabetic patient who sought dental care for prosthetic reasons. The intraoral examination revealed cortical bone expansion in the anteroinferior region. The panoramic radiograph revealed an extensive radiolucent area on teeth 32, 31, 41, 42 and 43. The treatment consisted of conservative endodontic treatment without the need for surgery similar to the first case. Radiographic control after one year showed decreased radiolucency and bone healing. They concluded that surgery is not always indicated for cases of large periradicular lesions and clinical and radiographic follow-ups are of utmost importance for the treatment. Radiographic control after one year showed decreased radiolucency and bone healing.

Sousa *et al*. (2014), in a clinical study measured endotoxin levels in infected root canals (CRs) and exudates related to acute apical abscesses (AAAs). In addition, the efficacy of root canal procedures in reducing endotoxin levels was monitored. Paired samples of infected root canals and exudates from acute apical abscesses were collected from 10 subjects using paper points. RC samples were collected before (RCS1) and after chemical-mechanical preparation (PQM) (RCS2), after EDTA 17% (RCS3) and after 30 days of intracanal medication ($Ca[OH]_2$ + chlorhexidine) (RCS4). A kinetic turbidimetric assay of limulus amebocyte lysate was used for endotoxin measurement. The results showed that endotoxins were detected in 100% of basal samples from acute apical abscesses and infected root canals (RCS1) with mean values of 175 EU/mL and 41.5 EU/mL, respectively ($P < 0.05$). After chemical-mechanical preparation (RCS2), endotoxins were reduced to a mean value of 0.54 EU/mL. Subsequent irrigation with EDTA (RCS3) was not significantly effective in reducing endotoxin levels (median = 0.37 EU/mL) ($P = 0.07$). However, intracanal medication for 30 days (RCS4) reduced endotoxins to mean values of 0.03 EU/mL. They concluded that there is a strong association between the high levels of endotoxins found in acute apical abscesses and infected root canals collected from the same tooth. Furthermore, the efficacy of chemical-

mechanical preparation in reducing root canal endotoxin levels in acute endodontic infection was improved by the use of RC medication.

Souza Netto *et al*. (2014) investigated on the point of view of endodontists registered in the dental practice council of Florianópolis/SC about endodontic treatment in a single appointment or multiple appointments, identifying the basis on which the choice is made and how the information needed for the choice is acquired. The results showed that endodontic treatment in a single visit is performed in 59.5% of cases with biopulpectomy, 31.0% of necropulpectomy cases without injury and only 11.9% in cases of necropulpectomy with periradicular injury. The presence of vital pulp (81.4%) and a canal without exudate (93.0%) are the most important criteria for endodontic treatment in a single visit. The most commonly used intracanal medication was calcium hydroxide. The lack of studies comparing long-term success in single visit endodontic treatment is considered an important issue in determining this therapy. They concluded that endodontists in Florianópolis-Brazil prefer multiple consultations over single visit endodontic treatment in cases of pulp necrosis. When pulp vitality is not compromised there is an increase in the number of endodontists who choose single visit endodontic treatment.

Adl *et al*. (2015), in a clinical study determined the effect of 7-day intracanal dressing with calcium hydroxide on the amount of bacterial lipopolysaccharide (LPS; endotoxin) in human teeth with necrotic and infected pulp and apical periodontitis. Twenty-five unirradicular teeth with necrotic pulps and apical periodontitis were selected. Samples were collected before (S1), after root canal preparation (S2), and after 7 days of intracanal calcium hydroxide dressing (S3). LPS was present in 100% of root canals before (S1), after preparation (S2), and after 7 days of intracanal dressing (S3). A significant reduction, equal to 29.54%, was found after root canal preparation ($P < 0.05$). A significant difference (equal to 25. 26% reduction) was also detected between S2 and S3 ($P < 0.05$). The total endotoxin reduction (S3 compared to S1) was 47.34%. The endotoxin concentration of infected root canals was reduced after root canal preparation and also after 7 days of dressing the canals with calcium hydroxide; however, relatively high endotoxin values remained in the root canals.

Carvalho *et al*. (2016), in a clinical study investigated the effects of endodontic treatment using different irrigants (lime water + NaOCl and polymyxin B + NaOCl) and intracanal medication on endotoxins in teeth with primary endodontic infection and radiographically visible apical periodontitis. Thirty-three teeth with pulpal necrosis and periradicular lesions from different patients were selected for this study. Samples were collected after coronal opening (S1) and after instrumentation (S2). The root canals were divided into 3 groups (n = 11) according to the combination of irrigants used: NaOCl + LW: 2.5% NaOCl + calcium hydroxide solution (0.14%, lime water); NaOCl + PmB: 2.5% NaOCl + 10,000 IU/mL polymyxin B; 2.5% NaOCl (control). The third collection (S3) was performed after ethylenediaminetetraacetic acid and the fourth (S4) after the samples had 14 days with intracanal medication with 2% chlorhexidine gel + calcium hydroxide. Endotoxins (lipopolysaccharides) were quantified by chromogenic Limulus amebocyte lysate (LAL). Endotoxins were detected in all root canals

after coronal opening (S1). The NaOCl + PmB group showed the highest reduction of endotoxins after instrumentation (76.17%), similar to the NaOCl + LW group (67.64%, $p<0.05$) and different from the NaOCl group (42.17%, $p<0.05$). After the intracanal medication period (S4), there was a significant increase in the neutralization of endotoxins. They concluded that 2.5% NaOCl + 10,000 IU/mL polymyxin B promoted the greatest reduction in endotoxin levels, followed by 2.5% NaOCl + calcium hydroxide solution (0.14%, lime water).

Donyavi *et al*. (2016) compared root canal microbial counts of necrotic teeth after irrigation with 6% sodium hypochlorite (NaOCl) (single session treatment) and two-session endodontic treatment with application of calcium hydroxide mixed with 0.2% for two weeks chlorhexidine as intracanal medication in a randomized clinical trial. Necrotic uniradicular teeth were divided into two groups. The root canal was irrigated with 2 mL of 6% NaOCl in one group and a mixture of 0.2% chlorhexidine and calcium hydroxide powder as intracanal medication for two weeks in the other group. Samples of the root canal were obtained before and after the intervention and the number of colony forming units was counted at each stage. The results showed that the reduction of colony forming units of *Enterococcus faecalis* was not insignificantly different between the two groups, but the colony forming units of aerobic and anaerobic bacteria was significantly lower in the calcium hydroxide group mixed with 0.2% for two weeks chlorhexidine. They concluded that the application of calcium hydroxide mixed with 0.2% for two weeks chlorhexidine caused a significant reduction in aerobic, anaerobic and *E. faecalis colony* counts. Thus, it may be beneficial to perform primary endodontic treatment of necrotic teeth with endodontic lesions in two sessions with intracanal medications to obtain predictable results.

Maia *et al*. (2016) compared the endodontic treatment of teeth with apical periodontitis in one or two appointments using cone beam computed tomography (CBCT). Twenty-six pairs of teeth (13 patients) were divided into two groups: single appointment group (GSS): Instrumentation and obturation of the root canal in the same appointment; and two appointments group (GTS): Calcium hydroxide intracanal medication (Calen(®) paste) was used for 14 days between two appointments. Cone-Beam Computed Tomography scans were obtained before and 12 months after treatment. The results showed that volume reduction was greater in the group of two visits (GTS - 79.25%) than in the group of one visit (GSS - 68.35%), but without significant difference. After 12 months, complete repair was not observed in any specimen. Lesion volume reduction > 50% was significantly greater with the use of intracanal medication. They concluded that 12 months after treatment, CBCT did not show complete repair in any of the teeth, suggesting that this follow-up period is not sufficient for complete regression of the lesion. In both groups, similar volume reduction of the apical periodontitis lesion was observed after 12 months, with more advanced repair (> 50% volume reduction) in teeth medicated with calcium hydroxide intracanal dressing.

Manfredi *et al*. (2016) determined whether completing endodontic treatment in a single visit or in two or more visits, with or without medication, makes any difference in terms of effectiveness or complications. Twenty-five randomized clinical trials were included in the review, with a total of 3,780

participants, of which they analyzed 3,751. The results showed that only one study reported data on tooth extraction for endodontic problems. This study found no difference between treatment at one appointment or treatment at multiple appointments (1/117 participants from a single appointment lost a tooth versus 2/103 participants from multiple appointments). They found no evidence of a difference between single visit and multiple visit treatment in terms of radiological failure; immediate postoperative pain; incidence of swelling or exacerbation; sinus tract or fistula formation; or complications. They concluded that the most commonly used intracanal medication was calcium hydroxide, however there is no evidence to suggest that one treatment regimen (endodontic treatment in one or multiple visits) is better than the other. Neither can prevent all short and long term complications. Based on the available evidence, it seems likely that the benefit of single visit treatment, in terms of time and convenience for both patient and dentist, comes at the cost of more frequent late post-operative pain (and, as a consequence, analgesic use).

Zancan *et al*. (2016) evaluated the pH, calcium release, solubility and antimicrobial action against biofilms of calcium hydroxide + saline solution, Calen (SS White Artigos Dentários Ltda, Rio de Janeiro, Brazil) (HC/P), Calen paramonochlorophenol camphorate (CMCP) (HC/CMPC) and calcium hydroxide + chlorhexidine pastes (HC/CHX). The pH of the pastes was determined with a calibrated pH meter placed in direct contact with each paste. The root canals of acrylic teeth (N = 10) were filled with the aforementioned intracanal dressings and immersed in ultrapure water to measure hydroxyl release (pH meter) and calcium ion release (atomic absorption spectrophotometer) at time intervals of 3, 7, 15, and 30 days. For antimicrobial analysis, mono-species and biospecies biofilms were induced in vitro on dentin blocks (N = 20). Then, they were treated with the pastes for 7 days. The results showed that the highest OH - ion release values were found at 3 and 30 days. Ca 2+ releases were highest in Calen paramonochlorophenol camphorate (HC/CMCP). Calen (HC/P) and Calen paramonochlorophenol camphorate (HC/CMCP) showed higher percentage volume loss values. Calcium hydroxide + chlorhexidine pastes (HC/CHX) showed the highest antimicrobial action. They concluded that Calen (HC/P) and Calen paramonochlorophenol camphorate (HC/CMCP) showed higher solubility values in the analyzed period. Seven days of contact may be insufficient for calcium hydroxide pastes + saline solution, Calen (HC/P) and Calen paramonochlorophenol camphorate (HC/CMCP) to kill the bacterial cells in the biofilms studied. Chlorhexidine added to calcium hydroxide favored greater efficacy against the aforementioned bacterial biofilms.

Ahangari *et al*. (2017) compared the antimicrobial efficacy of calcium hydroxide as an intracanal medication and antibacterial photodynamic therapy (aPDT) against *Enterococcus faecalis* and *Candida albicans* in teeth with periradicular lesions. They conducted an *in vivo* study in 20 patients with unirradicular mandibular premolars with previously failed endodontic treatment. After conventional chemical-mechanical root canal preparation (manual and rotary instruments and 2.5% NaOCl), microbiological samples were obtained with sterile paper tips, stored in thioglycolate solution and transferred to a microbiology laboratory. Group 1 specimens (n = 10) were subjected to aPDT (808 nm

diode laser + 50 mg/mL methylene blue), while in group 2, creamy calcium hydroxide paste was used for 1 week. A control sample was taken with sterile paper points and F3 Protaper rotary file. The results showed that the number of colony forming units decreased significantly in both groups after the interventions; however, there was no significant difference in colony counts between the 2 groups. They concluded thatPDT and calcium hydroxide therapy showed the same antimicrobial efficacy on *E. faecalis* and *C. albicans*.

Rabello *et al*. (2017) evaluated the efficacy of supplemental photodynamic therapy (PDT) in optimizing the removal of bacteria and endotoxins from primarily infected root canals after one- and two-appointment treatments. Twenty-four primarily infected root canals with apical periodontitis were selected and randomly divided into one appointment (n=12) and two appointment (n=12) treatment groups. The chemical-mechanical preparation (PQM) was performed using the reciprocal technique of single file + 2.5% NaOCL and a final rinse with 17% EDTA. The photosensitizing agent (methylene blue 0.1mg/mL) was applied to the root canals for 60s before laser application at 60mW power and 129J/cm 2 energy density for 120s after CMP in the treatment of one appointment and after 14 days medication between appointments with $Ca(OH)_2$ + Saline Solution (SSL) in the treatment of two appointments. The results showed that bacteria and endotoxins were detected in 100% of the initial samples, with mean values of 1.97×10 5 CFU/mL and 24.983EU/mL, respectively. The PQM used was the single-file reciprocal technique and was effective in reducing bacteria and endotoxins. Supplemental photodynamic therapy (PDT) was effective in reducing the bacterial load in the single appointment, but not in the two appointment treatment after using Ca(OH) medication$_2$ for 14 days. In the two-visit group, after 14 days of interconsultation medication with $Ca(OH)_2$, a significant reduction in mean endotoxin levels was found compared with chemical-mechanical preparation alone (from 1.041 to 0.094EU/mL). Despite the type of treatment, supplemental photodynamic therapy was not effective against endotoxins. They concluded that photodynamic therapy optimized disinfection of bacteria from root canals in the treatment modality of one appointment, but not two appointments with calcium hydroxide medication. Despite the treatment type, supplemental photodynamic therapy was not effective against endotoxins.

Riaz *et al*. (2018) compared calcium hydroxide and the combination of calcium hydroxide and 2% CHX based on radiographic evidence of resolution of periradicular radiolucency when used as an intracanal dressing/medication for 14 days. A total of 60 patients of both genders were included in the study. The age range was 15 to 60 years with radiographic evidence of radiolucency 2 to 4 mm in size. Both maxillary and mandibular teeth up to the first molar were selected. Teeth with previous endodontic treatment, mentally disabled, and terminally ill patients were excluded. The selected patients were randomly placed in Group 1 (calcium hydroxide alone) and Group 2 (calcium hydroxide in combination with 2% chlorhexidine gel). Permanent obturation and filling were done on day 14. The patient was called back after 90 days of obturation and a radiograph was taken. The final result was measured at the end of the 90th day of filling. The results showed that the mean percent reduction in apical radiolucency size at 3 months was 91.03% for

group 1 and 97.26% for group 2 with a p value of 0.13 (not significant). The results suggested equivalent results after medication with 2% chlorhexidine with calcium hydroxide, but 2% chlorhexidine still showed better results than the group without CHX in terms of healing. They concluded that calcium hydroxide in combination with 2% chlorhexidine as an intracanal medication results in better percentage of resolution of periradicular radiolucency.

Barbosa-Ribeiro *et al*. (2019) investigated *in vivo the* effects of calcium hydroxide-based intracanal medication (MIC) on levels of bacteria, pro-inflammatory cytokines (PICs), and matrix metalloproteinases (MMPs) in root canals and periradicular tissues of teeth with failed root canal treatment and apical periodontitis. Twenty infected root canals from uniradicular teeth were randomly divided into two groups according to the irrigant used for PQM (n = 10 per group): G1 - 2% chlorhexidine gel (CHX) and G2 - 6% sodium hypochlorite (NaOCl). The root canal contents were obtained with paper points before PQM (S1) and after 30 days of calcium hydroxide-based intracanal medication (MIC S2). The results showed that the culturable bacteria (101.2 ± 79.2), bacteria levels, pro-inflammatory cytokines (PICs) (IL-1β 1.2 ± 0.4 and TNF-α 8,8 ± 4.7), MMP-2 (803.7 ± 96.4), MMP-3 (453.9 ± 229.3), MMP-8 (245.9 ± 122.4), MMP-9 (129.4 ± 29.6) and MMP-13 (70.8 ± 12.8) were present in all S1 samples. After 30 days of calcium hydroxide-based intracanal medication (MIC S2), 99.5% microbial reduction was observed along with significant reduction in levels of bacteria, pro-inflammatory cytokines (PICs) in all groups. Overall, decreased levels of matrix metalloproteinases (MMPs) were observed (S2), except MMP-13, which was found at increased levels after calcium hydroxide-based intracanal medication, ($P < 0.05$), regardless of groups. They concluded that calcium hydroxide-based intracanal medications had a positive effect on microbial reduction by decreasing levels of bacteria, pro-inflammatory cytokines (PICs), and matrix metalloproteinases (MMPs). Both auxiliary chemicals (i.e. 2% chlorhexidine gel (CHX) and 6% sodium hypochlorite (NaOCl) showed similar effects when calcium hydroxide was used as an intracanal medication. Teeth with endodontic treatment failure and apical periodontitis, and consequently high levels of bacteria, pro-inflammatory cytokines (PICs) and matrix metalloproteinases (MMPs), may show a better prognosis after 30 days of calcium hydroxide-based MIC.

Duque *et al*. (2019) investigated the effects of a calcium hydroxide-based intracanal medication on periodontal and endodontic infectious/inflammatory contents and periodontal clinical parameters in teeth with primary periodontal lesion and secondary endodontic involvement. Ten patients with abnormal pulpal test results and deep probing depth derived from primary periodontal disease with secondary endodontic involvement were included. Samples were collected from root canals and periodontal pockets to investigate microbiological status, endotoxin levels, cytokines and matrix metalloproteinases, before and after the use of a calcium hydroxide-based intracanal medication. The results showed that the calcium hydroxide-based intracanal medication did not reduce the number of microorganisms in periodontal pockets and root canals, except *Fusobacterium nucleatum* in root canals. There was a significant reduction in endotoxin levels in periodontal pockets after the use of calcium hydroxide-based intracanal medication. In root canals, the

levels of endotoxin, cytokines, and matrix metalloproteinases remained unchanged; however, the levels of the other cytokines and matrix metalloproteinases were reduced. After 1 year of root canal treatment, tooth mobility was significantly reduced. They concluded that the use of intracanal medication based on calcium hydroxide showed positive effects for the prognosis of periodontal treatment, because it reduced the levels of endotoxins, cytokines in the periodontal pockets. Patients with high probing depth and in periodontal treatment for at least 6 months, with no positive response to periodontal therapy, may benefit from endodontic treatment.

Madurantakam (2019) compared the clinical efficacy of calcium hydroxide to formocresol or camphor phenol in acute pulpitis of deciduous teeth requiring endodontic treatment. The primary endpoint was clinical efficacy, while the secondary endpoint was the incidence of endodontic emergencies between visits. The results showed that a total of 16 randomized studies informed the meta-analysis. The clinical efficacy of calcium hydroxide was compared to formocresol in 12 studies, and the pooled data indicated that calcium hydroxide was significantly better in terms of clinical efficacy, and was associated with a significant decrease in inter-consultation emergence. Calcium hydroxide was compared to camphor phenol in seven studies and was shown to be significantly superior in its clinical effectiveness. He concluded that the limited available evidence suggests that calcium hydroxide was superior to formocresol and phenol camphor as an intracanal medication in the treatment of acute pulpitis in deciduous teeth.

Ibrahim *et al*. (2020) evaluated on pain and exacerbation effects of calcium hydroxide (HC) as an intracanal medication (ICM) in mature non-vital teeth. Only randomized clinical trials (RCTs) were included comparing calcium hydroxide to other intracanal medications in mature non-vital teeth. The results showed that 16 articles were included in 6 comparisons at different time points for different endpoints. Calcium hydroxide reduced the risk of pain than no intracanal medication at the 1-14 day interval ($p < 0.05$) and than triple antibiotic paste on day 1 and was similar to the corticosteroid/antibiotic combination. Chlorhexidine (CHX) or calcium hydroxide/CHX, however, reduced pain levels than calcium hydroxide alone. Calcium hydroxide showed a higher risk of exacerbation than chlorhexidine. They concluded that most comparisons for different outcomes are based on very few studies. Thus, the available evidence is considered insufficient to support or refute the efficacy of calcium hydroxide or to recommend one intracanal medication over another. Therefore, more larger and well-designed RCTs are needed.

Karatas *et al*. (2020) evaluated the antimicrobial efficacy of Ca(OH) paste$_2$ combined with ibuprofen or ciprofloxacin in infected root canals of teeth with asymptomatic apical periodontitis. Forty-five patients were randomly divided into three groups using a web program according to the selected medication: $Ca(OH)_2$: 1 g $Ca(OH)_2$ powder with 1 mL propylene glycol, $Ca(OH)_2$ + Ibuprofen: 50 mg ibuprofen was added to 950 mg $Ca(OH)_2$ powder and mixed with 1 mL propylene glycol, $Ca(OH)_2$ + Ciprofloxacin: 50 mg Ciprofloxacin was added to 950 mg $Ca(OH)_2$ powder and mixed with 1 mL propylene glycol. Bacteriological samples from the root canal were collected before root canal treatment (S1) and after chemical-mechanical procedures (S2). After root canal preparation, intracanal medications were placed in

the root canals at a level approximately 1 mm below working length using K-files and the access cavities were filled temporarily. Participants were scheduled for a second visit 7 days later, when the medication was mechanically removed, and after irrigation of the root canals, the final samples (S3) were collected. The samples were subjected to quantitative real-time polymerase chain reaction to assess the number of total bacteria, *Enterococcus faecalis* and *Streptococcus* species. The results showed that there was a significant reduction in the number of intracanal bacterial cells from S1 to S2 and from S2 to S3 in all drug groups. Although there was no significant difference between the groups when comparing the quantitative data from S1 or S2, there were significantly lower bacterial counts in the $Ca(OH)_2$ + Ciprofloxacin group (0.49 × 10 2) than in the pure $Ca(OH)_2$ (1.25 × 10 2) and $Ca(OH)_2$ + Ibuprofen groups (0.76 × 10 2) in S3. The percentage reduction from S1 to S3 and from S2 to S3 was significantly greater in the $Ca(OH)_2$ + Ciprofloxacin groups than in the pure $Ca(OH)_2$ and $Ca(OH)_2$ + Ibuprofen groups. In the $Ca(OH)_2$ + Ciprofloxacin group, there were significantly fewer positive cases (8/15) than the pure $Ca(OH)_2$ (13/15) and $Ca(OH)_2$ + Ibuprofen (13/15) groups. They concluded that the addition of Ciprofloxacin to $Ca(OH)_2$ provided greater antibacterial efficacy when used as an intracanal drug *in vivo* during endodontic treatment.

Maral *et al*. (2020) investigated the use of calcium hydroxide as an effective intracanal medication in persistent periradicular infections. They found that the basic goal of endodontic therapy is to prevent or stop pulpal or periradicular infection. A widely used intracanal medication, calcium hydroxide ($Ca[OH]_2$) introduced by Hermann in 1920 has numerous biological properties, such as antimicrobial activity, tissue dissolving ability, inhibition of resorption and bone formation associated with non-surgical periradicular healing with fewer adverse reactions. Most articles concluded that Ca $(OH)_2$ in any form of vehicle promoted periradicular healing with fewer adverse effects in persistent periradicular infections. They concluded that large persistent periradicular lesions can be resolved by nonsurgical endodontic therapy employing intracanal Ca(OH) medication$_2$ and should be attempted as the first approach in all cases with periradicular lesions. The surgical approach is only necessary if the conservative approach fails. Healing of periradicular lesions will not only be achieved by surgical removal of the periradicular lesion, but also requires disinfection and adequate obturation of the root canal $Ca(OH)_2$ in any form of vehicle is effective as an intracanal drug in persistent periradicular lesions. In the case of large periradicular lesions, conventional endodontic therapy alone may not be sufficient. Associated procedures such as aspiration, decompression, nonsurgical aspiration, and irrigation may be necessary.

Best *et al*. (2021), in a retrospective cohort case series was twofold: (1) evaluated the outcomes of teeth with necrotic pulps and apical periodontitis using long-term calcium hydroxide ($Ca[OH]_2$) (healing was assessed using the periapical index [PAI] system) and (2) explored the possible association of fractures in relation to prolonged exposure to $Ca(OH)_2$. A total of 242 cases, diagnosed with pulpal necrosis and apical periodontitis, were treated with long-term $Ca(OH)_2$ using a standardized protocol. Injectable and powdered $Ca(OH)_2$ were placed sequentially into the root canal system. All cases were reevaluated in a 3-month period until radiographic healing was observed. Clinical and radiographic evaluations were

performed annually. The results showed that of the 242 cases, 219 participants completed treatment with annual follow-up. The mean time to $Ca(OH)_2$ was 5.4 months with a range of 1-12 months. Overall, at the last follow-up visit, 90.0% (197/219) were classified as "cured." They concluded that long-term use of $Ca(OH)_2$ in the treatment of teeth with necrotic pulps and periradicular periodontitis resulted in a predictably high outcome. No association was observed between long-term use of $Ca(OH)_2$ and the incidence of fractures during this study. $Ca(OH)_2$ is a suitable material of choice as an interconsunctional dressing for teeth diagnosed with pulp necrosis and periradicular periodontitis.

Espaladori *et al*. (2021) evaluated the behavior of selenium (Se) when used as an endodontic dressing on teeth with pulp necrosis. In addition, its effects were also compared with calcium hydroxide (HC), which is used globally as an endodontic dressing, and the combination of HC with Se (HC + Se). The sample consisted of 60 patients in need of endodontic treatment who were divided into groups, i.e., without intracanal medication (empty) and with the following medications: selenium (Se), HC calcium hydroxide, and calcium hydroxide + selenium (HC + Se) (n = 15). After coronary opening, three dots of absorbent paper were placed on the SCR and held for 2 min for microbial evaluation. After cleaning and shaping procedures, new paper points were introduced into the root canal system, passively passing through the root apex (2 mm) into the periapical tissues for 2 min for immunological evaluation. Collections were performed again 15 days later. Real-time polymerase chain reaction (PCR) quantified the expression of prokaryotic 16S ribosomal RNA. The results showed that there was a significant reduction in microbial load only in the groups that received endodontic dressing. The cytokines IFN-γ, TNF-α, IL-1α, IL-17A, IL-10, IL-6 and MCP-1, were also quantified by real-time polymerase chain reaction (PCR). There was an increase in the gene expression level of the cytokines (T15) TNF-α and IL-10 in the HC group compared to the other groups. The expression of IFN-γ mRNA was reduced in the groups treated with the medications (Se, HC and HC + Se). They concluded that in the case of multiple appointment treatment, the use of endodontic dressing is essential to prevent microbial recolonization of the root canal system (RSC). Selenium potentiated the effects of calcium hydroxide by inducing an anti-inflammatory response in the periradicular tissues.

Nascimento *et al*. (2021) addressed in a systematic review the following common clinical question: What is more effective in reducing or eliminating endotoxin in endodontic infections - single visit or multiple visit treatments with calcium hydroxide medications? Nine studies were included. The meta-analysis revealed lower endotoxin levels for multiple appointment and medication treatment. However, 14-day and 30-day $Ca(OH)_2$ medication was more effective than single appointment treatment. Overall, the evidence supports that multiple appointment disinfection protocols with Ca(OH) medication placement$_2$ are more effective in reducing endotoxin levels of root canal infections compared to single appointment when applied for 14 and 30 days.

Toia *et al*. (2021) compared the efficacy of endodontic retreatment of teeth with post-treatment apical periodontitis performed at 1 versus 2 visits on the reduction of culturable bacteria (colony forming

units [CFUs]), lipopolysaccharides (LPSs) , lipoteichoic acid (LTA) and periradicular lesion volume (mm^3) after 18 months of follow-up. Forty patients diagnosed with post-treatment apical periodontitis (PAPT) were selected and randomly divided into 2 groups: retreatment in 1 visit and retreatment in 2 visits with the placement of calcium hydroxide medication for 14 days. Cone beam computed tomography was performed in 2 stages: preoperative and after 18 months of follow-up. The results showed that all samples had higher baseline values than those collected after the retreatment protocol for all investigated parameters. A higher bacterial load and lower ATL level were found in the group of 2 visits after the retreatment protocol, with no statistical differences between the groups regarding endotoxin levels and peri-radicular lesion volume (mm^3) at the 18-month follow-up. They concluded that endodontic retreatment in 1 or 2 visits with placement of calcium hydroxide medication for 14 days showed equally favorable periradicular healing at 18 months, with no statistically significant differences between groups.

Ahmad *et al*. (2022), in a systematic review evaluated the effectiveness of calcium hydroxide as an intracanal medication compared to no dressing and/or other intracanal medications to control postoperative pain in patients with apical periodontitis requiring primary endodontic treatment. The results showed that 18 studies with 1,192 participants were included. There was a significant improvement in postoperative pain within 24 hours in favor of calcium hydroxide over no intracanal medication. They found that Ledermix (Lederle Germany) (steroid antibiotic) and chlorhexidine were significantly more effective than calcium hydroxide in controlling pain at 72 hours post-procedure. Silver nanoparticles were more effective than calcium hydroxide at 6 and 24 hours, and combinations of calcium hydroxide with dexamethasone or lidocaine HCl were significantly more effective than calcium hydroxide alone in improving postoperative pain.

Alghamdi *et al*. (2022) investigated the success rate and impact effect of endodontic treatment performed with calcium hydroxide in the treatment of periradicular lesions. The outcomes of this review were the status of the periradicular lesion at the end of follow-up. They retrieved 8 studies with 481 participants. The success rate of HC in this review was 75.5%. The HC success rate was 16% in patients with periradicular cysts and 74% in patients with apical periodontitis after intracanal medication with HC. The post-treatment follow-up period showed a high success rate in patients with > 1 year post-treatment follow-up (62%), while the success rate was 30% at 6 months - 1 year post-treatment follow-up. HC has greater healing effect in lesions ≤ 5 mm diameter than > 5 mm diameter (81.6% vs. 18.4%). Finally, intracanal HC has a clinically significant effect on healing of periradicular lesions. This review suggests orthograde endodontic treatment with calcium hydroxide as an alternative to periradicular surgery.

3 CURRENT STATE OF THE EVIDENCE ON THE USE OF CALCIUM HYDROXIDE

Calcium hydroxide has been the most used intracanal medication (VERA *et al*., 2012; SOUZA NETTO et *al.*, 2014; MANFREDI et *al.*, 2016; BARBOSA-RIBEIRO et *al.*, 2019; NASCIMENTO et *al.*, 2021), being considered as the gold standard (RIAZ *et al.*, 2018), with positive effect in improving the

microbiological state of the root canal system (VERA *et al*., 2012), preventing its recolonization (ESPALADORI *et al*., 2021), decreasing the levels of bacteria, pro-inflammatory cytokines (PICs) and matrix metalloproteinases (MMPs) (BARBOSA-RIBEIRO *et al*., 2019; DUQUE *et* al., 2019). Even in cases of large lesions similar to periapical cysts, according to Thomas et *al*. (2012) and Alghamdi et *al*. (2022), non-surgical endodontic therapy employing calcium hydroxide intracanal medication can be employed.

Clinical evidence indicates its use before definitive root canal obturation in teeth with apical periodontitis (MAIA *et al*., 2016). It is also an effective anti-endotoxin agent (OLIVEIRA *et al*., 2012; MARINHO et al., 2014; ADL *et al.,* 2015; DUQUE *et al.,* 2019; NASCIMENTO et *al*., 2021). However, according to Adl *et al*. (2015) relatively high endotoxin values remained in root canals.

It is noted, that the permanence of the intracanal medication calcium hydroxide varies between studies, and may be recommended for at least a week (VERA *et al.*, 2012; ADL et al., 2015; MAIA et al., 2016; AHANGARI et *al.*, 2017); for 14 days (OLIVEIRA et al., 2012; DONYAVI *et al*., 2016; RABELLO et *al.*, 2017; IBRAHIM et *al.*, 2020; NASCIMENTO *et al.*, 2021; TOIA *et al.*, 2021), or even for 30 days, potentially achieving a better prognosis (MARINHO *et al.*, 2014; SOUSA *et al.*, 2014; ZANCAN et *al.*, 2016; BARBOSA-RIBEIRO et *al.*, 2019; NASCIMENTO *et al.*, 2021).

The vehicles can contribute to potentiate the effects of calcium hydroxide inducing an anti-inflammatory response in periapical tissues (MARINHO *et al.*, 2014; ESPALADORI *et al*., 2021). Among the most commonly used can be highlighted saline solution (MARINHO *et al.*, 2014; RABELLO et *al.*, 2017; ZANCAN et *al*., 2016), paramonochlorophenol camphorate (ZANCAN *et al*., 2016; MADURANTAKAM, 2019), chlorhexidine (OLIVEIRA et al., 2012; SOUSA *et al.*, 2014; ZANCAN *et al.*, 2016; RIAZ *et al.*, 2018; IBRAHIM *et al.*, 2020; AHMAD et *al.*, 2022), selenium (SPALADORI *et al.*, 2021).

The combination of calcium hydroxide with chlorhexidine, according to the studies of Matos *et al*. (2014), Sousa *et al. (*2014), Donyavi et al. (2016), Zancan *et al. (*2016), Riaz *et al*. (2018), showed greater efficacy against bacterial biofilms and the results have been well documented. For Barbosa-Ribeiro *et al*. (2019), both 2% chlorhexidine gel (CHX) and 6% sodium hypochlorite (NaOCl), have shown similar effects when calcium hydroxide was used as intracanal medication, corroborating with the study of Carvalho *et al*. (2016), whose result showed that 2.5% NaOCl + 10,000 IU/mL polymyxin B promoted the greatest reduction in endotoxin levels, followed by 2.5% NaOCl + calcium hydroxide solution (0.14%, lime water).

According to Manfredi *et al*. (2016) there is a higher frequency of late postoperative pain and, as a consequence, use of analgesics in the case of a single visit. However, According to Ahmad *et al*. (2022), this postoperative pain in patients with apical periodontitis, can be controlled when calcium hydroxide is used as an intracanal medication, especially when combined with dexamethasone or lidocaine HCl.

However, they found Ledermix (Lederle Germany) (steroid antibiotic) and chlorhexidine to be more effective than calcium hydroxide in controlling pain within 72 hours post-procedure.

Ahangari *et al*. (2017) concluded that both photodynamic therapy (aPDT) and calcium hydroxide therapy have the same antimicrobial efficacy on *E. faecalis* and *C. albicans*. Otherwise, Rabello *et al*. (2017) emphasized the need to use supplemental photodynamic therapy (PDT), to optimize the removal of bacteria and endotoxins from root canals, especially when the use of calcium hydroxide for 14 days is not effective. Already, Taneja and Kumari (2012)found that when the most commonly used medications fail to eliminate symptoms, then a triple antibiotic paste (metronidazole, ciprofloxacin and minocycline) can be used clinically to treat teeth with large periradicular lesions. However, Maral *et al*. (2020) pointed out that in such cases, when conventional endodontic therapy alone is not sufficient, associates such as aspiration, decompression, nonsurgical aspiration and irrigation may be required. However, Karatas *et al*. (2020) concluded that the addition of Ciprofloxacin to $Ca(OH)_2$ provided greater antibacterial efficacy when used as an intracanal drug *in vivo* during endodontic treatment.

It is important to highlight that there is a controversy regarding the performance of endodontic treatment in a single visit or in two visits with intracanal medication of calcium hydroxide in teeth with periradicular lesions. According to Ibrahim *et al*. (2020) most comparisons for different outcomes are based on very few studies, so the available evidence is considered insufficient to support or refute the efficacy of calcium hydroxide or to recommend one intracanal medication over another. Therefore, the lack of studies comparing long-term success of single-visit or two-visit endodontic treatment is considered an important issue in determining this therapy (SOUZA NETTO *et al*., 2014).

In this direction, Paredes-Vieyra and Enriquez (2012) cited several factors that play an important role in the decision-making process of 1-visit versus 2-visit endodontics, such as: the preoperative diagnosis, ability to obtain infection control, root canal anatomy, complications of the procedure, and subjective factors such as patient signs and symptoms. According to Souza Netto *et al*. (2014), in cases of pulp necrosis, multiple visits are more effective over single-visit endodontic treatment. However, when there is no impairment of pulp vitality, single-visit treatment can be used.

When compared to therapy in one appointment, endodontic treatment in two appointments with calcium hydroxide intracanal medication, according to Maia *et al*. (2016), provided a similar reduction in apical periodontitis lesion volume after 12 months, with more advanced repair (> 50% volume reduction) in teeth medicated with calcium hydroxide intracanal dressing.

However, there is no statistically significant evidence to suggest that endodontic treatment in one or several visits, with the use of calcium hydroxide is better than the other. This result was observed in the studies by Paredes-Vieyra and Enriquez (2012), Manfredi *et al*. (2016), Toia *et al*. (2021). Whereas, Manfredi *et al*. (2016) concluded that it seems likely that the benefit of a single-visit treatment, in terms of time and convenience for both patient and dentist, comes at the cost of a higher frequency of late postoperative pain (and, as a consequence, analgesic use).

4 FINAL CONSIDERATIONS:

a) The treatment with calcium hydroxide as intracanal medication presents as advantages the improvement of the microbiological state of the root canal system, decreasing the levels of bacteria, pro-inflammatory cytokines (PICs) and matrix metalloproteinases (MMPs), standing out as an effective anti-endotoxin agent, being also able to minimize the intensity or severity of postoperative pain after endodontic treatment;

b) The use of calcium hydroxide as intracanal medication is considered the gold standard, and is indicated for multiple visits for endodontic treatment of teeth with apical periodontitis before definitive obturation of the root canal;

c) Its permanence as intracanal medication varies between at least a week or even for 30 days, achieving a better prognosis when with single visit endodontic treatment.

d) However, the evidence available in the literature is considered insufficient, thus highlighting the need for more studies comparing the long-term success of treatment.

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