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Review Article

Investigation of different sodium hypochlorite volumes, concentrations and times of irrigation in endodontic therapy: a systematic review

Investigação de diferentes volumes, concentrações e tempos de irrigação do hipoclorito de sódio na terapia endodôntica: uma revisão sistemática

Investigación de diferentes volúmenes, concentraciones y tiempos de irrigación de hipoclorito de sodio en la terapia endodóntica: una revisión sistemática

José Alcides Almeida de **ARRUDA**[1]
Lauren Frenzel **SCHUCH**[1]
Adzo **PEREIRA**[2]
João Luiz Gomes Carneiro **MONTEIRO**[2]
Paulo Maurício Reis **MELO-JÚNIOR**[2]
Ricardo Alves **MESQUITA**[1]
Amália **MORENO**[1]
Gerhilde **CALLOU**[2]

[1]*Department of Oral Surgery, Pathology and Clinical Dentistry, School of Dentistry, Federal University of Minas Gerais (UFMG), 31.270-901, Belo Horizonte, MG, Brazil*
[2]*Department of Oral Pathology and Medicine, School of Dentistry, University of Pernambuco (FOP-UPE), 54.753-220, Camaragibe, PE, Brazil*

Abstract
Although the sodium hypochlorite (NaOCl) solution has been part of the endodontic arsenal for more than one century, current investigations have been unable to determine which NaOCl volume and concentration or which time of application are able to dissolve organic matter without weakening the dental structure during the phase of biomechanical preparation of the root canal. Thus, the objective of the present study was to conduct a systematic literature review with no restriction of publication year or language in order to resolve these questions. The search strategy included the following databases: PubMed, LILACS, Web of Science and ClinicalTrials.gov, and only *in vivo* human clinical trials were included in the final review. After the removal of duplicates, the systematic literature review yielded 3,717 articles. Of these, 3,685 were excluded after applying the exclusion criteria (*ex vivo* studies, animal studies, cell-culture studies, narrative review, and studies with no available full texts). A total of 32 full-text articles were assessed for eligibility. After evaluating the full text, all articles were excluded for different reasons. No studies fulfilled our inclusion criteria. This review was unable to answer what time of irrigation, concentration or volume of NaOCl solution can be of maximum effectiveness in endodontic treatment without producing significant changes in the mechanical properties of dentin. Thus, future human clinical studies are needed in order to resolve these questions.
Descriptors: Endodontics; Sodium Hypochlorite; Review.

Resumo
Embora a solução de hipoclorito de sódio (NaOCl) tem feito parte do arsenal endodôntico por mais de um século, as investigações atuais têm sido incapazes de determinar qual volume de NaOCl e concentração ou qual tempo de aplicação são capazes de dissolver a matéria orgânica sem enfraquecer a estrutura dentária durante a fase de preparação biomecânica do canal radicular. Assim, o objetivo do presente estudo foi realizar uma revisão sistemática da literatura, sem restrição de ano de publicação ou idioma para resolver estas questões. A estratégia de pesquisa incluiu os seguintes bancos de dados: PubMed, LILACS, Web of Science e ClinicalTrials.gov. Somente estudos *in vivo* foram incluídos na revisão final. Após a remoção de duplicatas, a revisão sistemática da literatura ofereceu 3.717 artigos. Destes, 3.685 foram excluídos depois dos critérios de exclusão aplicados (estudos *ex vivos*, estudos em animais, estudos de cultura de células, revisão narrativa e estudos com textos completos indisponíveis). Um total de 32 artigos com texto completo foram avaliados para elegibilidade. Depois de avaliar o texto completo, todos os artigos foram excluídos por razões diferentes. Não existiu estudos cumpridos nossos critérios de inclusão. Esta revisão foi incapaz de responder em que tempo de irrigação, concentração ou volume de solução de NaOCl podem apresentar máxima eficácia no tratamento endodôntico sem produzir mudanças significativas nas propriedades mecânicas da dentina. Assim, futuros estudos clínicos em humanos são necessários para responder essa pergunta.
Descritores: Endodontia; Hipoclorito de Sódio; Revisão.

Resumen
A pesar de que la solución de hipoclorito de sodio (NaOCl) ha sido parte del arsenal endodóntico por más de un siglo, las investigaciones actuales no han podido determinar el volumen exacto del NaOCl, concentración y el tiempo de aplicación capaces de disolver la materia orgánica sin debilitar la estructura dental durante la fase de preparación biomecánica del conducto radicular. El objetivo del presente estudio fue realizar una revisión sistemática de literatura, sin restricción de año de publicación o de idioma para responder estas preguntas. La estrategia metodológica utilizada fué consultar las siguientes bases de datos: PubMed, LILACS, *Web of Science* y ClinicalTrials.gov. Y se incluyeron solamente estudios *in vivo* en la presente revisión. Después de la eliminación de duplicados, la revisión sistemática tuvo 3.717 artículos. De estos, 3.685 fueron eliminados según los criterios de exclusión (estudios *ex vivos*, estudios en animales, estudios de cultivo de células, revisión narrativa y estudios con textos completos no disponibles). Un total de 32 artículos completos fueron escogidos y evaluados. Después de evaluar los textos completos, todos los artículos tuvieron que excluirse por diferentes razones. No fueron encontrados estudios cumpliendo con nuestros criterios de inclusión. Esta revisión no fue capaz de responder en qué tiempo de irrigación, concentración o volumen de solución de NaOCl puede presentar máxima eficacia en el tratamiento endodóntico sin alterar significativamente las propiedades mecánicas de dentina y disolver la matéria orgánica de los conductos radiculares. Siendo así, los futuros estudios clínicos en humanos se hacen necesarios para responder a nuestra pregunta.
Descriptores: Endodoncia; Hipoclorito de Sodio; Revisión.

INTRODUCTION

Chemical and mechanical preparation is used for root canal cleaning, expansion and modeling. These steps essentially involve filing of dentinal walls with the aid of endodontic instruments[1] plus the action of irrigating chemical substances on the components of the root canal system[2] for residue removal and for an antimicrobial action[3,4].

An important challenge is the choice of the chemical substance to be used since, so far, none of them has proved to have ideal qualities needed for the disinfection of root canals[5]. However, sodium hypochlorite (NaOCl) is the auxiliary substance

universally chosen by clinicians and endodontists because of its ability to neutralize the content of toxic-necrotic material and to dissolve organic matter in the root canals[6-8]. The recommended NaOCl concentrations range from 0.5 to 6%, but there is no consensus about NaOCl concentration or volume or time of irrigation in clinical practice[9].

The properties of NaOCl for the dissolution and degradation of organic matter are directly proportional to its concentration and volume which, when elevated, may be toxic and favor dentin fragility after endodontic treatment[10]. Although many studies have assessed the development of this fragility such as root fractures related to excessive expansion of the root canals, pressure transmission to canal walls during shaping and obturation, presence of a post or an isthmus, and occlusal overload by masticatory forces,[11,12] few investigations have concentrated on the use of NaOCl and its possible deleterious action on root dentin[12].

For these reasons, clinicians and endodontists are concerned about the ideal concentration and volume of NaOCl and the time needed for its action during the biomechanical preparation of root canals in order to dissolve and disinfect organic matter without weakening the dental root. On the basis of the above considerations, the objective of the present study was to conduct a systematic literature review aiming at the resolution of these questions.

MATHERIAL AND METHOD

- *Information sources and search strategy*

This study followed the PRISMA guidelines for systematic reviews[13] and the PICO strategy (Patient, Intervention, Comparison and Outcome) was used to formulate an adequate research question. Table 1 presents the four components of this strategy for the present study. The review protocol was registered with PROSPERO (registration No. CRD 42017054317).

A systematic review with no restriction of publication year or language was carried out. The search strategy included the following databases: PubMed (National Library of Medicine), LILACS (via BVS, Latin America), Web of Science (Thomson Reuters), and ClinicalTrials.gov and the reference list of selected articles. The search was undertaken in September 2017. The following search criteria were applied to the PubMed, BVS and Web of Science databases: (NaOCl OR sodium hypochlorite) AND (endo* OR root canal). For the ClinicalTrials.gov database, the term sodium hypochlorite was applied in the search field "other terms".

- *Eligibility criteria and study selection*

Articles had to be *in vivo* human clinical trials to be included in the final review. The exclusion criteria were *ex vivo* studies, animal studies, cell-culture studies, narrative review, and studies with no available full texts.

Studies were selected by two independent authors (G.C. and A.P.) and kappa scores were calculated. First, titles and abstracts were screened for inclusion. Those whose titles clearly showed that they were *in vitro* or animal studies were excluded in this first stage. If there was insufficient information in the abstract the full texts were retrieved and read for possible inclusion. Any disagreements regarding the articles included in the final review were resolved by a third investigator (P.M.R.M.J.) with experience in the subject. The Mendeley Desktop Software (1.17.11, Mendeley LTD., London, UK) was used.

- *Risk of bias assessment and data analysis*

The "Risk of bias tool" of the Cochrane Collaboration was used to assess the risk of bias of the studies included if randomized clinical trials fulfilling the inclusion criteria were found. The Review Manager 5.3 software (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) was used to perform meta-analysis if appropriate.

Table 1. PICO strategy used to formulate the research question

Population	Permanent vital tooth Permanent teeth with necrotic pulp Teeth with periapical lesions
Intervention	Irrigation with sodium hypochlorite at different concentrations
Comparison	Irrigation with another irrigation solution or with different sodium hypochlorite concentrations Volume Irrigation time
Outcome	Disinfection of root canal systems Dissolution of organic matter Tooth structure fragility

RESULTS

Inter-examiner agreement based on kappa was 0.83. After duplicate removal, the systematic literature review yielded 3,717 articles, 3,685 of which were excluded after applying the exclusion criteria. A total of 32 full-text articles were assessed for eligibility (Table 2). After evaluating the full-text, all articles were excluded for different reasons.

The flowchart of study selection is illustrated in figure 1. Nineteen of them only assessed one NaOCl concentration, six were *in vitro*, three were reviews, one was an *ex vivo* study, one was an animal study, one used irrigation with chlorhexidine, and one was a letter to the editor.

Therefore, no studies fullfilled our inclusion criteria. Also figure 2 shows flow chart about controlled clinical investigations involving young adult patients with anterior teeth showing radiographically visible endodontic lesions and two options of NaOCl treatment.

Table 2. Articles excluded after full text evaluation and reasons for exclusion

Byström e Sundqvist[4] Bacteriologic evaluation of the effect of 0.5 percent sodium hypochlorite in endodontic therapy	Not selected Only one NaOCl concentration
Hand et al.[14] Analysis of the effect of dilution on the necrotic tissue dissolution property of sodium hypochlorite	Not selected Animal studies
Thé[15] The solvent action of sodium hypochlorite on fixed and unfixed necrotic tissue	Not selected Only one NaOCl concentration
Ringel et al.[16] In vivo evaluation of chlorhexidine gluconate solution and sodium hypochlorite solution as root canal irrigants	Not selected Only one NaOCl concentration (2.5%)
Ercan[17] Antibacterial activity of 2% chlorhexidine gluconate and 5.25% sodium hypochlorite in infected root canal: in vivo study	Not selected Only one NaOCl concentration (5.25%)
Siqueira et al.[18] Bacteriologic investigation of the effects of sodium hypochlorite and chlorhexidine during the endodontic treatment of teeth with apical periodontitis	Not selected In vitro study
Estrela et al.[19] Efficacy of sodium hypochlorite and chlorhexidine against Enterococcus faecalis--a systematic review	Not selected Review
Fedorowicz e Sequeira[20] Efficacy of sodium hypochlorite and chlorhexidine against Enterococcus faecalis--a systematic review	Not selected Letter to the Editor
Gomes et al.[21] Comparison of 2.5% sodium hypochlorite and 2% chlorhexidine gel on oral bacterial lipopolysaccharide reduction from primarily infected root canals	Not selected Only one NaOCl concentration (2.5%)
Abbaszadegan et al.[22] Comparison of antimicrobial efficacy of IKI and NaOCl irrigants in infected root canals: an in vivo study	Not selected The same concentration of 2.5% NaOCl
Bashetty K, Hegde[23] Comparison of 2% chlorhexidine and 5.25% sodium hypochlorite irrigating solutions on postoperative pain: a randomized clinical trial	Not selected Only one NaOCl concentration (5.25%)
Haapasalo et al.[24] Irrigation in endodontics	Not selected Review
Huffaker et al.[25] Influence of a passive sonic irrigation system on the elimination of bacteria from root canal systems: a clinical study	Not selected The same concentration of 0.5% NaOCl
Kandaswamy e Venkateshbabu[26] Root canal irrigants	Not selected Review
Kaya et al.[27] Evaluation of radicular dentin erosion and smear layer removal capacity of self-adjusting file using different concentrations of sodium hypochlorite as an initial irrigant	Not selected In vitro study
Paudel et al.[28] Different pharmacological solutions in intracanal irrigation	Not selected Only one NaOCl concentration
Rôças e Siqueira Junior[29] Comparison of the in vivo antimicrobial effectiveness of sodium hypochlorite and chlorhexidine used as root canal irrigants: a molecular microbiology study	Not selected Only one NaOCl concentration (2.5%)
van der Vyver et al.[30] Antimicrobial efficacy of nine different root canal irrigation solutions	Not selected Only one NaOCl concentration
Beus et al.[31] Comparison of the effect of two endodontic irrigation protocols on the elimination of bacteria from root canal system: a prospective, randomized clinical trial	Not selected Chlorexidine used
Keenan[32] No evidence favouring one irrigant versus another in root canal treatments	Not selected In vitro study
Pawar et al.[33] Influence of an apical negative pressure irrigation system on bacterial elimination during endodontic therapy: a prospective randomized clinical study	Not selected Only one NaOCl concentration (0.5%)
Cohenca et al.[34] Antimicrobial efficacy of two irrigation techniques in tapered and non-tapered canal preparations. A randomized controlled clinical trial	Not selected Only one NaOCl concentration (6%)
Guo et al.[35] Efficacy of four different irrigation techniques combined with 60 °C 3% sodium hypochlorite and 17% EDTA in smear layer removal	Not selected In vitro study
Mashalkar et al.[36] Comparative evaluation of root canal disinfection by conventional method and laser: an in vivo study	Not selected Only one NaOCl concentration (3%).
Martins et al.[37] Outcome of Er,Cr:YSGG laser-assisted treatment of teeth with apical periodontitis: a blind randomized clinical trial	Not selected Only one NaOCl concentration (3%)
Ma et al.[38] The effects of sodium hypochlorite and chlorhexidine irrigants on the antibacterial activities of alkaline media against Enterococcus faecalis	Not selected In vitro study
Podar et al.[39] In vivo antimicrobial efficacy of 6% Morinda citrifolia, Azadirachta indica, and 3% sodium hypochlorite as root canal irrigants	Not selected Only one NaOCl concentration (3%)
Arias-Moliz et al.[40] Effects of dentin debris on the antimicrobial properties of sodium hypochlorite and etidronic acid	Not selected In vitro study
30. Rôças et al.[41] Disinfecting effects of rotary instrumentation with either 2.5% sodium hypochlorite or 2% chlorhexidine as the main irrigant: a randomized clinical study	Not selected Only one NaOCl concentration (2.5%)
Kist et al.[42] Comparison of ozone gas and sodium hypochlorite/chlorhexidine two-visit disinfection protocols in treating apical periodontitis: a randomized controlled clinical trial	Not selected Only one NaOCl concentration (3%)
Nourzadeh et al.[43] Comparative antimicrobial efficacy of Eucalyptus Galbie and Myrtus Communis L. extracts, chlorhexidine and sodium hypochlorite against Enterococcus Faecalis	Not selected In vitro study

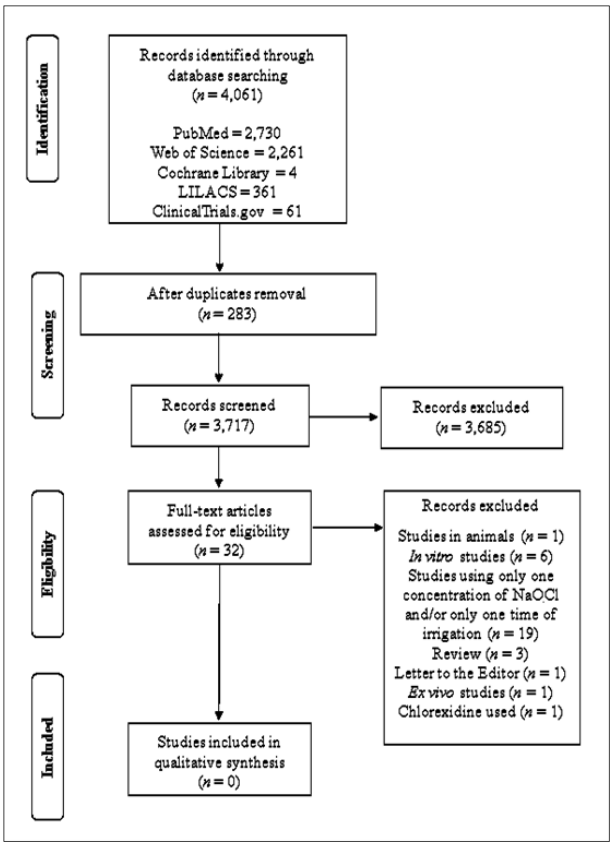

Figure 1: Flow chart showing the results of the search process.

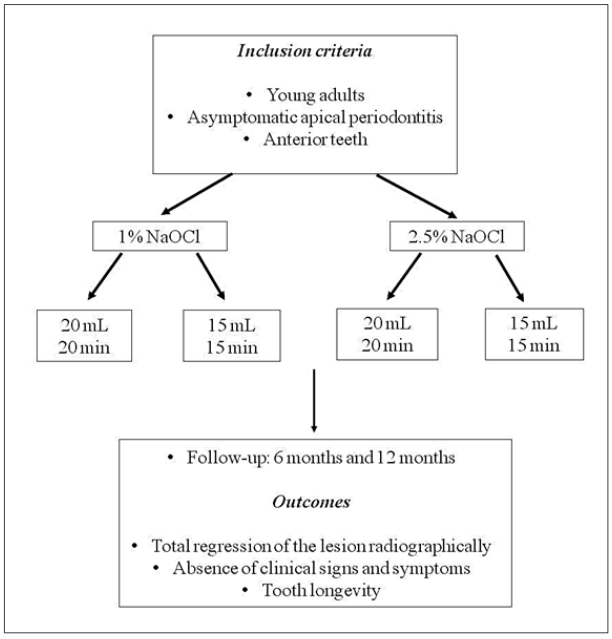

Figure 2: Flow chart suggesting controlled clinical investigations involving young adult patients with anterior teeth showing radiographically visible endodontic lesions using two options of NaOCl concentration, volume, and time of irrigation.

DISCUSSION

Sodium hypochlorite was first used by Henry Dakin in 1915 to clean wounds and its use in endodontics was suggested by Coolidge in 1919. In 1922, Walker proposed its use for the irrigation of root canals, with the procedure being later disseminated by Grossman[44-46]. Today, this is definitely the solution most extensively used

worldwide for root canal instrumentation[23]. It is an alkaline solution with an approximate pH of 11 to 12 whose germicidal and antibacterial action has been demonstrated by many investigators[30].

Although NaOCl has been part of the endodontic arsenal for more than one century, current investigations have been unable to determine the time of application, the volume or the concentration of this solution that can dissolve organic matter without weakening the dental structure during the phase of biomechanical preparation of the root canal. The present investigation was surprising by showing that no clinical trials on humans for the assessment of the concentrations, volumes and irrigation time with NaOCl solution were detected. And this result obligatorily stimulates the proposal of scientific methods that may resolve these questions.

Suggesting human studies that will provide an answer to this question is a challenge because of different variables. Other factors should be considered in addition to time of irrigation and concentration of the NaOCl solution[10]. Age-related structural changes in dentin may also be detrimental to its mechanical properties[47] since dentin becomes dehydrated and therefore more fragile with age[48]. Gender has also been suggested to influence the number of roots and root canal system configuration in human permanent teeth. Thus, it is another variable that needs to be controlled in future trials[49]. Different endodontic diagnoses also need to be standardized in future studies since the time of regression of lesions such as periapical granulomas or cysts is longer than that for regression of only inflamed pulp.

Another provocative factor is the time of irrigation. Establishing the time necessary for the action of NaOCl during biomechanical preparation of the root canal system, i.e., 5, 10, 15, or 20 minutes as observational intervals, may render it enviable to obtain results due to aspects such as expertise of the clinicians and endodontists, the selection of endodontic systems, the protocols used, and patient collaboration. It should be pointed out, for example, that Nourzadeh et al.[43] obtained an effective protocol by using 5.25% NaOCl for 10 minutes. However, that was an *in vitro* study.

Also, the NaOCl concentrations used vary from values such as 0.5% (Dakin's fluid)[4], 1% (Milton's solution), 2.5% (Labarraque's liquor), and 4 to 6% chlorinated soda[5,50]. Different NaOCl irrigation protocols may alter the mechanical properties of dentin such as microhardness and modulus of elasticity[51,52]. NaOCl solutions of 5.25% have been shown to be potently antimicrobial in an *in vitro* study[43] and in a clinical investigation by Paudel et al.[28]. However, this result was obtained without a comparative analysis and using a reduced sample. Siqueira et al.[53] demonstrated the killing efficacy of lower NaOCl concentrations, such as 4.0%, against *E. faecalis*, and van der Vyver et al.[30] demonstrated it using a 3.5% concentration. However, these were laboratory studies using isolated bacterial species. An effective antimicrobial action of 2.5% NaOCl was detected in human trials, although the results were only compared to 0.2% or 0.12% chlorhexidine[16,22] and to potassium iodide[54]. In contrast, according to a clinical study conducted by Gomes et al.[21], a 2.5% NaOCl solution was ineffective in the elimination of endotoxins in primary infections of root canals of teeth with pulp necrosis and apical periodontitis.

Regarding the dissolution of organic tissue, there is no consensus about an ideal concentration for an effective action, although Thé[15] proposed that 3% NaOCl is the ideal concentration able to dissolve necrotic tissues. More recently, van der Vyver et al.[30] stated that the irrigating solution is an ideal solvent of organic matter both for a vital and a necrotic pulp. However, they observed that this solution is intensely irritating for periapical tissues, especially at high concentrations. In our survey we did not detect comparative studies regarding different times and volumes of irrigation. Soares e Pires Júnior[55], for example, compared three different concentrations (1%, 2.5% and 5%) without varying time or volume. Podar et al.[39] and Rôças et al.[41] suggested a volume of 15 mL for the reduction of the number of aerobic and anaerobic bacteria per root canal.

The importance of the present investigation may perhaps reside in the feeling of absolute frustration it caused among the authors. The fact that there are no studies able to answer the key question leads us to suggest controlled clinical investigations involving young adult patients with anterior teeth showing radiographically visible endodontic lesions using two options of NaOCl concentration, volume, and time of irrigation, as shown in figure 2. After 12 years, Zehnder's[5] comment that we are living in the age of evidence-based medicine, and any new concept or technique to be used in the clinic should ideally be assessed in randomized controlled trials is still timely and valid. This, however, represents a major problem in endodontic research.

CONCLUSION

This systematic review was unable to indicate what time of irrigation, concentration or volume of NaOCl solution can be of maximum effectiveness in endodontic treatment without causing significant changes in the mechanical properties of dentin. Thus, future controlled human clinical trials should be encouraged in view of the different factors that may bias and confuse the results.

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CONFLICTS OF INTERESTS

The authors declare no conflicts of interests.

CORRESPONDING AUTHOR

Amália Moreno
amalia_moreno@yahoo.com.br

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