Review Article

Continuous Chelation Concept in Endodontics

Ayat H. Adham[1*], Ahmed H. Ali[2], Francesco Mannocci[3]

1Ministry of Health, Baghdad Al-Rusafa Health department, Istiqlal sector, Baghdad, Iraq.

2Assistant Professor, Aesthetic and restorative dentistry department,College of Dentistry,University of Baghdad, Baghdad, Iraq.

3Department of Endodontics, Faculty of Dentistry, Oral & Craniofacial Sciences, Centre of Oral Clinical & Translational Sciences, Guy's Dental Hospital, King's College London, London, UK.

* Correspondence: ayat.hashem1204a@codental.uobaghdad.edu.iq

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Abstract : Background:Continuous chelation can be defined as the concept of using a single mix of a weak chelator with NaOCL throughout the entire root canal preparation procedure without causing a reduction in the antimicrobial and proteolytic activity of NaOCL. Etidronic acid, also known as "1-Hydroxyethylidene-1, 1-Bisphosphonate" HEBP, or HEDP, is a soft biocompatible chelator utilized in direct combination with sodium hypochlorite to form an all-in-one deproteinizing, disinfecting, and chelating solution. It's the only chelator available as a certified commercial product, "Dual Rinse HEDP," approved for endodontic usage. This review aims to analyze and bring up-to-date data about the continuous chelation protocol using a combination of HEDP with sodium hypochlorite in endodontic irrigation. Data: only papers that were published electronically were searched within the review. Sources: “Google Scholar”,” PubMed” websites were used for searching data by using the following keywords: : Bisphosphonates, Continuous chelation, Dual rinse HEDP, Etidronate, HEBP. The most relevant papers related to the topic were chosen, specifically the original articles and clinical studies, including only English-language articles from 2005 to September 2022. Conclusion:Combining a weak chelator with NaOCL solution, a single irrigation solution mixture with soft tissue dissolving ability and antibacterial properties with chelating capability can be created, which can be considered a good alternative to the conventional irrigation protocol (sequential irrigation) with NaOCL followed by using a strong chelator such as EDTA. The obvious benefit is that only one solution is required for root canal cleansing and decontamination, also decreasing the time for irrigation and providing better conditioning of root canal walls for root-filling materials.

Keywords: Bisphosphonates, Continuous chelation, Dual rinse HEDP, Etidronate, HEBP

Introduction

The goal of a root canal treatment is three-dimensional obturation with a complete seal of the root canal system [1]. Sodium hypochlorite (NaOCL) is a proteolytic agent with significant tissue solvent action, microbicidal, and anti-biofilm properties and is utilized in concentrations ranging from (0.5–6%) [2, 3].

The inorganic tissue remnants and debris that developed throughout the instrumentation technique are not removed by NaOCl [4]. As a result, a sequestering or chelator, such as ethylenediaminetetraacetic acid (EDTA), the most frequently used chelator in endodontics, should be utilized afterward. This standard technique is known as sequential chelation, the most commonly applied irrigation regimen in endodontic treatment. However, it has several disadvantages, including widening in the opening of dentinal tubules, and significant decalcification of the intertubular dentin surface [5]; as a result, dentin flexural strength will be reduced by these microscopic and chemical changes [6,7] .Furthermore, when mixed with NaOCl, EDTA decreases the quantity of free available chlorine, reducing NaOCL's tissue-dissolving ability [8].

To address all of the previous issues with NaOCL \ EDTA, a new irrigation protocol based on continuous chelation was established in 2005 by Dr. Matthias Zehnder from the University of Zurich, Switzerland [9]. In 2012, the actual terminology was used for the first time. This protocol combines a weak chelator called etidronic acid "1-Hydroxyethylidene-1, 1-Bisphosphonate" HEBP, or HEDP, with NaOCL as a single irrigant solution during the instrumentation procedure [10].

In 2016, a commercially certified etidronate chelation powder product Dual Rinse (HEDP) (Medcem GmbH, Weinfelden, Switzerland) that has been clinically approved for endodontic use became available. It's manufactured in the form of capsules and each one contains 0.9 g powder of etidronate, which must be added to 10 mL of sodium hypochlorite solution immediately before root canal therapy, yielding a combination irrigant that contains both active chlorine and nearly 9% HEDP [11].

According to the studies, using a mild chelator such as etidronic acid (HEDP) in a freshly formed mixture with NaOCL has several advantages, including not interfering with the antibacterial and tissue-dissolving capabilities of the resultant mixture [9, 12], preventing the accumulation of hard tissue debris and smear layer [13], and NaOCL's disinfection efficacy in experimentally contaminated dentin was improved [14].

To our knowledge, no previous inclusive review article on the continuous chelation protocol is in the literature. This review aims to review most, if not all, of the available studies about continuous chelation as a novel irrigation protocol. Most of the research is centered on the weak chelator etidronate.

Methods\search strategy

A comprehensive electronic search was conducted on the following websites: PubMed database and Google scholar. The search was limited to manuscripts published in the English language from 2005 till September 2022 by utilizing the following keywords: Bisphosphonates, Continuous chelation, Dual rinse HEDP, Etidronate, HEBP. A further manual search of the references list of the relevant articles was also performed. The following types of articles were excluded: Articles not published in a highly ranked journal , studies not conducted on human dentin, studies unrelated to the topic, personal opinions,editorials and social media sources. After filtering process, only 50 articles were included.

Common chelators used in continuous chelation

In a continuous chelation protocol, a chelator combined with sodium hypochlorite can be utilized as a single irrigant throughout the root canal instrumentation procedure [15] . The chelator etidronate in this procedure is the only commercially available product [11] . Nevertheless, studies exist on two additional chelators, EDTA and clodronate, at alkaline pH. The concentration of the anion hypochlorite, which is responsible for organic tissue disintegration, is maximized when alkalinity is maintained[12] . The characteristics of EDTA are affected by whether it is provided as a disodium or tetrasodium salt[9]. The acidic pH of the EDTA disodium salt is close to neutral. The sodium hypochlorite's action disintegrates organic tissue and causes antibacterial activity, which is reduced when acidifying the media. On the other hand, the EDTA tetrasodium salt has a basic pH of nearly 11, making it stable with NaOCl without changing its features [9, 15] . As a result of the increased depletion of free available chlorine that happens when alkaline EDTA (Na4 EDTA) is combined with sodium hypochlorite, it is not suitable to be used in continuous chelation [15] . Another study found that the compatibility of Na4 EDTA with NaOCl is less than that of tetrasodium etidronate (Na4 etidronate). After 20 minutes, the level of free available chlorine in solutions of 5% Na4 EDTA and 2.5 % NaOCl was 12% at room temperature and 6% at 35 °C. As a result, it is not recommended to use these solutions in continuous chelation protocol [16] .

It's thought that the better compatibility of sodium hypochlorite with HEDP "etidronate" than EDTA is because HEDP is a non-nitrogenous chelating agent that comprises phosphorus rather than nitrogen. The chlorine atoms in sodium hypochlorite have a positive charge and will attack the nitrogen atoms' electrophilic centers. Because phosphorus has less electronegativity than nitrogen, it has a lower chance of reacting with NaOCl [17] . Biel et al. (2017) compared Na4EDTA salt with HEDP, and the findings revealed that Na4EDTA is compatible with sodium hypochlorite at low concentrations and for a short time [15] . Nevertheless, for clinical practice, HEDP appears to be superior to its EDTA counterpart [9, 15]. Despite these promising results, the combination of etidronate and NaOCL is chemically unstable and loses its free available chlorine with time. At room temperature, solutions containing 18% etidronate and 5% NaOCL [15] or 9% Dual rinse \ 2.5% sodium hypochlorite[11] had a usage life of 1 and 2 hours, respectively.

On the other hand, clodronate "novel chelator," is more stable in NaOCl combinations than etidronate[18] . Recently, a study was carried out to assess the efficacy of clodronate. It was reported that a mixture of NaOCL and clodronate does not lose free available chlorine after 18 hours and can eradicate the smear layer, despite a reduced degree of opening of dentinal tubules than etidronate[19]. Similarly, etidronate or clodronate combinations with NaOCL were just as efficient as NaOCL against Enterococcus.faecalis[20] .

In terms of organic tissue dissolution, Wright et al. (2020) found that 7.6% clodronate \2.5 % sodium hypochlorite can dissolve organic tissue just like 2.5% sodium hypochlorite [21]. Furthermore, clodronate combinations dissolve organic tissue with greater residual Free Available Chlorine (FAC) than etidronate mixes. However, more studies and investigations should be carried out to assess the effect of the novel chelator clodronate and its safety in a continuous chelation approach in clinical practice.

Biocompatibility assessment of etidronate

Numerous questions about biocompatibility and toxicity must be addressed whenever new materials are utilized in different concentrations or with different procedures. An in vitro study by Ballal et al. (2019) assessed whether the incorporation of Dual rinse HEDP product into NaOCL induced genotoxic or cytotoxic effects using a micronucleus test for determining genotoxicity and the tetrazolium dye MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assay and the clonogenic assay for assessing cell viability. For all assays, no untoward effects were detected for the etidronate-NaOCl combination [22]. Also, a randomized safety clinical trial was performed on adult patients who presented with teeth affected by primary asymptomatic apical periodontitis comparing irrigation using 2.5% NaOCL with 2.5%\9%Dual rinse HEDP during the cleaning and shaping procedure, and it was shown that no adverse effect was found by adding etidronate to NaOCL[23].

Effect of continuous chelation on the properties of sodium hypochlorite:

1.Effect of continuous chelation on antimicrobial\antibiofilm activity of NaOCL

The main goal of chemomechanical endodontic treatment is the reduction or elimination of microorganisms from the root canal system [24]. Adequate mechanical preparation, copious and effective irrigation, and intracanal medications are used to eliminate the bacteria and their products are required for successful root canal treatment [25]. The antibacterial effects of continuous chelation have been studied using E. faecalis [9, 14, 26-32], and Candida albicans were also included in one study[31]. Alkaline EDTA has only been investigated in one study using colony counting and the adenosine triphosphate assay. It was determined that 10 % or 10% EDTA\2.5 % sodium hypochlorite was equally effective against 3-week-old E. faecalis biofilms as was 2.5 % sodium hypochlorite [30]. Nevertheless, an exothermic reaction occurs when an oxidizing agent (NaOCl) is combined with a chelating substance frequently used in endodontics (EDTA or citric acid). Consequently, the free available chlorine in sodium hypochlorite solutions is depleted, and their antimicrobial and tissue-dissolving abilities are compromised [33].

Primarily, Zehnder et al. (2005) examined the antibacterial activity of etidronate in continuous chelation using 1:10 and 1:100 dilutions of 3.5%etidronate-0.5% NaOCl using a planktonic suspension. The disinfection duration was 15 minutes, and it was shown that combining EDTA or citric acid (CA) with NaOCl in 1:100 dilutions decreased the latter's antibacterial activity completely. On the other hand, etidronate didn't show any adverse effect on the ability of NaOCL to kill bacteria. After 1 hour, the free available chlorine content was decreased by the HEBP solution. This decline was dose-dependent. However, fresh mixtures contained 100% free chlorine. At the same time, the free available chlorine level in CA/NaOCl combinations dropped to zero in less than a minute [9].

Earlier investigations have reported that mixing sodium hypochlorite with HEDP resulted in a 20% reduction in FAC after 1 hr. while preserving the NaOCl's proteolytic/antibacterial effects, making this mixture theoretically suitable for chemomechanical preparation and as a final irrigant[5, 9, 26]. A clinical trial compared irrigation protocols of 9 % etidronate\2.5 % sodium hypochlorite to irrigation with 2.5 % sodium hypochlorite using paper points to sample the root canal bacteria and found that there is a lack of culturable microorganisms in 50% of the root canals in the HEDP\ NAOCL group, compared to 40% in the 2.5 % sodium hypochlorite group, indicating that the antimicrobial efficacy of sodium hypochlorite is not affected by HEDP when both irrigants are freshly mixed [34].

In the existence of a smear layer, there is little evidence about how the mixture of sodium hypochlorite with HEBP exhibits antibacterial efficacy against infected dentin. Morago et al. (2016) stated that the antibacterial activity of 2.5 % sodium hypochlorite when mixed with 9% HEBP was unaffected by the presence of the smear layer, and the combined solution could be utilized in any condition irrespective of the smear layer amount in the walls of the root canal. If there is a smear layer, the mixed solution will eliminate it, allowing the NaOCl to act, and in the absence of the smear layer, there would be no interference[29]. The greater activity of NaOCL\ HEBP compared to NaOCL alone is likely due to HEBP's ability to remove the smear layer, permitting sodium hypochlorite to infiltrate into the structure of dentin and exert its antibacterial activity [5].

Only a few studies have been carried out on the antimicrobial effectiveness of commercial Dual Rinse HEDP in sterile saline solution. Because of the lack of antibacterial activity and the inability to remove the smear layer, HEDP solution mixed with saline must not be used as a single irrigant [(35)].

2.Effect of continuous chelation on tissue dissolving ability of NaOCL

The sodium hypochlorite tissue-dissolving capability is proportional to the amount of free chlorine in the solution [(36)], which comprises hypochlorous acid (HOCl) and the hypochlorite ion (OCl).
The chelator Na4EDTA has been used in only one tissue dissolution study, and it was reported that there was no significant difference in the percentage of reduction in bovine muscle tissue between 5-10 % tetrasodium EDTA\2.5 % sodium hypochlorite mixtures and a 2.5 % sodium hypochlorite control during 15 minutes [(37)]. Tartari et al. (2015) evaluated the effect in tissue dissolution of single and combined use of sodium hypochlorite (HEDP) and EDTA, and they found that the combination of sodium hypochlorite with EDTA (pH 7.4) was not associated with tissue dissolution, while the combination of sodium hypochlorite with HEDP (pH 11.2) had a superior ability in tissue dissolution. As a result, HEDP had only a minor effect on NaOCL, indicating that if utilized during instrumentation, this mixture can efficiently dissolve organic tissues [(12)]. The non-dissolution of organic materials by the combination of sodium hypochlorite and EDTA could be because of the decrease in the release of the OCl ion, which encourages the tissue-dissolving action of NaOCL [(38)].

When examining the combination of sodium hypochlorite and HEDP, a minor change in organic matter dissolution was found, which was most likely because this chemical is a weak chelating agent [(39, 40)], which causes some reduction in the FAC amount after 1 hour of mixing [(9)]. Another etidronate study investigated the effect on the removal of bovine muscle from concavities made within human root canals by utilizing passive ultrasonic irrigation and the XP-endo shaper, and it has been shown that without activation or with the use of passive ultrasonic irrigation NaOCL\EDTA caused a similar amount of tissue removal as the water. In contrast, the effects of the combination etidronate\ NaOCL were comparable to plain sodium hypochlorite. All the irrigants were used in the canal for only 2 min; the result is not surprising. A 1 min application of sodium hypochlorite was followed by another min of EDTA for the sequence. Compared to the NaOCl control or the etidronate-NaOCl mixture, the specimens in the sequence were exposed to NaOCl for half the time. As a result, the sequence NaOCL \EDTA is unlikely to dissolve as much organic tissue. Given the short time frame, the equivalent results for the NaOCl control and the etidronate mixture are reasonable [(41)].

3. Effect of temperature on NaOCL stability combined with etidronate

Heating the sodium hypochlorite/Dual Rinse combinations harmed the FAC content, with a full loss of that component after one hour, but the pure sodium hypochlorite solutions preserved all of their FAC, indicating that heating of Dual Rinse and NaOCL should be avoided. HEDP breaks down into the components utilized to make it, notably acetic and phosphonic acid [(42)]. Sodium hydroxide buffers the acetic and phosphonic acids that arise. Then, NaOCL will break down under the effect of temperature and light.

Then, the FAC (in the forms of OCl-, HOCl, and NaOCl) will undoubtedly be lost as soon as these reactions occur [11]. On the contrary, it was found that when the NaOCl/HEDP mixture was heated to 40°C, it dissolved more organic matter than when it was kept at ambient temperature (25°C)[43]. Also, another study has shown that heating sodium hypochlorite alone or in combination with HEDP has been demonstrated to boost their ability to dissolve organic tissue and eliminate the smear layer. The temperatures of 60 °C for sodium hypochlorite alone and 37 °C for its combination with HEDP were the optimum temperatures for the properties studied, but they needed to be refreshed frequently to maintain their benefits. The increase in collisions between the molecules of sodium hypochlorite and the organic tissue and the replenishment of the combination before each immersion of the specimens likely contributed to these results. Nevertheless, after 10 minutes, no differences between the 37°C, 48°C, and 60°C groups were detected. Heating was not advantageous for the mixture of NaOCl and Na4EDTA, likely due to the quick loss of FAC. Because the improved efficiency of preheated solutions is restricted to the time they are vigorously introduced and the rapid temperature equilibrium inside the root canal, they must be regularly replenished throughout root canal therapy [44].

Effect of continuous chelation on the chemical composition and ultrastructure of dentin

Rath et al. (2020) characterized and compared the effects of two different irrigation protocols on ultrastructural characteristics of dentin: sequential chelation (NaOCl (3.0, 6%)/17.5% EDTA) and continuous chelation (HEDP Dual rinse). They discovered that sequential chelation leads to the exposure of thick collagen bundles on the surface, whereas continuous chelation results in a thin, frail layer of exposed collagen on the surface. In contrast to the organic-components-rich dentin surface after sequential chelation treatment, continuous chelation resulted in a homogeneous organic and inorganic structure of the dentin surface. When HEDP-treated dentin was compared to sodium hypochlorite/EDTA-treated dentin, the collagen fibers had shorter and thinner strands. The root canal dentin was imaged using a Transmission Electron Microscope. It revealed a dense collagen network that was parallelly oriented without any loss of banding pattern in the sub-surface layer, indicating partial degradation of the surface fibers exposed by HEDP and proteolyzed by sodium hypochlorite. While EDTA-induced dentin surface demineralization results in a surface with loosely arranged, "naked" collagen fibrils reaching up to 880 nm into the dentin[45].

Effect of continuous chelation on removal of Smear layer and debris from dentinal tubules

The smear layer is formed during the instrumentation process due to the action of endodontic instruments during the shaping process and it should be removed as it might decrease the overall success of endodontic therapy [46]. During continuous chelation, there is some evidence that less dentin debris accumulates. In a study performed by Paque et al. (2012) using microcomputed tomography, they found that debris accumulation in the isthmuses of the mesial roots of extracted lower molars was less in the case of irrigation with 9% tetrasodium etidronate\2.5% sodium hypochlorite compared to 2.5% sodium hypochlorite and this decrease seemed to occur throughout the whole root canal, including apical ramifications, rather than only in the isthmus [13]. However, comparing it with NaOCl is unreasonable because rinsing with EDTA after applying NaOCl has been shown to minimize dentine debris accumulation [4]. It would have been more conclusive to compare etidronate combinations to standard sequences. The smear layer is a thin layer formed during mechanical root canal instrumentation that is made up of organic and inorganic material from the dentine and pulp tissue, as well as microorganisms and their products in infected teeth [47].

Regarding continuous chelation mixture using Etidronate, Zehnder, et al. (2005) demonstrated that 17 % EDTA is more effective in eliminating the smear layer than 3.5 % tetrasodium etidronate\0.5 % sodium hypochlorite over 1 min, and this finding could be attributed to the low concentration of Etidronate and the short period of application [9]. Also, De-Deus et al. (2008) evaluated the chelating capability of Etidronate as compared with EDTA using co-site optical microscopy, and they revealed that EDTA is more effective in removing the smear layer than HEBP. The kinetics of demineralization endorsed by both 9 and 18 % HEBP were slower than those promoted by 17 % EDTA [39]. While Lottani et al. (2009) showed that protocols employing 1% NaOCl \17% EDTA, 1% NaOCl \ 2.25% peracetic acid, and 1% NaOCl \9% etidronic acid left the same amounts of smear layer in the walls of the root canals. Furthermore, compared to 1 % sodium hypochlorite for 15 min followed by 17 % EDTA for 3 min, less Ca^{2+} is eluted from the root canal when dentine discs are subjected to 9 % tetrasodium etidronate\1% sodium hypochlorite for 15 min. As a result, the etidronic acid \NaOCL mixture can be used as a single irrigation solution throughout canal instrumentation without causing dentin decalcification [5]. Also, Kfir et al. (2020) reported that there is no substantial difference between the sequential chelation protocol (3% NaOCL \EDTA) and continuous chelation protocol (3%NaOCL \9%HEDP) in the removal of smear layer and debris. Moreover, neither protocol could completely remove the smear layer from the root canal walls [48].

The stability constant measures a chelator's capacity to bind metal ions, with a larger number suggesting stronger binding. Compared to Etidronate, EDTA has a higher stability constant [49]. Deari et al. (2019) found that Etidronate removed less smear layer as compared with EDTA at neutral pH, and this finding could be due to Etidronate having lower stability constant and higher PH as compared with EDTA [50]. Morago et al. (2016) stated that continuous irrigation with 2.5% sodium hypochlorite/9% HEBP solution as a substitute for using sodium hypochlorite followed by a strong chelator resulted in less debris and smear layer. This will reduce the reactivity of sodium hypochlorite with the residual debris, which means less depletion of the FAC and, thus, higher stability of the mixture [29].

Conclusions

Continuous chelation is beneficial since it facilitates the clinical procedure while improving debris removal from the root canal. Combining an oxidation-resistant chelator with NaOCL can expedite and simplify root canal cleaning during endodontic treatments. Lastly, because of its better antibacterial effect despite a higher surface tension value, sodium hypochlorite /Dual Rinse HEDP may be a feasible substitute for NaOCl + EDTA.

Directions for future studies

It's unclear if continuous chelation protocol will improve the outcome of root canal therapy, especially in retreatment cases. Accordingly, more clinically relevant studies should be carried out to confirm the real effectiveness of continuous chelation innovative protocol in clinical practice. Furthermore, one of the main issues that should be taken into consideration is the compatibility with NaOCL in continuous chelation mixture and preservation of free available chlorine despite the promising results of chelators such as etidronate but still, there is gradual loss of Free available chlorine with time. Consequently, future studies should be conducted using other more compatible chelators such as clodronate to ensure high maintenance of free available chlorine which results in preserving and enhancing the main functions of NaOCL.

Conflict of interest: None

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مفهوم الاستخلاب المستمر في علاج جذور الأسنان

الباحثون: ايات هاشم ادهم , احمد حامد علي , فرانسيسكو مانوش

المستخلص

الاهداف: يمكن تعريف عملية الاستخلاب المستمر على أنها مفهوم يتضمن استخدام مزيج واحد من مستخلب ضعيف مع هيبوكلوريت الصوديوم طوال عملية التحضير بأكملها دون التسبب في انخفاض نشاط مضادات الميكروبات والمحلل البروتيني لهيبوكلوريت الصوديوم. حمضEtidronic المعروف ايضا باسم "1- Hydroxyethylidene-1, 1-Bisphosphonate" HEDP or HEBP، عبارة عن مستخلب ناعم متوافق حيويًا يمكن استخدامه في توليفة مباشرة مع هيبوكلوريت الصوديوم لتشكيل محلول مطهر ومستخلب "الكل في واحد" وهو المستخلِب الوحيد المتاح كمنتج تجاري معتمد" Dual rinse HEDP " تمت الموافقة عليه للاستخدام اللبي. تهدف هذه المراجعة إلى التحليل الشامل وتحديث البيانات الموجودة حول بروتوكول الاستحلاب المستمر المبتكر باستخدام مزيج من HEDP مع هيبوكلوريت الصوديوم في الري اللبي وتأثيره على خصائص عاج قناة الجذر وخصائص NaOCL . البيانات :تم البحث فقط في الأوراق التي تم نشرها إلكترونيًا ضمن المراجعة. المصادر: تم استخدام مواقع "الباحث العلمي من "Google و "PubMed" للبحث عن البيانات باستخدام الكلمات المفتاحيه الاتيه Bisphosphonates, Continuous chelation, Dual rinse HEDP, Etidronate, HEBP: وتم اختيار معظم الأوراق البحثية ذات الصلة بالموضوع ، وتحديداً المقالات الأصلية والدراسات السريرية ، بما في ذلك مقالات باللغة الإنجليزية فقط من 2005 حتى ايلول 2022. الاستنتاجات :من خلال الجمع بين المستخلب ضعيف و محلول هيبوكلوريت الصوديوم ،يتم الحصول على خليط محلول ري واحد قادر على اذابة الأنسجة الرخوة ، ولديه خاصية مضادة للبكتيريا مع قدرة استخلابيه يمكن اعتبارها بديلاً جيدًا للري التقليدي باستخدام NaOCL \ EDTA. الفائدة الواضحة هي أن هناك محلولا واحدًا فقط مطلوبًا لتطهير قناة الجذر وإزالة التلوث ، وكذلك تقليل وقت الري وتوفير تكييف أفضل لجدران قناة الجذر لمواد حشو الجذر