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Modification and Methods to Improve the Efficiency of Sodium Hypochlorite as a Root Canal Irrigant

Sreelakshmi SB[1], Anjaneyulu K[1]*, Geetha RV[2]

[1]*Department of Conservative Dentistry and Endodontics, Saveetha Dental College and Hospitals, Saveetha Institute of Medical and Technical Sciences [SIMATS], Saveetha University, Chennai, India*

[2]*Department of Conservative Dentistry and Endodontics, Saveetha Dental College and Hospitals, Saveetha Institute of Medical and Technical Sciences [SIMATS], Saveetha University, Chennai, India*

ABSTRACT

The main aim of the root canal treatment is to disinfect the entire root canal system. This can be achieved by mechanical instrumentation and chemical irrigation, with medication of the root canal. Microorganism and their byproducts are the major cause of pulpal and periodical pathos is. To reduce or eliminate bacteria and pulp tissue remnants, various irrigation solutions have been suggested to be used during treatment. Sodium hypochlorite (NaOCl), a reducing agent, is a clear, straw-colored solution containing about 5% of available chlorine. It is the most widely used irrigating solution. NaOCL is an excellent non-specific proteolytic and antimicrobial agent, most common irrigant during root canal therapy. New equipment introduced into root canal irrigation includes the EndoActivator , Vibringe, and various ultrasonic devices where the irrigant is directed into the canal through the vibrating tip.It is indicated that these devices may facilitate irrigation, particularly in the difficult to reach areas of the canals, such as fins and isthmuses and in large lateral canals. With this background, the main aim of the study is to review the method and modification to improve the efficacy of sodium hypochlorite as root canal irrigant and thereby prevent the failure of root canal treatment.

Keywords: Sodium hypochlorite, Irrigants, Antibacterial, Techniques, Microorganisms

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Corresponding author: Anjaneyulu K
e-mail✉: kanjaneyulu.sdc@saveetha.com
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INTRODUCTION

The microorganisms remaining in the root canal space after treatment or re-colonising the root canal system are the main cause of endodontic failure. Bacteria are the primary factors in the development of pulp and periapical lesions. The main objective of the root canal treatment is to remove and eliminate bacteria from the root canal space and the prevention of reinfection [1]. Reinfection or continued periapical inflammation can be caused due to the number of bacteria found within the root canal space and dentinal tubules, but the actual number of viable bacteria required for this process of reinfection and inflammation is unknown [2]. In failed endodontic cases, Enterococcus faecalis is the important species isolated. E. faecalis can remain viable in root-filled canals for 12 months after surgery, and it is also capable of penetrating into the dentin tubules up to 100 mm from the canal lumen [3]. Among the procedures involved in the control of root canal infections, irrigation is the important process in eliminating microorganisms from the root canal space. Root canal cleaning procedures are dependent on the mechanical instrumentation and chemical effects of the irrigant used. The important qualities of an irrigant are the ability to dissolve pulp tissue, ability to remove the smear layer, and low toxicity while providing a bactericidal/bacteriostatic effect [4]. Through the years, many different irrigating solutions have been recommended. A stream of hot water discharged from an insulated syringe, physiologic saline solution, 30% solution of urea, urea peroxide solution in glycerin, solution of chloramine, sodium hypochlorite in conjugation with Ethylene Diamine tetra acetic acid (EDTA) are just a few [5]. NaOCl have several properties that contribute to the effective chemo mechanical debridement of a root canal system.NaOCl acts as a lubricant for instrumentation and can flush out debris from root canals. NaOCl is an effective antimicrobial agent with the capability of detoxifying the root canal system. In addition, NaOCl is effective in dissolving both vital and nonvital tissues [6].

Many factors contribute to the survival of E. faecalis in teeth. Those factors include bacterial starvation, short exposure to irrigants, lack of instrumentation after contamination, and reduction in the efficacy of the irrigant. The time and concentration of the irrigant play a significant role in the ability of an irrigant to eliminate the bacteria from the root canal space. Siqueira et al evaluated the chemomechanical reduction of the bacteria by using 1%, 2.5%, and 5.25% concentrations of NaOCl. Baumgartner et al compared the antimicrobial efficacy of 1.3% NaOCl/BioPure MTAD with 5.25% NaOCl/15% ethylenediaminetetraacetic acid (EDTA) as a root canal irrigant, and Berber et al evaluated the efficacy of 0.5%, 2.5%, and 5.25% concentrations of NaOCl for reducing E. faecalis in the root canals and dentinal tubules by using various instrumentation and irrigation techniques [7]. Clegg et al examined the effect of exposure to 1%, 3%, and 6% concentrations of NaOCl on apical dentin biofilms, and Vianna and Gomesassessed the efficacy of 1%, 2.5%, and 5.25% NaOCl alone and combined with chlorhexidine gluconate against E. faecalis in vitro by using an agar diffusion method [8]. Till today, there is no general agreement regarding the optimal concentration of NaOCl or irrigation time necessary to eliminate bacteria from the canal system [9]. The irrigation with 1.3% or 2.5% NaOCl is ineffective in eliminating this strain of E. faecalis in human teeth in less than 40 minutes. On the other hand, 5.25% NaOCl was 100% effective at 40 minutes. Clinically, actual root canal systems are more complex [10]. In addition, technological advances have made procedures more efficient, leading to reduced irrigation contact time [11].

With this background, the main aim of the study is to review the method and modification to improve the efficacy of sodium hypochlorite as root canal irrigant and thereby prevent the failure of root canal treatment.

MATERIALS AND METHODS

This study included 50 articles from the various search engines. The search engines used in the present study include PUBMED, Google scholar, cochrane,MESH core,biorxiv. The articles were searched based on the keywords which include Endodontic irrigant, methods to improve the efficiency of sodium hypochlorite, modification of sodium hypochlorite etc.The articles were collected from the duration of 2000- 2020. However few articles, due to unavailability in recent years were also selected for the study.

Inclusion criteria: The articles related to the topic were included in the present study.

Exclusion criteria: The articles which are not related to the topics are not included.

DISCUSSION

Ideal Requirement for An Irrigant

An ideal endodontic irrigant should have most of the ideal recommendations which include 1.anti-microbial activity 2. it mechanically flushes out the debris from the root canal 3. It must be non-toxic and biocompatible 4. It should dissolve necrotic and vital pulp tissues 5. services as a lubricant 6.removes the smear layer 7. should have low surface tension. However, none of the currently available irrigating solutions have all the property needed. A combined use of Separate irrigants in the clinical protocol recommended to ensure successful outcome of endodontic treatment [12].

Commonly Used Irrigants

Sodium hypochlorite (NaOCl), a reducing agent and a clear, straw-colored solution containing about 5% of available chlorine [13]. It is the most widely used irrigating solution. The mechanism of action of NAOCL follows three steps namely, saponification, amino acid neutralization and chloramination.The most effective concentration recommended is 5.2% sodium hypochlorite. It has tissue dissolution ability. EDTA, the chelating agent and commonly called ethylenediaminetetraacetic acid (EDTA), was introduced into endodontic practice by Nygaard-ostby. 17% EDTA is relatively nontoxic and only slightly irritating in weak solutions. It forms highly stable metal chelates when combined with heavy metals or alkaline earth ions. It removes the organic part of the smear layer [14]. Chlorhexidine digluconate (CHX) is a cationic bisbiguanide which is utilized as both irrigating solution and intracanal medicament [15]. Chlorhexidine digluconate possesses a broad spectrum of antimicrobial activity against most common endodontic pathogens [16]. It also possesses bacteriostatic and bactericidal activity [17]. MTAD, the newly introduced irrigants which employs a mixture of a tetra-cycline isomer, citric acid, and a detergent (Tween 80). It is used as a final rinse to remove the smear layer. It is commonly employed after initial irrigation with 1.3% NaOCl.

Irrigation Guidelines

The technique of root canal irrigation is simple. The only instrument required for the irrigation is disposable luer lock syringe with an endodontic blunt ended side vented needle.

The needle is inserted halfway and passively without binding into the root canal. Sufficient space between the needle and canal wall is maintained for the return flow of the solution and forcing of solution into the periradicular tissues should be avoided.

In the upper anterior teeth, the needle is inserted a few milli meter shorter than the working length without binding. When the needle does not bind, the solution can be ejected from the syringe with little or no pressure on the plunger [18].

The objective is only to irrigate the canal and not to force the solution under pressure into the periradicular tissues.

In narrow root canals, the tip of the needle is placed near the root canal orifice and the irrigant is discharged until it fills the entire pulp chamber.

The backflow of solution is caught on a gauze sponge or is aspirated. Irrigation should be followed by air drying of the root canals after the completion of shaping and cleaning. Final drying should be affected with absorbent points [19].

Care must be taken to avoid extrusion of the irrigant due to its toxicity. Possible extrusion and "sodium hypochlorite accident" can be avoided by employing a needle with side vents as they minimize the apical irrigating pressure

Equipment'sfor irrigation

The typical way of irrigating the root canal space is with a syringe and a needle. Small size 27-gauge or preferably 30-gauge needles are used during irrigation [20]. Irrigant reaches only 1 to 3mm, depending on the needle type and irrigant flow. Side-vented needles provide safer irrigation than normal needles in positive pressure irrigation. Agitation of the irrigant and constant refreshment leads to the increased effectiveness of the solutions. When there is a problem in reaching a apical canal by the irrigation needle, a gutta-percha point in a size corresponding to the dimensions of the apical canal can be used to facilitate irrigation [21]. When comparingtherecent method for agitation of the irrigant by active needle irrigation, sonic and ultrasonic activation withpassive irrigation (no activation or refreshment) the recent method is effective in increasing the speed of tissue dissolution by NaOCl. New equipment introduced to root canal irrigation includes the EndoActivator ,Vibringe,and various ultrasonic devices where the irrigant is introduced into the canal through the vibrating tip [22].Several reports have indicated that the various devices may facilitate irrigation, particularly in the difficult areas of the canals to be reached, such as fins and isthmuses and in large lateral canals [23]. The EndoVac uses the negative pressure to achieve safe irrigation of the apical canal [24]. In the EndoVac system, the direction of the flow of irrigant has been reversed, which creates the negative pressure at the apical foramen and thereby prevents the possibility of irrigant extrusion [25,26]. The improved cleanliness or antimicrobial effect in the most apical canal is achieved with the EndoVac when compared to positive pressure irrigation.

Mechanism of sodium hypochlorite

Overall reaction: $Naocl+H_2O \leftrightarrow NaOH+Hocl \leftrightarrow Na^++OH^-+H^++ocl^-$

Step 1 Saponification: Sodium hypochlorite acts as a solvent for organic and fat degrading fatty acids. Which inturn transforms them into fatty acid salts (soap) and glycerol (alcohol) and reduces the surface tension of the remaining solution [27].

Fatty acids+NaOH←>soap+glycerol

Step 2 Amino acid neutralization: Sodium hypochlorite neutralizes the amino acids by forming water and salt. With the release of hydroxyl ions, there is a reduction in pH. Hypochlorous acid, a substance present in sodium hypochlorite solution, when it comes in contact with the organic tissues it acts as a solvent and releases chlorine,which then combines with theamino group andforms chloramines. These chloramines interfere in cell metabolism [28]. Hypochlorous acid (HOCl-) and hypochlorite ions (OCl-) an important compound of the NaOCl helps in amino acid degradation and hydrolysis.

Amino acid+NaOH←>salt+H_2O

Step 3 chlorination: Chlorine which is a strong oxidant has an antimicrobial action by inhibiting the bacterial enzymes leading to an irreversible oxidation of SH groups (sulfhydryl group) of essential bacterial enzymes [29].

Amino acids+HOCl ←> chloramine+H_2O

Effects of ultrasonic on increasing efficacy of naocl

The endodontic procedure requires a thorough cleansing of the root canal system, canal preparation, and dimensional obturation. Irrigation is an integral part of the biomechanical phase of the treatment [30]. Irrigation aids in the removal of tissue debris, bacterial count reduction, and canal disinfection of the root canal space [31]. The ultrasound adds significant effects on antimicrobial agents. The two types of ultrasonics used in dentistry are magnetostrictive and piezoelectric, respectively. The ultrasonic device in dentistry is defined as the "sonosynergistic" system for cleaning and sterilizing the root canal space. The field of ultrasonic technology has made great advances in the recent years. Ultrasonics and other physical agents are playing an important synergistic and valuable role in helping and enhancing biocidal mechanisms on the microorganism present in the root canal space [32]. This is achieved by the ultrasonic waves which tend to accelerate the chemical reaction that creates cavitational effect which leads to the superior cleansing action. Until now, paper points, cotton pellets, luer-lock syringes, files and reamers have been the ways of introducing the irrigants into the canal [33]. None of this will enable the irrigating solution to penetrate adequately in the root canal system. The ultrasonic is used in the root canal system for the better efficiency of NaOCl [34]. The ultrasonic (acoustic waves of frequency higher than the normal ear can hear) waves can force a solution into all dimensions and also to the inaccessible canal system. The chemical effects of ultrasonic are based upon bonding, dissociation efforts, activation of radicals, and oxidation. The physical accepts of ultrasonic are provided by cavitation of the solution. Cavitation is formation of the submicroscopic voids due to shearing of fluid medium, by the alternating pressure of the sound waves [35]. As successive waves pass along the root canal system, the acrostic shearing effect develops an enlarged Bubble that grows until implosion occurs. The implosion effect creates a void that is filled with the surrounding solution under extreme hydro dynamic pressure which causes radiating shockwaves. The effect can rupture a cell wall of the microorganism present inside the root canal and clean the space by the mechanism of irregular agitation. Along with cavitation, there is also an increase in local temperature with accompanying pressure changes. This action enables bactericidal irrigant solutions to penetrate the cells rapidly and enhances the chemical effect of the solution. The biological action of ultrasonics includes the release of active radicals, oxidation, the gradation of molecules, somatic distractions, and increased cell wall permeability [36]. This is how the ultrasonic helps an irrigant with a bactericidal agent to clean and disinfect the root canal system.

Effects of lasers on increasing efficacy of naocl

Removal of the smear layer and disinfection of root canals are the primary objectives of the root canal cleaning procedure [37]. To achieve this objcetive lasers were introduced into the field of dentistry. Today, the use of lasers to remove the smear layers and to disinfect root canals has greatly developed (38). The dental lasers commonly used today are Erbium, Nd:YAG,Diode and Co_2, which had been used for debris and smear removal from the canals. Each type of lasers has specific biological effects and different procedures are associated with them. Er:YAG is the most appropriate laser for intra canal debris and smear removal used in the dentistry . In addition to that different laser wavelengths have been used directly or as an adjunctive to disinfect canals [39].Lasers penetrate secondary canal and lateral canal where the actual mechanical instrumentation cannot go and it also reduces the microorganism present .Because of the complex structure of the root canal , the complete elimination of bacteria from the root canal space is a major challenge [40]. The present treatment protocol includes the mechanical cleaning of root canal space followed by chemical irrigation and then root canal sealing. During endodontic procedure it's highly possible to regain infection because of the presence of a smear layer which leads to the inactivation of the irrigating substance and failure of the endodontic treatment [41]. Photodynamic theory (PTT) has been first introduced for elimination of cancer cells and treatment of cancer and lately innovative methods have been developed for disinfecting root canal. Photodynamic therapy works on the principle of activation of the photosentising molecule attached to the bacterial or fungal membrane with light of an appropriate wavelength. This Photo activation of a photosensitising molecule in the presence of oxygen produces highly reactive oxygen species such as singlet oxygen superoxide, hydroxyl radicals that destroy the microorganisms [42]. Low power lasers are the most frequently used as a light source because their wavelength is specific for activation of photosensitizers in PDT. The laser energy causes cell dissolution or destruction by initiating specific light induced chemical reaction in the target tissues [43]. During the usage, the direct radiation with the optic fibre is placed between the root canal to the total lenght , permitted in emitting light at the tip and from lateral side, thus leading to the even light distribution for disinfection effect both vertically and horizontally. PTT results in better reduction of pathogens in a shorter period than the conventional one [44].

Effects of sonic devices on increasing the efficiency of Naocl

There are several limitations that have been identified with the use of ultrasonics. One among them is the wall contact with the oscillating instrument dampens the energy and constrains the file movement and therefore ultrasonic devices oscillate freely in the curved canals. Even in the straight root canals an ultrasonic instrument meets the wall during at least 20% of the working time. Moreover, ultrasonic devices have noncutting edges which are made of metal with the high risk of changing root canal morphology [45]. In order to avoid damage caused by the ultrasonic activation, sonic irrigation with non-cutting edges are prefered. These sonic scalers convert high frequency air pressure into high frequency sound waves. Their frequencies range from 2500-7000 cps. The sonic device is composed of a handpiece and interchangeable scaling tip which is driven by the compressed air. Sonic units use a high or low speed air source from the dental unit [46]. Water is delivered via the same tube which used to deliver water to a dental handpiece. Sonic scaler tips are universal with large diameter tips in it. A sonic scaler tip works in an elliptical or orbital stroke pattern. This stroke pattern allows the instrument to be adapted to all tooth surfaces.The types of sonic devices used are rispisonic file and endo activator. Among these devices, the EndoActivator device appears to be the best documented system [47]. The principle of sonic devices is the usage of polyamide tip to activate the solution which prevents the active cutting of the root canal walls or opening of the apical constriction. Passive sonic activation at low frequency is inferior to passive ultrasonic irrigation (PUI) with respect to bringing irrigation solution to the apex in variously tapered and curved canals [48]. The maximum frequency of the sonic irrigation system used in the root canal is 190 Hz. A novel sonic activation device has been developed that can be coupled to an air scaler that operates at 6000 Hz [49]. Passive sonic irrigation at 6000 Hz performs equal to or better than passive ultrasonic irrigation.

Effects of buffering on increasing the efficiency of naocl

Most endodontists use commercially available bleach (5.25% of Naocl) to irrigate the root canals or sometimes diluted with water or saline solution. The pH of unbuffered hypochlorite is 12, and at 5.25%, it is very hypertonic [50]. Although this solution is quite safe for household use,the concentrated unbuffered sodium hypochlorite is problematic in dentistry. Serious incidents have occurred when concentrated hypochlorite solution was introduced into the periapical tissues during the endodontic irrigation [51]. The solution originally used by Dakin was 0.5% sodium hypochlorite buffered with sodium bicarbonate to a pH of 9. It was found to be more aggressive on necrotic tissues than the vital tissues. Indeed 0.5% buffered sodium hypochlorite has a considerable toxicity compared with commercially available unbuffered 5.25% NaOCl , but the antimicrobial effect is maintained [52]. The Dakin's solution (dilute solution of NaOCl) was preferable over the unbuffered bleach as an endodontic irrigation. Yet, neither the aggressiveness of tissues nor the antimicrobial potential in root canals has ever been directly assessed with Dakin's solution or unbuffered sodium hypochlorite [53]. The buffering effects of sodium hypochlorite solutions is defined as the effectiveness in dissolving the decayed connective tissue and the aggressiveness on the fresh mucosa. NaOCl dissociates in water to Na+andOCl-/HOCl (hypochlorous acid) [54]. The pKa value of hypochlorite is 7.6. This means that at the pH of unbuffered hypochlorite and Dakin's solution, free available chlorine (OCl^-+HOCl) exists almost entirely as OCl^-. However, it has been clearly demonstrated that HOCl is the most bactericidal form of the molecule [55]. Therefore, buffering action of sodium hypochlorite can be beneficial only at acidic pH.

Root canal instrumentation

The ideal objective of instrumentation of the root canal is to clean and shape canals with minimal dentin removal and no transportation of the apical foramen. The transportation means the undesirable, unwanted eccentric and excessive removal of root dentin surrounding the original canal [56]. The purpose of instrumentation is the mechanical debridement of the root canal system and the creation of a space for delivery of antimicrobial substances that are the intra canal medicaments.Moreover,a well cleaned and shaped root canal space allows for the proper tight placement of root canal filling (obturation) and prevents the growth of microorganism within the canal [57]. Since this mechanical instrumentation has more disadvantages there are measures taken to improve instrumentation such as vacuum devices and hypochlorite perfusion of the root canal system. First, there is the risk of instrument separation within the canal and preparation errors [58]. The infected non-vital teeth with periapical radiolucency such as apical periodontitis, radicular cysts and technical complications such as perforations into the periodontal ligament, instrument fractures, and the inability to reach the apical portion of the root canal section by instrumentation have a significant negative impact on treatment outcome [59]. Secondly, a smear layer which is produced on the instrumental canal wall is the combination of both organic and inorganic materials which include debris, pulp remnants etc [60]. This deposit helps in the penetration of the bacteria which leads to the formation of biofilms that are adhering to root canal walls. Furthermore, this smear layer interferes with the adaptation of root canal sealers to dentin walls, and therefore result in microleakage. Third, mechanical instrumentation of the root canal space either removes the microorganism from the infected canal, nor the formation of a smear layer [61]. With both current instruments such as nickel titanium and stainless steel, almost half of the root canal walls are left unprepared.

Effect of heating on increasing efficiency of NaOCl

The one of the modifications to improve the effectiveness of sodium hypochlorite in the root canal system is by increasing the temperature of low-concentration NaOCl solutions. By increasing the temperature of NaOCl it facilitates the effectiveness of tissue-dissolution capacity [62]. Moreover, the heated hypochlorite solution of NaOCl has better ability in removing the organic debris from dentine shavings more efficiently than unheated solution [63]. Before 1936, the effect of NaOCl temperature on Mycobacterium tuberculosis survival was demonstrated. By numerous experiments, bactericidal rates of sodium hypochlorite solutions are more than doubled for each 5°C rise in temperature in the range of 5-60°C [64]. The capacity of 1% NaOCl at 45°C is capable of dissolving the human dental pulp was found to be equal to that of a 5.25% solution at 20°C and the short-term efficacy in the root canal system, the systemic toxicity of pre heated NaOClirrigants should be lower than the one of the more concentrated non-heated solutions as the temperature equilibrium is reached relatively quickly.

Silver nanoparticles incorporated as irrigants

Root canal disinfection includes mechanical cleaning and irrigation using solutions with antimicrobial potential [65]. Sodium hypochlorite is the commonly used root canal irrigant, because of its antimicrobial efficacy and tissue dissolution properties. However, the direct application of sodium hypochlorite on the patient can be harmful because it is associated with cellular destruction of the tissues. To improve the characteristics of antibacterial agents used in root canal treatment, innovative antimicrobial delivery systems have been developed, such as nanoparticles [66]. Nanomaterials are defined as particles with dimensions of 1–100 nm, presenting small sizes, large surface/area mass ratio and increased chemical reactivity. The greater surface area and charge density of nanoparticles enable them to interact to a greater extent with the negatively charged surface of bacterial cells, resulting in enhanced antimicrobial activity thus, they have been applied in many health cares fields [67]. Silver nanoparticles have the ability to attach to the microorganism and penetrate into the cell walls of both gram positive and gram negative bacteria, disturbing cell function by releasing silver ions, thus they are used for the treatment and prevention of drug resistant microorganisms and inhibition of the biofilm formation .In dental practice, silver nanoparticles have been used in several forms due to their antimicrobial effects, such as incorporation into bonding agents and restorative materials to prevent biofilm formation and reduce caries, orthodontic adhesives and into implant materials [68]. Nanoparticles introduced in the endodontic field as the attempt to reduce E. faecalis adherence to dentine, eliminate biofilms and enhance root canal disinfection of dentinal tubules [69]. Silver nanoparticles also used as endodontic irrigants and intra- canal medicaments, added to calcium hydroxide as a vehicle incorporated into endodontic filling materials and calcium silicate cements and with lower levels of cytotoxicity [70].

Naocl along with plant extract

NAOCL is a widely used irrigant across the world and considered as the gold standard root canal irrigant. Despite these properties the efficacy of NAOCL can be improved by adding some more alternatives. One such alternative is the addition of herbal extracts, plant extracts. Herbal medicines have been used since ancient times [71]. Anciently they were used to relieve gum related problems, toothache, bad breath etc. [72]. photo dentistry is emerging branch off dentistry which uses the medicine plants and the exact which are natural in origin as used as medicine or health promitency agent in dentistry [73]. The medical plant which can be used as an endodontic irrigants include green tea, Triphala, mustard, Neem extract, Indian mulberry, cucuma longa etc. These have therapeutic properties like antibacterial, anti-inflammatory, anti-cariogenic anti plaque, anti-inflammatory and cytostatic properties due to the active phytochemical compounds which are found in these medicinal plants [74]. Herbal extracts are effective in use because they interact with specific receptors in the body and one pharmacodynamic sense, the patency of the extract used might vary, so the herbal extracts which are selected have the optimal concentration [75].

LIMITATIONS

Only there are limited studies regarding the modifications and methods to improve the efficiency of NaOCL as root canal irrigant. More studies must be conducted invitro and invivo before we use it clinically.

FUTURE SCOPE

There should be more upcoming studies regarding the modification and methods to improve the efficiency of NaOCl as root canal irrigant. This incresed efficiency of NaOCl will lead to the less failure of root canal treatment. These promising modifications and methods to increase the efficiency of NaOCl have more potential and clinical applications.

CONCLUSION

Within the limitations of this review it can be concluded that sodium hypochlorite is one of the most widely used irrigant with antibacterial and tissue dissolving properties, but the major drawback is its cytotoxicity at high concentrations. To avoid this, we can use sodium hypochlorite with lesser concentrations along with various irrigant activation methods like heating, increasing the ph, sonics, ultrasonics and lasers.

CONFLICT OF INTEREST

Conflict of interest declared as none.

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