

# Does increase in temperature of sodium hypochlorite have enhanced antimicrobial efficacy and tissue dissolution property? – A systematic review and meta-regression

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## Abstract

**Objectives:** The objective of this study was to analyze the available evidence on the performance of increase in temperature of sodium hypochlorite on its antimicrobial efficacy and tissue dissolution property.

**Materials and Methods:** The study was conducted according to PRISMA guidelines, and a modified Joanna Briggs Institute (JBI) tool was used for quality assessment of the included studies. Two reviewers independently performed an electronic search in four databases along with the reference lists of the included articles.

**Results:** This systematic review included a total of 12 studies: antimicrobial efficacy ( $n = 6$ ) and tissue dissolution property ( $n = 6$ ). For the studies that were chosen, the overall risk of bias was moderate. Quantitative assessment through meta-regression was performed for tissue dissolution property. Low-concentration sodium hypochlorite irrigant ( $\leq 3\%$ ) shows a 0.13-unit times increase in tissue dissolution ability with a degree rise in temperature although not statistically significant.

**Conclusion:** Due to inconsistency in the study parameters, results pertaining to the exclusive effect of increase in the temperature of sodium hypochlorite remain inconclusive.

**Keywords:** Antimicrobial efficacy; irrigant; sodium hypochlorite; temperature; tissue dissolution

## INTRODUCTION

The ultimate goal of endodontic treatment is to achieve a complete reduction or elimination of pathogens from the root canal space, removal of pulpal remnants, and prevention of any sort of recontamination after the treatment. Pulp tissue remnants prevent complete three-dimensional obturation of the root canal and serve as a potential site for the growth of bacteria. In the literature, there is no solid

evidence that mechanical instrumentation alone is sufficient for total root canal disinfection and debridement.<sup>[1]</sup> Because of the abovementioned shortcomings, it was concluded that using irrigating solutions was more vital to reach the intricate anatomy of root canal systems, such as the fins, isthmus, and lateral canals.<sup>[2]</sup> Root canal infections are polymicrobial in nature.<sup>[3,4]</sup> Among endodontic pathogens, *Enterococcus faecalis*, a Gram-positive facultative anaerobic bacterium, is the most tolerant species found in contaminated root canals and is frequently referred to as a therapy-resistant pathogen, and thus, the authors claim that elimination of *E. faecalis* from root canals could be the pinnacle of endodontic achievement in the future.<sup>[3,5]</sup> As an irrigant during endodontic treatment, sodium hypochlorite

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shows exceptional qualities. The antibacterial efficacy and tissue-dissolving capabilities of hypochlorite solutions are dependent on the concentration.<sup>[6]</sup> When increased concentration of hypochlorite solution is accidentally driven into the periapical tissues, or put in contact with the patient's skin through the leaky rubber dam can result in serious accidents.<sup>[7]</sup> As a result, simply increasing hypochlorite concentrations to make them more efficacious may not be a good option. Siqueira *et al.*, on evaluating the antibacterial efficacy of various concentrations of NaOCl irrigants, concluded that to compensate for the negative effects of high concentration, a low concentration of NaOCl should be used in greater volume and at more often intervals.<sup>[8]</sup> Irrigants can also be activated via a variety of methods, such as manual activation of irrigants using GP, file agitation, endodontic microbrushes, pressure alteration devices, ultrasonic activation, subsonic/sonic agitation, laser activation, and multisonic activation, which improves the desirable properties of sodium hypochlorite.<sup>[9]</sup> Alternatively, research on the effectiveness of a low-concentration hypochlorite irrigant with increase in temperature is blooming in the field of endodontics. Temperature activation has shown to improve the chemical reaction rates and thus can amplify their immediate tissue-dissolution capacity and antimicrobial effect which is the primary goal of root canal therapy.<sup>[10]</sup> Decision-making during contemporary endodontic practices should always be based on high-quality evidence provided by a systematic review. Owing to the lack of conclusive evidence on the role played by the increase in temperature of a sodium hypochlorite irrigant following root canal treatment, this systematic review was undertaken to determine the influence of the same.

## MATERIALS AND METHODS

### Research question

Does increase in temperature of a sodium hypochlorite root canal irrigant bring about significant improvement in its antimicrobial and tissue dissolution property?

In order to identify cross-sectional studies based on the aspects of the PICO(S) question, the following eligibility criteria for the terminology used in the research were defined:

1. Population: Extracted human/bovine tooth and tissue samples (as our outcome measured both antimicrobial efficacy and tissue dissolution property)
2. Intervention: Increase in temperature of sodium hypochlorite
3. Comparison: Room temperature sodium hypochlorite
4. Outcome: Antimicrobial efficacy and tissue dissolution property
5. Study: *In vitro* studies.

### Literature search strategy

The suggested PRISMA guidelines for performing systematic reviews and meta-analyses were used ([http://](http://www.prisma-statement.org)

[www.prisma-statement.org](http://www.prisma-statement.org)). An extensive literature search was conducted in the following online databases from all articles published until the end of December 2022: PubMed, Lilacs, Cochrane Library, EBSCOhost, and Google Scholar. In addition, the *Journal of Endodontics*, *International Endodontic Journal*, *Journal of Dentistry*, and *Journal of Conservative Dentistry* were handsearched. The following keywords with Boolean operators were used for search in electronic databases [Table 1]. In addition, the references given in the retrieved full-text articles were checked to see whether there were any more publications that were relevant.

### Eligibility criteria

The exclusion criteria were applied as follows:

1. Studies not done on human tooth/tissue or bovine samples
2. Studies without full texts and not mentioning the temperature range
3. Studies not in the English language
4. This review did not contain any descriptive studies, letters to the editor, and case reports.

**Table 1: Search Strategies and Electronic Databases Searched**

Mesh Terms
<p><b>PubMed: 189</b></p> <p>((((( ((((((((((effect) OR (effects)) OR (antibacterial)) OR (antimicrobial)) OR (bactericidal)) OR (efficacy) OR (efficiency)) OR (action)) OR (dissolution))) AND (((temperature) OR (increased temperature) OR (altered temperature)))))) AND (( sodium hypochlorite))) AND (((((((((((biofilm) OR (oral biofilm)) OR (root biofilm)) OR (human tooth)) OR (human teeth)) OR (bovine tooth)) OR (bovine teeth)) OR (dentin disc)) OR (bovine disc)) OR (human pulp tissue)) OR (bovine tissue)) OR (root dentin))</p>
<p><b>Cochrane: 33</b></p> <p>#1 biofilm OR oral biofilm OR root biofilm OR human tooth OR human teeth OR bovine tooth OR bovine teeth OR dentin disc OR bovine disc OR human pulp tissue OR bovine tissue OR root dentin                      #2 temperature OR increased temperature OR altered temperature                      #3 sodium hypochlorite OR hypochlorite                      #4 effect OR effects OR antibacterial OR antimicrobial OR bactericidal OR efficacy OR efficiency OR action OR dissolution                      #5 ( #1 and #2 and #3 and #4 )</p>
<p><b>Lilacs: 53</b></p> <p>Biofilm OR oral biofilm OR root biofilm OR human tooth OR human teeth OR bovine tooth OR bovine teeth OR dentin disc OR bovine disc OR human pulp tissue OR bovine tissue OR root dentin and temperature OR increased temperature OR altered temperature and sodium hypochlorite or hypochlorite and effects OR antimicrobial OR antibacterial OR bactericidal OR efficacy OR efficiency OR action OR dissolution</p>
<p><b>Ebsco host: 9</b></p> <p>S1 antibacterial OR antimicrobial OR bactericidal OR dissolution                      S2 temperature OR increased temperature OR altered temperature OR activated                      S3 sodium hypochlorite                      S4 biofilm OR human tooth OR bovine tooth OR dentin disc OR root dentin OR human pulp tissue OR bovine tissue                      S5 ( S1 AND S2 AND S3 AND S4 )</p>

## Data extraction

The two reviewers reviewed selected articles individually, and the following details associated with the study were acquired through customized extraction forms: year of publication and authors, type of sample, instrumentation, irrigation protocol (concentration, temperature, volume, and contact time), type of microbial specimens, method of analysis, and conclusion. Disputes between the reviewers were settled by a third reviewer's input.

## Qualitative assessment

The Joanna Briggs Institute tool<sup>[11]</sup> critical assessment checklist for nonrandomized experimental studies was thoroughly analyzed and adapted to incorporate all essential topics related to the methodology based on the PICOS structure and research question. As a result, six criteria were devised. The checklist evaluates methodological aspects through questions answered as “yes,” “no,” or “unclear.” The answer “No” was given when the included study failed to meet the given criteria, “unclear” when not mentioned clearly in detail and when the study answered the criteria, “yes” was considered. Two authors independently graded the articles, and in the event of disagreement, a third author assisted in reaching a consensus.

## Quantitative assessment

Quantitative antimicrobial efficacy analysis was not done due to significant heterogeneity in the included studies. For the pulp dissolution property, a quantitative synthesis of the results was performed. To investigate the potential sources of variability between studies, meta-regression analysis and subgroup analysis were used. The statistical analysis was carried out using the STATA version 16 software. Quantitative analysis was done with this version software tool. A funnel plot was utilized to see if there was any possibility of publication bias.

## RESULTS

### Search results

Figure 1 shows a flowchart depicting the selection procedure. With the defined criteria, electronic database searches via PubMed, Cochrane, Lilacs, and EBSCOhost retrieved 284 articles. Additionally, 10 articles were retrieved from Google Scholar and other journals were handsearched. After the process of duplicate removal, 281 articles were identified, of which 20 articles fulfilled the initial selection criteria with relevance to title and abstracts. After full-text screening, 9 articles were excluded<sup>[10,12-19]</sup> [Table S1]. The qualitative review finally contained papers that met the eligibility requirements (antimicrobial efficacy =6 and tissue dissolution property =6)<sup>[20-31]</sup> [Table 2.1 and 2.2].

## Study characteristics

Differences in the following factors were noticed in the included studies: (a) type of sample used, (b) irrigation (concentration, volume, and duration), (c) temperature of the irrigant, and (d) microbial specimens assessed (*Streptococcus faecalis*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *E. faecalis*, *Candida albicans*, and biofilm). Furthermore, considerable heterogeneity in the conclusions claimed by the authors in both antimicrobial efficacy and tissue dissolution capacity was analyzed and tabulated. The general characteristics of the included studies are summarized in Table 2.1 and 2.2.

## Risk of bias assessment

A total of 12 articles including the primary and secondary outcomes were evaluated for the possibility of bias [Figures 2 and 3]. Sample size calculation was not performed in any of the included studies. In three of the included studies in tissue dissolution property (Cunningham *et al.*,<sup>[26]</sup> George Sirtes *et al.*,<sup>[27]</sup> and Giampiero Rossi-Fedele *et al.*<sup>[28]</sup>), specimen standardization was not mentioned, and in one of the included studies (Cunningham *et al.*<sup>[26]</sup>), the control group was not given. One study assessing antimicrobial efficacy did not mention the pre- and postoutcome measurement (Giardino *et al.*<sup>[23]</sup>). Contemplating the results, the risk of bias is moderate since the majority of the articles from the research have a low or unknown risk of bias.

## Quantitative analysis

### Statistical analysis

To evaluate potential sources of heterogeneity between research analyzing the tissue-dissolving property, meta-regression was performed. Two studies that assessed the tissue dissolution ability of sodium hypochlorite below 3% concentration at or above the body temperature were taken into consideration for quantitative analysis (Cunningham *et al.*<sup>[26]</sup> and Stojicic *et al.*<sup>[29]</sup>). The effect magnitude was measured using standardized mean differences. The random effect model was preferred due to heterogeneity in the included studies ( $I^2 > 50\%$ ). The pooled effect for tissue dissolution was 6.88% with significant heterogeneity between studies ( $I^2 = 97.76\%$ ) [Figure 4]. Meta-regression with temperature showed that with a degree rise in temperature, there is a 0.13-unit times increase in tissue dissolution property with  $P < 0.05$  and hence not statistically significant [Table 3]. For the detection of publication bias, effect estimates are plotted against their standard errors in a funnel diagram, created using STATA version 16 software. Quantitative analysis was done with this version software tool. The vertical axis was used to illustrate the intervention effect's standard error. Due to the asymmetry in the summary estimate of the analysis, the presence of publication bias is evident in the studies included in this review [Figure 5].

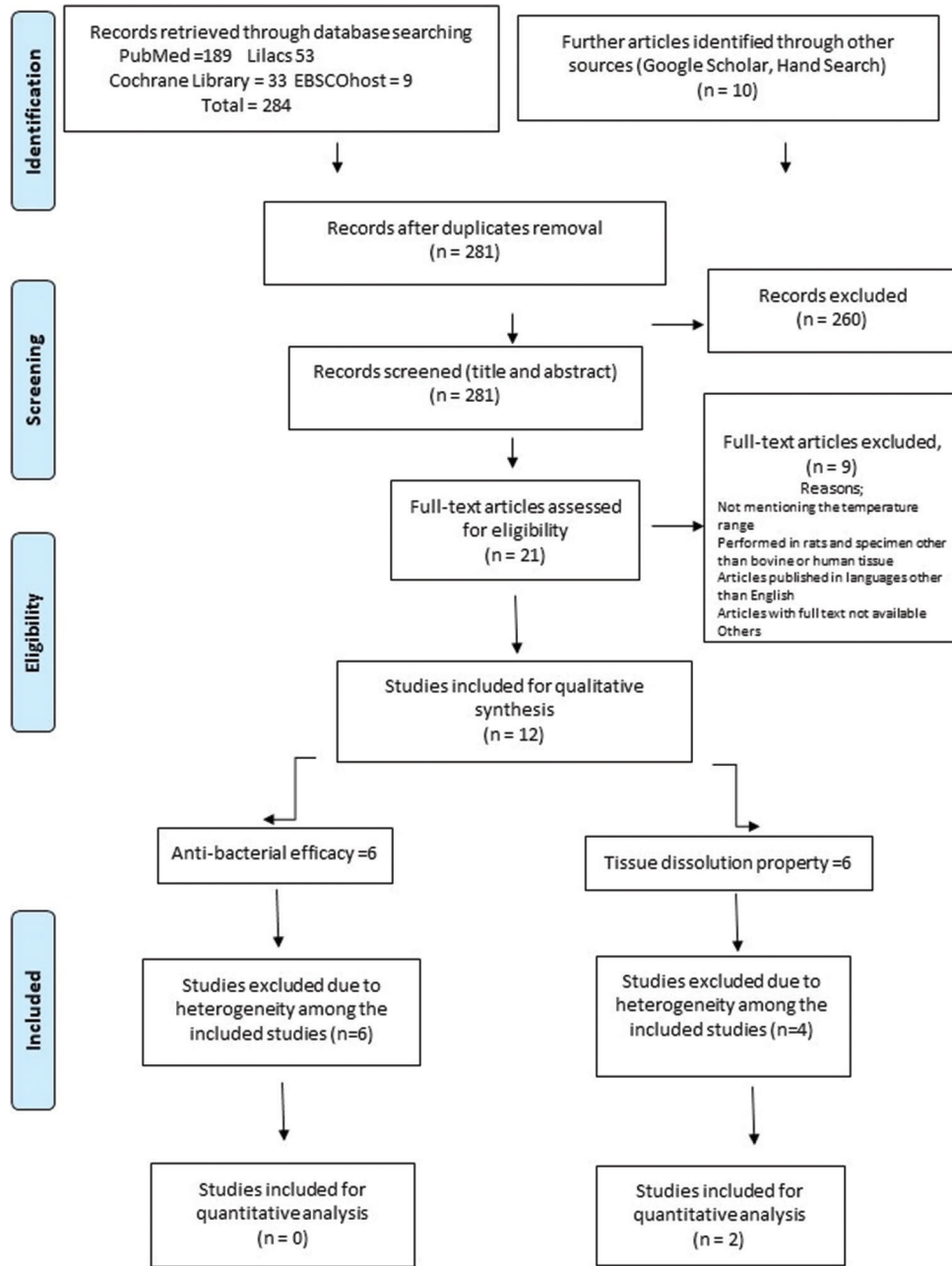


Figure 1: PRISMA flowchart

## DISCUSSION

The prime objective of root canal debridement is just to eradicate all pathogens and their by-products, including any hard tissue debris that has accumulated.<sup>[32-37]</sup> Previous studies have stated that around 35% of the canal wall surfaces are left unprepared by rotary instruments during mechanical preparation.<sup>[38,39]</sup> The untouched area will contain debris and tissue remnants including bacterial cells which clearly explains that the conventional irrigation of NaOCl irrigant would not be sufficient to clean these areas. To overcome the above lacunae, some source of activation

will be required to enhance the irrigant's activity. The saponification and chloramination processes which take place largely on the surface cause the organic tissue to liquefy.<sup>[6]</sup> At the same time, the NaOCl molecules implicated in the reactions are depleted, resulting in a decrease in local activity. For improved efficacy, it is also necessary to maintain chlorine content and deliver active hypochlorite to the area, as well as to eliminate the leftovers of dissolved tissue.<sup>[40]</sup>

The review began with collecting evidence on *in vivo* studies, but there were no clinical studies showing a direct result in relation to irrigant activation with a heat source.

**Table 2.1: General Characteristics of Included Studies – Antimicrobial Efficacy**

Author	Samples	Instrumentation	Irrigating Solution	Microbial Specimens	Temp	Microbial Analysis	Conclusion
Raphael <i>et al.</i> , 1981 <sup>[20]</sup>	390 single rooted teeth <i>n</i> =30 (control group)	K files, H files & GG drills	5.25% NaOCl solution. 5ml 1 min	Strep. Faecalis Staph. Aureus Ps. Aeruginosa	21°C, 29°C, and 37°C	Culture	Direct relationship does not exist between the bactericidal efficiency and the temperature of the NaOCl solution. Pseudomonas aeruginosa was particularly difficult to eliminate.
Gulsahi <i>et al.</i> , 2014 <sup>[21]</sup>	115 single rooted teeth <i>n</i> =3 (control group)	GG drills	2.5% NaOCl solution. 3ml (30 sec, 1 min and 5 mins)	E. faecalis & C. albicans	25°C and 37°C	SEM & CFU	To eradicate E. faecalis, the duration of NaOCl irrigation was more beneficial than the temperature, while the pre-warmed NaOCl solution to 37°C improved its action on C.albicans within 5 minutes .
Del Carpio-Perochena <i>et al.</i> , 2015 <sup>[22]</sup>	40 dentin bovine blocks		1%, 2.5% NaOCl solution. 2ml (5&20 mins)	Biofilm	22°C and 37°C	Total biovolume & % viable cells CLSM	The contact time and concentration of NaOCl have a greater impact on antimicrobial activity than the temperature.
Giardino <i>et al.</i> , 2016 <sup>[23]</sup>	170 dentin blocks – bovine <i>n</i> =20 (control)		5.25% NaOCl solution. 3ml ,27G syringe until dentinal tubules were filled. 10 mins	E. faecalis	20°C and 45°C	CFU	Heated irrigant solutions ChlorXtra and Hypo clean improve the antimicrobial property of NaOCl solutions in dentin blocks of bovine roots.
Ghassan Yared <i>et al.</i> , 2020 <sup>[24]</sup>	88 single rooted mandibular premolars <i>n</i> =8(control)	Reciproc 50	5.25% NaOCl 9ml 3 mins	E. faecalis	System B elements heat source at 150°C with heat carrier was used.	culture	Intracanal warming of 5.25 percent NaOCl solution could be used as a substitute to standard irrigation treatments with sonic or ultrasonic agitation as infection clearance is more effective.
Rathore <i>et al.</i> , 2020 <sup>[25]</sup>	80 single rooted, single canal mandibular premolars	Protaper rotary system upto F3	5% NaOCl 5 mins 5ml	E.faecalis	60°C Preheated 180°C intracanal heated using system B source Laser heated	CFU	When compared to extra canal heated (60°) and room temperature NaOCl solution, intracanal heating using laser and other heat sources enhanced antimicrobial efficacy.

Furthermore, clinical studies have not been performed as the irrigant's temperature cannot be maintained within the root canal. There were few *in vitro* studies that have given a positive result by increasing the temperature of irrigant, and it should be emphasized that these tests were carried out in a lab setting, and the results may not be immediately applicable to clinical conditions. Furthermore, heat transfer via radicular dentin may imperil the surrounding periodontal tissues.<sup>[41]</sup> However, available evidence suggests that irrigating fluids used in clinical settings would establish a thermal equilibrium quite quickly.<sup>[14,42]</sup> As a result, concentrated NaOCl irrigants will be more hazardous than warmed NaOCl irrigants at lower concentrations. Human dentin also has a low thermal conductivity and is regarded as an excellent insulator.<sup>[43,44]</sup> The thermal conducting property along with surrounding vascularity aids to disperse the heat rise on the radicular surface, which is called heat sink capacity.<sup>[2]</sup> As a result, it was decided to conduct a systematic review by

analyzing data from several *in vitro* experiments. Considering both the primary and secondary endodontic infections, studies with different microorganisms were considered for this review. However, in this review, the studies that evaluate the antimicrobial effect and tissue dissolution property with increase in temperature of sodium hypochlorite were considered.

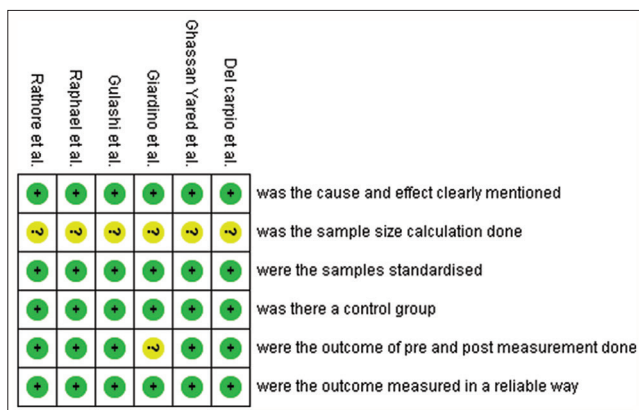
### Critical appraisal of the included studies in primary outcome – antimicrobial efficacy Type of teeth

In four of the included studies, single-rooted teeth were included, but there was no mention of the type of teeth, age of the teeth, and whether they were maxillary or mandibular teeth.<sup>[20,21,24,25]</sup> Two more studies used bovine dentin blocks as their study sample, though they remain comparable to human dentin, the results might differ if performed on an extracted tooth.<sup>[22,23]</sup>



**Table 2.2: General Characteristics of Included Studies – Tissue Dissolution Property**

Author	Samples	Temperature	Concentration	Time Interval	Conclusion
Cunningham <i>et al.</i> ,1980 <sup>[26]</sup>	Bovine tendon collagen	21°C and 37°C	2.5% and 5% sodium hypochlorite	4, 8 and 12 min	In a 12-minute reaction period at 37°C, the 2.6 percent solution dissolved a greater proportion of collagen.
Sirtes <i>et al.</i> ,2005 <sup>[27]</sup>	22 teeth (10 3 <sup>rd</sup> molars & 12 premolars)	20°C, 45°C and 60°C	1% & 5.25%	1 min	1% at 45°C is equal to 5.25% at 20°C. 60°C was more effective than both
Giampiero Rossi-Fedele <i>et al.</i> ,2008 <sup>[28]</sup>	20 standardized pieces of pulp tissue extracted from bovine canines and incisors.	20.5°C- distilled water, 45°C, 60°C, 75°C	4% sodium hypochlorite	From the moment it came into contact with the solution, the time was recorded in minutes.	The speed of dissolving of bovine pulp was increased when the temperature of NaOCl was raised to around 45°C. Increasing the temperature to 60°C did not boost the dissolving rate any further.
Stojicic <i>et al.</i> ,2010 <sup>[29]</sup>	Bovine muscle tissue	(37°C and 45°C; ) With and without ultrasonic and sonic agitation	1%, 2%, 4% and 5.8% - 5ml	5 min	Higher concentration – increased tissue dissolution; high temperature and activation – enhances the efficacy of the NaOCl irrigant.
Markus Haapasalo <i>et al.</i> ,2014 <sup>[30]</sup>	Fresh meat from the same bovine specimen.	21°C, 40°C	0.5%, 3%, and 6% sodium hypochlorite	5 mins	As the temperature of the NaOCl solution was increased the rate of tissue dissolution increased ( $P < .05$ ). The Multisonic Ultracleaning System provided the quickest rate of tissue dissolution.
İhsan Furkan Ertuğrul <i>et al.</i> ,2015 <sup>[31]</sup>	154 bovine muscle tissues	25°C, 45°C	5.25% sodium hypochlorite	5 mins	The tissue-dissolving ability of the solution can be improved by activating NaOCl with micro-electric current. Furthermore, to generate a synergistic impact of NaOCl on tissue disintegration, this procedure can be supplemented with other techniques, such as heating.



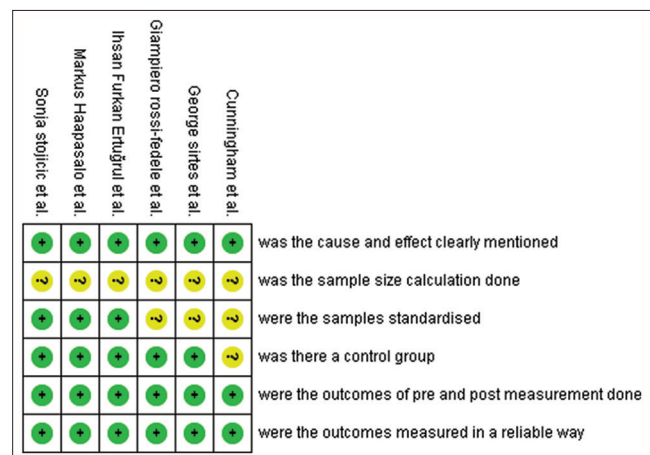
**Figure 2:** Risk of bias summary – antimicrobial efficacy (review author’s judgments about each risk of bias domain for the included studies)

**Instrumentation**

The instrumentation size and taper play a vital role in the reduction of microbial load. Only four studies have mentioned the kind of instrumentation followed: Hedstroem file, Reciproc,<sup>[20,24]</sup> Gates Glidden drills,<sup>[21]</sup> and ProTaper rotary system.<sup>[25]</sup> Other studies make no mention about the instrumentation of the samples used. Overall, there is not much concurrence between the studies.

**Irrigation protocol**

Among the included studies, there were variations which were observed in relation to concentration, volume, and contact time which has a greater influence on the result.<sup>[20,21,23-25]</sup> As the main aspect of the review is about the



**Figure 3:** Risk of bias summary – tissue dissolution property (review author’s judgments about each risk of bias domain for the included studies)

irrigant activity, these characteristics have to be considered, and contemplating all studies, it shows a greater amount of heterogenicity.

**Antimicrobial assessment**

The included studies used different evaluation methods for antimicrobial assessment. The organisms tested differ to a great extent in all studies, hence quantitatively assessing the antimicrobial efficacy from the included articles is difficult.

The presence of mean and standard deviation is seen to be critical for quantitative analysis of the research presented.

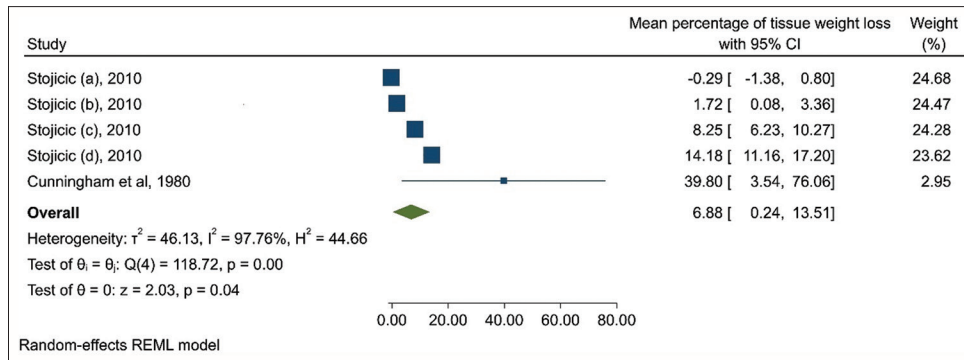


Figure 4: Forest plot – meta-regression model. CI: Confidence interval

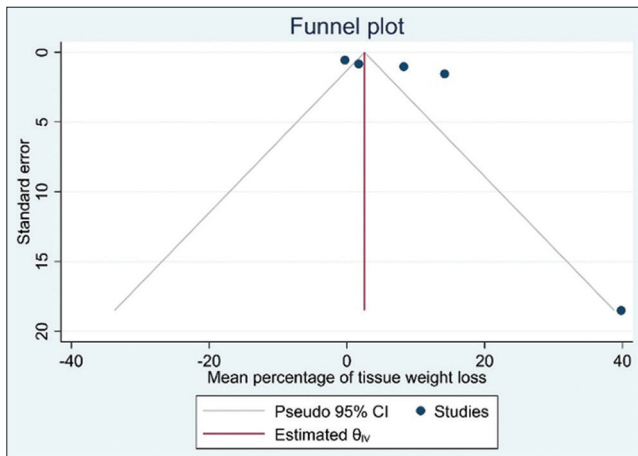


Figure 5: Funnel plot. CI: Confidence interval

Table 3: Meta-regression with temperature

_meta_es	Coefficient	SE	Z	P> z	95% CI
TempC	0.1271841	1.050102	0.12	0.904	-1.930978 -2.185346
_cons	2.155886	43.05756	0.05	0.960	-82.23538 -86.54715

Test of residual homogeneity:  $Q_{res} = \chi^2(3) = 108.02$   $P > Q_{res} = 0.0000$ .  
 SE: Standard error, CI: Confidence interval

Out of five studies in primary outcome, only three studies<sup>[23-25]</sup> mentioned the mean and standard deviation. Studies have used different methods such as System B Heat Source, hot water bath to increase the temperature of sodium hypochlorite solution. The method of evaluating the colony-forming units also differed in these three studies; thus, the quantitative analysis was not performed for the primary outcome. Analyzing the data given by the three studies which evaluated preheated sodium hypochlorite solution at 37°C did not prove to be more efficient in antibacterial property whereas the volume, concentration and the contact times significantly improved the performance.<sup>[20-22]</sup> Only three studies have been performed at a temperature above the body temperature. One study<sup>[23]</sup> that was performed by preheating NaOCl to 45°C with a concentration of 5.25% for 10 min has proven that the increase in temperature significantly eliminates

the *E. faecalis*, and in another study,<sup>[24]</sup> when a temperature of 150°C was achieved using a heat source and a carrier, the temperature on the radicular surface did not reach the point at which the periodontium could be injured, which is 47°C,<sup>[41]</sup> and this study concluded that intracanal heating of the irrigant increased antibacterial efficacy. Furthermore, the study by Rathore *et al.*<sup>[25]</sup> in 2020 has stated that intracanal heating to 180°C using System B Heat Source shows better antibacterial efficacy than preheated NaOCl at 60°C. Karates *et al.* (2021) stated that preheated NaOCl at 45°C does not provide any extra-antibacterial efficacy when compared to NaOCl at 25°C. This statement is contradictory because the concentration used was 1% with 1-min contact time which could greatly influence the results. The temperature of NaOCl used in the other three studies is lesser than the body temperature which may have influenced the results significantly.<sup>[20-22]</sup> Since the maximum tested temperature was at 37°C (body temperature) and only three studies were tested above the body temperature and showed positive results for the superior antibacterial property, it cannot be reported with great evidence that the increase in temperature shows the superior antibacterial property.

### Critical appraisal of the included studies in secondary outcome – tissue dissolution property

#### Type of sample

According to the literature evidence, the experimented study samples were porcine muscle tissue, rat connective tissue, rabbit liver, pig palatal mucosa which affects the credibility of the evidence obtained. Since bovine tissues are substantially larger than human pulps, they were utilized. Water makes up more than 90% of pulp tissue in general. The concentration and size of collagen in the pulp tissue of bovine animals and humans are different. According to Orłowski *et al.*, the concentration of collagen in bovine pulp is lower than in human pulp. The quantity of collagen fibers (type III) in pulp tissue of human premolar teeth, on the other hand, was comparable to that seen in bovine teeth. As a result, bovine pulp tissues are regarded almost similar to human pulp than other animal models despite

minor variances;<sup>[39]</sup> thus, one of the included studies used pulp tissue extracted from bovine incisors and canines. Three of the included studies in the systematic review used bovine muscle tissues,<sup>[29-31]</sup> and bovine collagen tendon was used in another included study.<sup>[26]</sup> The availability and simpler standardization of surface area of each specimen were the grounds for employing other tissues instead of human tooth pulp, but only three of the included studies standardized the initial mass, shape, and surface area of the specimen, and finally, one of the studies used human pulp tissue from 22 extracted teeth which included molars and premolars.<sup>[44]</sup>

### **Irrigation protocol**

The irrigant concentrations employed in the included experiments ranged from 1% to 6%. The volume of the irrigant used varied from 1 mL to 45 mL/min, and the contact time varied from 60 s to 12 min in the studies included. Collectively, there were variations in relation to concentration, volume, and contact time, which shows a greater amount of heterogeneity.

### **Temperature of the irrigant solution**

Temperature activation ranged from 37°C to 75°C in the included studies. All studies evaluated the solvent capability of NaOCl at a temperature above the body's temperature except for one.<sup>[26]</sup> It is important to maintain the temperature of the solution throughout the experiment; thus, the studies have mentioned the use of a thermometer to record the temperature.

### **The stability of sodium hypochlorite solution**

The ability of diluted sodium hypochlorite to dissolve soft tissue has been found to diminish.<sup>[16]</sup> The iodine/thiosulfate titration method was used in all of the included studies to verify the amount of active chlorine available. All of the included studies show good stability of available chlorine content for a span of time that is clinically relevant, which is a major factor to be satisfied to obtain an enhanced efficacy of the NaOCl solutions in clinical practice.

### **Tissue dissolution property assessment**

A predetermined time was standardized, and the weight of the samples was measured before and after exposure. Assessing the time and speed of tissue dissolution was the goal of one of the included studies, and hence, the weight of the tissue after treatment was not measured.<sup>[28]</sup>

### **Quantitative assessment of the included studies**

Quantitative synthesis was performed on secondary outcome (tissue dissolution property). Meta-analysis has been considered a dependable source of evidence for treatment efficacy in the field of health care. Nonetheless, it was not appropriate to reach conclusions from the pooled estimates of the treatment effect in the presence

of heterogeneity.<sup>[46]</sup> Meta-regression is a typical strategy in meta-analysis that uses the regression-based method to convey the influence of factors on research outcomes. We included studies at and above body ranges in our regression analysis with the low-concentration sodium hypochlorite irrigant ( $\leq 3\%$ ) and found that an increase in temperature was associated with increased percentage of tissue weight loss ( $P = 0.904$ ). There is a 0.13-unit times increase in tissue dissolution ability with a degree rise in temperature, which is not statistically significant.

In the absence of heterogeneity and bias, funnel plots are often funnel shaped and symmetrically centered around the analysis summary effect estimate, as imprecise and smaller studies depart further from the summary effect than precise and bigger research. Visual or analytical examination of the asymmetry of funnel plots is the most popular way for determining publication bias.<sup>[47]</sup> As a result, it can be seen that publication bias is present in the current study.

The limitations of this review are difference in the samples used in the included studies, various methods employed for heating of sodium hypochlorite irrigant with discrepancy in concentration, volume and duration of use, and dissimilar evaluation protocols. Hence, future studies with a standardization of all parameters of irrigation protocol are the need of the hour to reach a high-quality result.

## **CONCLUSION**

The included studies in our systematic review show that the duration, volume, concentration, and contact time along with the agitation of sodium hypochlorite solution greatly influences the efficacy of irrigant, and owing to inconsistency in the study parameters, results pertaining to the exclusive effect of increase in temperature of sodium hypochlorite still remain inconclusive. Considering the important factor of heat sink capacity, intracanal heating will provide desirable outcomes in antimicrobial efficacy and tissue dissolution property.

- a. Future studies should be performed with the use of low-concentration sodium hypochlorite solution at increased temperature which should be maintained above the body temperature to report conclusive evidence for better antimicrobial efficacy and tissue dissolution property
- b. Within the constraints of the current study, heat exhibited a beneficial synergistic effect on the tissue-dissolving characteristic of sodium hypochlorite.

### **Statement of clinical relevance**

- Intracanal heating of the low-concentration sodium hypochlorite irrigant above body temperature improved antimicrobial activity and tissue dissolution ability as compared to preheated counterparts



- Considering the important factor of heat sink capacity, it is critical to maintain an increased temperature inside the root canal as it attains an equilibrium state immediately.

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## SUPPLEMENTARY TABLE

**Table S1: Reasons for Excluding the Studies after Reading Full Text:**

Author/Year	Reasons for Exclusion
Cunningham <i>et al.</i> , 1980 <sup>[12]</sup>	Antibacterial efficacy was performed on wells and not on dentin samples
Woodmansey <i>et al.</i> , 2005 <sup>[10]</sup>	Full text not available
G.Cavalleri <i>et al.</i> , 1983 <sup>[13]</sup>	Article in Italian
Macedo R.G <i>et al.</i> , 2017 <sup>[14]</sup>	Antimicrobial efficacy was not evaluated
Diana dumitriu <i>et al.</i> , 2015 <sup>[15]</sup>	Reticulated and non-reticulated collagen matrices were mentioned but the specimen from which it was extracted was not mentioned
Abou-rass <i>et al.</i> , 1981 <sup>[16]</sup>	Specimens used were dermal connective tissues of rats
Massimo Amato <i>et al.</i> , 2018 <sup>[17]</sup>	Artificial canals with lateral canals simulated and the protocol followed varied from other experiments
G.Rossi Fedele <i>et al.</i> , 2014 <sup>[18]</sup>	Temperature is not mentioned
Iandalo <i>et al.</i> , 2019 <sup>[19]</sup>	Different concentrations of NaOCl were used but at one standard temperature (26°C)