Journal of Pharmaceutical Research International

32(17): 64-76, 2020; Article no.JPRI.59731
ISSN: 2456-9119
(Past name: British Journal of Pharmaceutical Research, Past ISSN: 2231-2919, NLM ID: 101631759)

Comparative Evaluation of the Antimicrobial Efficacy of Octenidine Dihydrochloride with Contemporary Root Canal Disinfectants: A Systematic Review

Rukhsaar Akbar Gulzar[1], P. Ajitha[1] and Haripriya Subbaiyan[1*]

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

Authors' contributions

This work was carried out in collaboration among all authors. Author RAG designed and managed the literature searches and also wrote the first draft of the manuscript. Authors PA and HS analysed the manuscript. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/JPRI/2020/v32i1730669
Editor(s):
(1) Mostafa A. Shalaby, Cairo University, Egypt.
Reviewers:
(1) Burak Buldur, Cumhuriyet University, Turkey.
(2) Huda Saleh El-Sheshtawy, Egyptian Petroleum Research Institute (EPRI), Egypt.
Complete Peer review History: http://www.sdiarticle4.com/review-history/59731

Systematic Review

Received 27 May 2020
Accepted 04 August 2020
Published 24 August 2020

ABSTRACT

Octenidine is a cationic disinfectant that has been tested for its wide range of antibacterial efficacy and biocompatibility. It finds its application in the medical field as an antiseptic for wounds and mucous membranes. The present systematic review aims to compare the antimicrobial efficacy of Octenidine Dihydrochloride with various root canal irrigants and medicaments. An electronic search strategy was planned to search the database of PUBMED CENTRAL and MEDLINE using the search terms alone and in combination using PUBMED search builder till September 2019 for related studies. In Vitro studies that compared the antibacterial efficacy of Octenidine Dihydrochloride to other irrigants and medicaments against *Enterococcus faecalis* and *Candida albicans* using extracted human teeth were included in the review. The primary outcome measure was the reduction in the microbial load which was assessed through either CFU or the percentage of viable and dead bacteria. A total of 7 studies that matched the inclusion criteria were included in

**Corresponding author: E-mail: sharipriya92@gmail.com;*

the systematic review. The studies indicated that Octenidine Dihydrochloride was highly effective in eliminating *E faecalis* and *C albicans* and could be a more biocompatible potential alternative or an adjunct to the existing irrigants and medicaments.

Keywords: Antimicrobial; calcium hydroxide; octenidine; root canal irrigants; sodium hypochlorite.

1. INTRODUCTION

The role of microorganisms in the development of pulp and periradicular diseases has been well documented in scientific literature [1]. The primary endodontic infections are associated with a mixed array of microorganisms [2] whereas *Enterococcus faecalis* is one of the predominant species associated with secondary infections [3]. In addition, yeast like microorganisms, particularly *Candida albicans* has also been found to be associated with secondary endodontic infections [4]. The goal of endodontic treatment is the successful eradication of the causative microorganism thereby increasing the chances of a favorable outcome. Therefore, the use of chemical disinfectants such as root canal irrigants and intracanal medications between appointments for the elimination of these bacteria and for disinfection of the root canal system is highly imperative [1,5]. These disinfectants along with having a broad antibacterial spectrum, should not be cytotoxic and should have sufficient time of action to eliminate bacteria.

Root canal irrigants play a vital role in removal of smear layer and elimination of microorganisms located in isthmuses, ramifications, deltas, irregularities, and dentinal tubules where mechanical means alone will not suffice [6]. Antibacterial effectiveness of mechanical instrumentation and irrigation was evaluated by Bystrom and Sundqvist [7]. They found that all the teeth had a positive culture after the first appointment despite a considerable reduction in bacterial counts after instrumentation and irrigation with saline. There was a significant improvement in the elimination of bacteria after they used sodium hypochlorite (NaOCl) separately or combined with ethylene diamine tetraacetic acid (EDTA) [7]. However, sodium hypochlorite is highly toxic and can cause a reaction when it comes in contact with soft tissues [8].

Intracanal medicaments are used for eliminating microorganisms that persist even after mechanical instrumentation, for teeth with chronic periapical lesions and for treating weeping canals [9]. Calcium hydroxide has been widely recommended as the gold standard medicament owing to its proven antibacterial properties, biocompatibility, periapical tissue healing stimulation and anti-exudate activity [10,11]. However, it fails to eliminate *E. faecalis* which is the most commonly observed pathogen in a retreatment endodontic case [12].

Octenidine Dihydrochloride is a cationic surfactant and has been in use as an antiseptic, in concentrations of 0.1 to 2.0% owing to its antibacterial activity against gram-positive and gram-negative bacterial strains. Octenidine is not absorbed through the mucous membrane, nor the skin and wounds [13]. Octenidine has been tested against *E. faecalis* and is a well-known disinfectant in medical facilities [14,15]. In addition, it is also highly biocompatible and is a substitute for chlorhexidine which has concerns about the carcinogenic impurity 4-chloroaniline [16].

Previously our team had conducted numerous clinical studies [17,18], case reports [19], in vitro studies [20–25], surveys [26,27] reviews [28–31] in various aspects of endodontics and conservative dentistry over the past five years [32] from which the idea of the present study has stemmed. This systematic review aimed to compare the antimicrobial effectiveness of Octenidine dihydrochloride with conventional root canal disinfectants used in routine practice. This review shall aid in understanding the efficacy of Octenidine dihydrochloride as a root canal disinfectant and its future prospects.

2. MATERIALS AND METHODS

2.1 Sources Used

To identify the studies to be included or considered for the present review a detailed search was carried out on the following databases:

- PubMed central (until September 2019)
- Pubmed Advanced Search (until September 2019)
- Cochrane Database of Systematic Reviews

2.2 Language

Only those articles that were in the English language were considered for inclusion during the electronic search

2.3 Hand Searching

The following journals were hand-searched

- International Endodontic Journal
- Journal of Endodontics
- Journal of Conservative Dentistry
- Australian Dental Journal

2.4 Inclusion Criteria

In Vitro studies that tested antimicrobial efficacy of irrigants against *E faecalis* or *C albicans* or both.

2.5 Exclusion Criteria

1. Animal studies
2. Review articles
3. Studies not meeting the inclusion criteria

2.6 Type of Intervention

Use of Octenidine Dihydrochloride as a root canal irrigant to eliminate the microorganism

2.7 Type of Control

Use of various other root canal irrigants or medicaments for the disinfection to eliminate the microorganism

2.8 Type of Outcome Measure

Evaluation of the antimicrobial efficacy in terms of colony forming units, percentage viable bacteria or number of dead cells.

3. RESULTS AND DISCUSSION

The electronic search identified 105 publications of which 89 were excluded after reviewing the title and the abstract. For further evaluation 16 full articles were obtained of which 9 were excluded. Therefore 7 publications fulfilled all the inclusion criteria and were included in the review (Fig. 1). Table 1 enlists the general information of the included studies. The results and interpretation of the studies are listed in Table 2. The seven studies that were included in the review were all in vitro studies that have a level of evidence 5. The present systematic review aimed to evaluate the antimicrobial effectiveness of octenidine dihydrochloride in comparison to the various other root canal irrigants and medicaments.

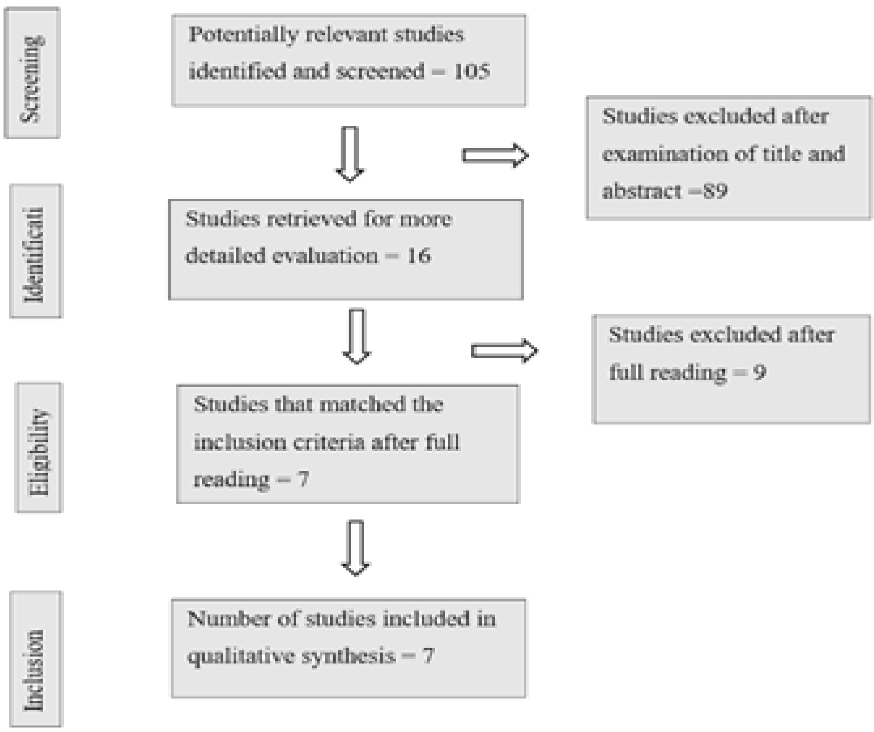

Fig. 1. Search flow chart

Table 1. Characteristics of included studies

S No	Author and year	Study Design	Sample Size	Study groups	Variable evaluated	Method of Evaluation	Statistical Analysis
1.	Tirali RE.et al 2012	In Vitro Study	N=80 permanent teeth and 80 primary teeth	Group 1: 5.25% NaOCl for 30 sec Group 2: 5.25% NaOCl for 1 min Group 3: 5.25% NaOCl for 5 min Group 4: 0.1% Oct for 30 sec Group 5: 0.1% Oct for 1 min Group 6: 0.1% Oct for 5 min Group 7: 2% CHX for 30 sec Group 8: 2% CHX for 1 min Group 9: 2% CHX for 5 min Group 10: Saline for 5 min	Antimicrobial activity against *E faecalis* and *C albicans*	Colony Forming Units	Kruskal-Wallis Test Mann Whitney U Test
2.	De Lucena JM. et al 2013	In Vitro Study	N=40	Group 1: Calcium hydroxide paste Group 2: Chlorhexidine gel 5.0% Group 3: Chlorhexidine gutta percha points Group 4: Octenidine gel 5.0%	Antimicrobial effectiveness against *E faecalis*	Percentage of viable bacteria Colony Forming Units	
3.	Eldeniz AU.et	In Vitro	N=70	Group 1: Light	Antifungal efficacy against *C*	Colony Forming	Independent two

S No	Author and year	Study Design	Sample Size	Study groups	Variable evaluated	Method of Evaluation	Statistical Analysis
	al 2013	Study		activated disinfection with toluidine blue Group 2: Octenidine hydrochloride Group 3: 2.5% Sodium Hypochlorite Group 4: 5.25% Sodium Hypochlorite Group 5: 2% Chlorhexidine Positive control group Negative control group	*albicans*	Units	sample t test
4.	Guneser MB.et al 2016	In Vitro Study	N=70	Group 1: 2.5% NaOCl Group 2: 5.25% NaOCl Group 3: 2% CHX Group 4: Chlorhexidine and Cetrimide Group 5: Methanol extract of S officinalis Group 6: Octenidine Positive control group: infected samples with no irrigant (n=5) Negative control group: sterile root canals (n=5)	Antimicrobial effect against *E faecalis*	Colony Forming Units	Kruskal Wallis test Mann Whitney U test

S No	Author and year	Study Design	Sample Size	Study groups	Variable evaluated	Method of Evaluation	Statistical Analysis
5.	Cherian B.et al 2016	In Vitro Study	N=48	Group 1: Conventional syringe irrigation (CSI) with 2% CHX Group 2: CSI with 0.1% OCT Group 3: Passive Ultra Sonic Irrigation (PUI) with 2% CHX Group 4: PUI with 0.1% OCT	Antimicrobial efficacy against *E faecalis*	Colony Forming Units	One-way analysis of variance (ANOVA) Scheffes multiple comparisons means Paired t test
6.	Bukhary S.et al 2017	In Vitro Study	N=90	Group 1: OCT (n=20) Group 2: 1% Alexidine (n=20) Group 3: 2% CHX (n=20) Positive control group: 5.25% NaOCL (n=15) Negative control group: saline (n=15)	Antibacterial Efficacy against *E faecalis*	Proportion of dead cells in biofilm using confocal laser scanning	Kruskal Wallis test Mann Whitney U test
7.	Varghese VS.et al 2018	In Vitro	N=160	Group 1: Octenidine Group 2: Octenidine with chitosan carrier Group 3: Calcium Hydroxide with chitosan carrier Group 4: Calcium Hydroxide	Antibacterial efficacy against *E faecalis* and *C albicans*	Colony Forming Units	One way ANOVA and Tuckey's multiple post hoc test

Table 2. Results of the included study

S No	Author and Year	Study Groups	Interpretation
1	Tirali RE .et al 2012	Group 1: 5.25% NaOCl for 30 sec Group 2: 5.25% NaOCl for 1 min Group 3: 5.25% NaOCl for 5 min Group 4: 0.1% Oct for 30 sec Group 5: 0.1% Oct for 1 min Group 6: 0.1% Oct for 5 min Group 7: 2% CHX for 30 sec Group 8: 2% CHX for 1 min Group 9: 2% CHX for 5 min Grpup 10: Saline for 5 min	The study showed that application of 0.1% Octenidine for 5 mins was most effective in eliminating *E faecalis* that penetrated into the dentinal tubules of both primary and permanent teeth whereas all irrigating solutions except saline were equally effective in eliminating *C Albicans*.
2.	De Lucena JM.et al 2013	Group 1: Calcium hydroxide paste Group 2: Chlorhexidine gel 5.0% Group 3: Chlorhexidine gutta percha points Group 4: Octenidine gel 5.0%	There was a significant reduction in the percentage of viable bacteria in test groups 2,3 and 4 but Octenidine yielded the maximum reduction with no cells being alive at 12 weeks.
3.	Eldeniz AU.et al 2013	Group 1: Light activated disinfection with toluidine blue Group 2: Octenidine hydrochloride Group 3: 2.5% Sodium Hypochlorite Group 4: 5.25% Sodium Hypochlorite Group 5: 2% Chlorhexidine Positive control group Negative control group	Octenidine hydrochloride, 5.25% and 2.5% sodium hypochlorite and 2% chlorhexidine were all equally effective in eliminating *C albicans* and were more effective than light activated disinfection.
4.	Guneser MB.et al 2016	Group 1: 2.5% NaOCl Group 2: 5.25% NaOCl Group 3: 2% CHX Group 4: Chlorhexidine and Cetrimide Group 5: Methanol extract of S officinalis Group 6: Octenidine Positive control group: infected samples with no irrigant (n=5) Negative control group: sterile root canals (n=5)	Sodium Hypochlorite 5.25% and 2.5%, 2% chlorhexidine and Octenidine were equally effective in eliminating *E faecalis* whereas methanol extract of *S officinalis* and the combination of chlorhexidine and cetrimide could not achieve total elimination of the strains.
5.	Cherian B.et al 2016	Group 1: Conventional syringe irrigation (CSI) with 2% CHX Group 2: CSI with 0.1% OCT	Octenidine 0.1% was more effective than chlorhexidine 2% both at 200 and 400 micrometer

S No	Author and Year	Study Groups	Interpretation
		Group 3: Passive UltraSonic Irrigation (PUI) with 2% CHX Group 4: PUI with 0.1% OCT	and passive ultrasonic irrigation enhanced the antimicrobial action of both the irrigants.
6.	Bukhary S.et al 2017	Group 1: OCT (n=20) Group 2: 1% Alexidine (n=20) Group 3: 2% CHX (n=20) Positive control group: 5.25% NaOCL (n=15) Negative control group: saline (n=15)	Octenidine was more effective than Alexidine and Chlorhexidine but Sodium Hypochlorite had significantly greater antimicrobial activity against *E faecalis*
7.	Varghese VS.et al 2018	Group 1: Octenidine Group 2: Octenidine with chitosan carrier Group 3: Calcium Hydroxide with chitosan carrier Group 4: Calcium Hydroxide	Octenidine showed significantly better antimicrobial activity than other groups

Tirali RE. et al conducted an in vitro study to compare the antimicrobial effectiveness of Sodium Hypochlorite, Chlorhexidine and Octenidine Dihydrochloride as root canal irrigants at different time intervals. The study was performed on sections of primary and permanent teeth. The total sample size was 80 and each group had 10 samples. The teeth were sectioned into 4mm, sterilized and then contaminated with *E faecalis* and *C albicans* strains. The sections were subjected to different irrigating solutions followed by neutralisers for inactivation. Dental shavings were placed in TSB and 10 microliter from each tube was then inoculated on agar plates and the colonies were counted microscopically. Kruskal-Wallis and Mann Whitney U tests were used for statistical analysis. Amongst all the solutions, application of 0.1% Octenidine was found to be the most effective in eliminating the strains of *E faecalis* from both primary and permanent teeth. But there was no statistical difference when comparing the effectiveness of the solutions in eliminating *C albicans* [33].

De Lucena JM.et al conducted a study to evaluate the effectiveness of calcium hydroxide, chlorhexidine gel, chlorhexidine active gutta-percha points and Octenidine as intracanal medicaments in eliminating *E faecalis* strains. A total of 40 root segments were included in the sample size with 10 samples per group. They were infected with *E faecalis* and the root dentin samples collected at 4 weeks were considered as baseline values. At week 8, the samples were randomly divided into four groups and were subjected to the various medicaments followed by incubation for 4 weeks. The outcome measure was expressed in the percentage of viable bacteria and colony forming units. In comparison to calcium hydroxide, chlorhexidine and octenidine were more effective in decreasing the viability of *E faecalis*, of which octenidine showed the most favourable results [34].

Eldeniz AU.et al conducted a study to compare the antifungal efficacy of light-activated disinfection and Octenidine Dihydrochloride with contemporary endodontic irrigants being 5.25% and 2.5% sodium hypochlorite and 2% chlorhexidine. Hence a total of 5 groups were present in the study along with a positive and negative control with the sample size being 10 per group. The samples were subjected to the test solutions for 3 mins and the irradiation time for light activated disinfection was 30 seconds. The dentin chips were collected from the inner walls of the canals after disinfection and transferred into vials containing phosphate buffered saline. The outcome measure was expressed in terms of colony forming units. All *Candida* cells were found to be totally eliminated in root canals that were treated with Octenidine, 2% chlorhexidine, 5.25% and 2.5% sodium hypochlorite suggesting Octenidine as a promising alternative to sodium hypochlorite and chlorhexidine [35].

Guneser MB.et al conducted a study where the antibacterial effects of Octenidine were compared with chlorhexidine-cetrimide combination, methanol extracts of *S officinalis* plant, 5.25% and 2.5% sodium hypochlorite and 2% chlorhexidine. For his study, seventy decoronated single rooted teeth were divided into 6 test groups (n=10) and two control groups (n=5) and were infected with *E faecalis*. They were subjected to the different irrigating solutions and the dentin chips obtained from the inner walls of the canals were subjected to analysis to determine the number of Colony Forming Units. They found out that Sodium Hypochlorite, Chlorhexidine and Octenidine could eliminate *E faecalis* cells thus suggesting Octenidine as a potential root canal disinfectant [36].

Cherian B.et al conducted a study to compare the antibacterial efficacy of Octenidine Dihydrochloride and Chlorhexidine with and without a Passive Ultrasonic Irrigation. Freshly extracted 48 teeth were allocated into four groups after growing a biofilm of *E faecalis* for seven days. They were subjected to the two irrigants with and without passive ultrasound post which the dental shavings at a depth of 200 and 400 micrometer were obtained and subjected to analysis for determining the colony forming units. The data was statistically analyzed using the ANOVA and paired t test. Their study concluded that 0.1% Octenidine was more effective than 2% Chlorhexidine at both the depths 200 and 400 micrometer and that passive ultrasonic activation increased their efficacy [37].

Bukhary S et al. conducted a study to determine the antibacterial efficacy of Octenisept, Alexidine, chlorhexidine and Sodium Hypochlorite against *E faecalis* biofilms. Octenisept, Alexidine, chlorhexidine groups had 20 samples whereas, the positive control, 5.25% sodium hypochlorite and negative control, saline had 15 samples per group. The root dentin discs were first infected with the strains of *E faecalis* and then subjected to the various irrigating solutions. The proportion of dead cells in the biofilm were determined and it was observed that sodium hypochlorite has the highest antibacterial activity followed by Octenidine thus suggesting it as a potential alternative to chlorhexidine [14].

Varghese V S.et al conducted a study to evaluate the antimicrobial efficacy of Octenidine Dihydrochloride and Calcium Hydroxide with and without chitosan carrier. The study consisted of a sample size of 160 extracted teeth which were divided into four groups. The samples were infected with strains of *E faecalis* and *C albicans* and were subjected to different medicaments. The antibacterial efficacy was evaluated based on the number of colony forming units at day 2 and day 7. The antibacterial and antifungal activity of all the four groups diminished from day 2 to day 7. Octenidine showed significantly better antibacterial efficacy as compared to Calcium hydroxide. The addition of chitosan carriers reduced their antibacterial and antifungal efficacy [38].

The results of this Systematic Review indicate that Octenidine Dihydrochloride is a more potent disinfectant for root canal systems than the existing contemporary disinfectants.

Octenidine dihydrochloride (octenidine) was introduced more than 20 years ago for skin, mucous membrane and wound antisepsis. Several *in vitro*, animal studies, prospective clinical trials have provided evidence for its efficacy, tolerance and safety. Octenidine represents an alternative to older substances such as chlorhexidine, povidone-iodine or triclosan and is nowadays an established antiseptic in a large field of applications [39]. In studies testing Octenidine for the oral cavity, it was found to be effective in efficiently controlling gingivitis and bleeding and plaque [40]. In another study comparing the effects of Octenidol, Glandomed and Chlorhexidine mouthwash, Octenidol was found to be the most effective in reducing the oropharyngeal flora [41]. Octenidine could also inhibit the adhesion of *C albicans* to human buccal epithelium [42].

The importance of disinfection in endodontics cannot be undermined. [27,28] Octenidine has shown promising antibacterial efficacy owing to its broad-spectrum antibacterial effect which include gram-positive as well as gram negative-organisms and yeast.

3.1 Limitation

A meta-analysis is performed for systematic reviews for the statistical pooling of data from individual studies when the studies are similar. A meta-analysis will help in yielding a more accurate estimate of the treatment effect. However, due to the heterogeneity of the groups in the studies included for the systematic review, a meta-analysis could not be performed. Hence only a descriptive evaluation of the data has been provided in the review.

3.2 Implications for Practice and Research

Opting for a medicament that is biocompatible and at the same time has a broad range of antibacterial effects will help in achieving the goal of endodontic treatment by efficiently eliminating the causative microorganisms without being toxic to the surrounding periapical tissue. This systematic review is a comparative analysis of the antimicrobial efficacy of Octenidine Dihydrochloride with the contemporary root canal irrigants and medicaments. There is scientific evidence to support the promising results of Octenidine Dihydrochloride as a potent root canal disinfectant. It could be a possible alternative or an adjunct to the contemporary disinfectants. Based on the results obtained from in vitro studies, further clinical studies can be carried out to prove its efficacy.

4. CONCLUSION

The systematic review concludes that Octenidine Dihydrochloride is a more potent antimicrobial agent against *E faecalis* and *C albicans* than the contemporary root canal disinfectants. The studies included in the review were *in vitro* studies which bring about the necessity of performing well designed randomized control trials so as to give concrete evidence on the clinical outcome of Octenidine Dihydrochloride as a root canal disinfectant.

CONSENT AND ETHICAL APPROVAL

As per university standard guideline, participant consent and ethical approval have been collected and preserved by the authors

ACKNOWLEDGEMENT

We would like to acknowledge the Department of Conservative Dentistry and Endodontics, Saveetha Dental College for their valuable inputs in this research

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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Peer-review history:
The peer review history for this paper can be accessed here:
http://www.sdiarticle4.com/review-history/59731