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Concentration of sodium hypochlorite disinfection in regenerative endodontic procedure: A systematic review

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Abstract

Objectives: To evaluate whether low concentration sodium hypochlorite (NaOCl) disinfectant protocol can achieve a sufficient amount of disinfection to provide a conducive environment for clinical and radiographic success of regenerative endodontic procedure. **Materials and methods:** This systematic review includes necrotic immature permanent anterior teeth below 20 years of age using triple antibiotic paste as an intra-canal medicament and autologous platelet concentrates as scaffold. The interventional group was low concentration (≤2%) NaOCl and comparator group included high concentration (>2%) NaOCl as disinfectant. Cochrane risk of bias assessment 2 (RoB 2) tool was used for assessment of risk of bias. Included studies were evaluated for the absence of clinical signs and symptoms, increase in root length and apical closure on radiograph, and positive response to vitality testing. **Results:** After evaluation, seven studies were included. Clinical success rate was seen in 98.33% cases in low concentration (≤2%) and 95% cases in high concentration (>2%) NaOCl. The radiographic success rate was 86.66% in low concentration (≤2%) and 80% in high concentration (>2%) NaOCl disinfection. Positive response for vitality testing was seen in 46.66% cases in low concentration (≤2%) and 38.70% in high concentration NaOCl (>2%). **Conclusion:** Low concentration (≤2%) NaOCl is as effective as high concentration (>2%) to achieve disinfection of the root canal. However, an increased success rate is associated with the use of low concentration (≤2%) NaOCl. Response to pulp vitality is observed to be superior with low concentration (≤ 2%) NaOCl although it might be attributed to a longer follow-up period.

Keywords: Platelet-rich plasma, Platelet-rich fibrin, Regenerative endodontics, Sodium hypochlorite, Triple antibiotic paste.

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INTRODUCTION

Conventional endodontic treatment for a tooth with incomplete root development poses various complications, including root fracture due to the thin walls and short roots or the accidental injection of fluids beyond the wide root apex [1]. Regenerative Endodontic Procedure (REP) has been a possibility due to the emergence of modern tissue engineering. It is designed to replace damaged structures, including dentin and root structures, as well as cells of the pulp-dentin complex [2]. Traditionally, three elements that are considered to be essential for the regeneration of pulp constitute stem cells, scaffold system, and growth factors [3] .

Use of a disinfection protocol that effectively disinfects the root canal and controls the infectious process is currently considered as an inevitable requirement to achieve pulp regeneration as the persistent infection hinders the stem cell attachment [2]. Hence, pulp space and dentinal walls must be sufficiently disinfected; wherein, chemical disinfection is essential as REP involves minimal or no filing of the root canal system. The chemical disinfection protocol for REP differs from the conventional endodontic therapy as it is necessary to create an environment conducive for survival, proliferation and, differentiation of stem cells. The propinquity of stem cells of apical papilla (SCAP) to the apices of teeth in continuum with the root canal space renders this rich source of stem cells readily available for regeneration [2]. The disinfection protocol

for the REP has been updated by the American Association of Endodontists (AAE) in 2021 suggesting use of lower concentrations of sodium hypochlorite (NaOCl), i.e. 1.5%-3% followed by irrigation with saline or ethylenediamine tetraacetic acid (EDTA) [4]. The primary disinfectant in use is NaOCl, (0.5% - 6%) as it has excellent bactericidal efficacy and tissue dissolution capacity. Additionally, it also serves as a lubricant for easy endodontic instrumentation. These properties are crucial for the disinfection of immature teeth [5]. It is essential to note that NaOCl evokes a concentration-dependent decrease in SCAP survival and odontoblast-like differentiation and hence a final rinse with 17% EDTA is used to solubilize these growth factors from dentin, thereby increasing their bioavailability.[2] In vitro studies have been conducted to assess the effect of concentration of NaOCl on survival of SCAP which varies between 1% and 6%. Martin et al., 2017 assessed the effect of 0.5%, 1.5%, 3%, and 6% NaOCl concentration followed by either 17% EDTA or normal saline. Negative effects have been observed even at 3% concentration of NaOCl on the survival and differentiation of SCAP. Hence, the studies have recommended to use 1.5% sodium hypochlorite as it has shown the least detrimental effect on SCAP when followed by 17% EDTA [2,5,6].

Although, AAE recommends a range of concentration of NaOCl i.e 1.5%-3%, various studies have shown detrimental effect even at 3% and have recommended to use 1-1.5% [2, 5-7]. As the success of the REP revolves around achieving primary, secondary and tertiary outcome i.e clinical, radiographic success rate and regaining pulp vitality, the goal of the systematic review is to find out if a low concentration (≤2%) NaOCl can further provide a conducive environment for achieving sufficient amount of disinfection contributing to clinical and radiographic success which remains the ultimate goal of REP. Hence, the present systematic review aims to formulate an evidence on effect of low (≤2%) and high concentration (>2%) of NaOCl as a disinfection protocol for regenerative endodontic in immature anterior permanent teeth.

Research question

The research question has been formulated according to Population, Intervention, Control, Outcome and Study design (PICOS) format according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement guidelines.

Whether low concentration (≤2%) NaOCl has better or similar efficacy than high concentration (>2%) NaOCl as a disinfection protocol for regenerative endodontic procedure in immature permanent anterior teeth with open apex?

- P - Immature permanent anterior teeth with an open apex.
- I - Disinfectant irrigant - ≤2% NaOCl (low concentration).
- C - Disinfectant irrigant - >2% NaOCl (high concentration).
- O- Primary - Absence of clinical signs and symptoms.

Secondary - Increased root wall thickness and/or increased root length on radiograph.

Tertiary – Positive response to vitality testing.

- S – Randomized Controlled Trials and Non- Randomized Controlled Trials

MATERIALS AND METHODS

Protocol Registration

This review was carried out following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement guidelines. The protocol of the review was registered at PROSPERO (International prospective register of systematic reviews) bearing registration number CRD42021293099.

Study Selection

Inclusion Criteria

1. RCTs and Non RCTs conducted during 1999 - 2021.
2. NaOCl as a primary disinfectant used in regenerative endodontics in immature permanent anterior teeth with an open apex.
3. Triple antibiotic paste as an intracanal medicament.
4. Autologous Platelet Concentrate (APCs) as a scaffold.
5. A minimum of 12 month follow-up

Exclusion Criteria:

1. Animal studies.
2. Study design other than RCTs and non RCTs on regenerative endodontics.
3. +3. Studies on primary teeth and posterior teeth.
4. Age group more than 20 years.
5. Articles in languages other than English.

Search Strategy and Data Extraction

Studies were identified by searching four electronic databases and scanning a reference list of articles. This search was applied to PubMed, Cochrane Library, Google Scholar and, Directory of Open Access Journal from 1999-2021. The last search was conducted on 10 January 2022. A limit of clinical trial was applied in all databases. Following keywords were used for data search: "Regenerative endodontic* OR Pulp revascularization OR Immature permanent tooth AND Disinfectant OR Sodium hypochlorite AND Triple Antibiotic Paste AND Platelet Rich Fibrin OR Platelet Rich Plasma".

Three reviewers were involved in applying the eligibility criteria and selecting studies for inclusion in the systematic review. The first and second reviewers individually collected and screened the records and the third one conducted a cross check on the records obtained by the first and second reviewer and vice-versa. In cases of divergence, the decision of whether to involve a paper or not was reached through discussion. During the selection of articles, the reviewers were blinded to the journals and the authors of the journals. Kappa coefficient used to test reliability amongst reviewers regarding data extraction was found to be highly reliable (k> 0.91).

Data Synthesis

Data were extracted using a table designed for the systematic review in detail using an Excel spreadsheet (Microsoft, Redmond, WA, USA). This data table contains information about the author, year of publication, country, type of study, age group of participants, scaffold system, the disinfectant regime, follow-up period, and study outcome such as elimination of symptoms and the evidence of bony healing on the radiograph, increased root wall thickness and/or increased root length on radiograph and pulp vitality.

Risk of bias assessment

The risk of bias was assessed by two independent reviewers for all the included clinical trials. This assessment was conducted by using the recommended approach for assessing the risk of bias in studies as per the Revised Cochrane risk-of-bias tool for randomized trials (RoB 2) using the tool RevMan 5.4.1.

Revised RoB 2 is two part tool having five domains with signalling questions as yes, probably yes, no, probably no, and no information with a possible risk of bias judgement as low risk, some concern, high risk.

RESULTS

Study Selection

This review included a total of seven randomized clinical trials (RCT).[8-14] The included articles were identified from a pool of 3626 articles retrieved from digital databases and manual search. After removal of duplicates and screening of title and abstract, full-text assessment was carried out for 19 articles, and 12 studies were excluded due to reasons reported in Figure 1.

Study Characteristics

The included articles were published between 2015 and 2020. Seven studies were included based on the inclusion criteria, wherein 60 teeth were included in low concentration and 60 teeth in high concentration of NaOCl within the age range of 7 - 20 years with a minimum of 12 month follow-up period. General characteristics and the operative protocols used in the trials have been presented in Table 1 and Table 2.

Since, the included studies showed heterogeneity in the outcome measures, meta-analysis could not be performed for the same.

Analysis of risk of bias of studies

The two-part tool to address the five specific domains (Randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result) was used. Two review authors undertook the risk of bias assessment independently and in duplicate as part of the data extraction process. Disagreements were resolved by discussion. After taking into account additional information provided by the authors of the trials, studies were grouped into the following categories (Figure 2 and 3). There was good reliability for the risk of bias assessment between the reviewers with a high kappa coefficient ($k > 0.89$). After analysis of the risk of bias, it was observed that the randomization process was mentioned in most of the included studies. But there were some concerns regarding the bias arising due to deviation in intended interventions and selection of reported results in the included studies. Over all, the included studies were at low risk of bias in most of the domains (Figure 2 and 3).

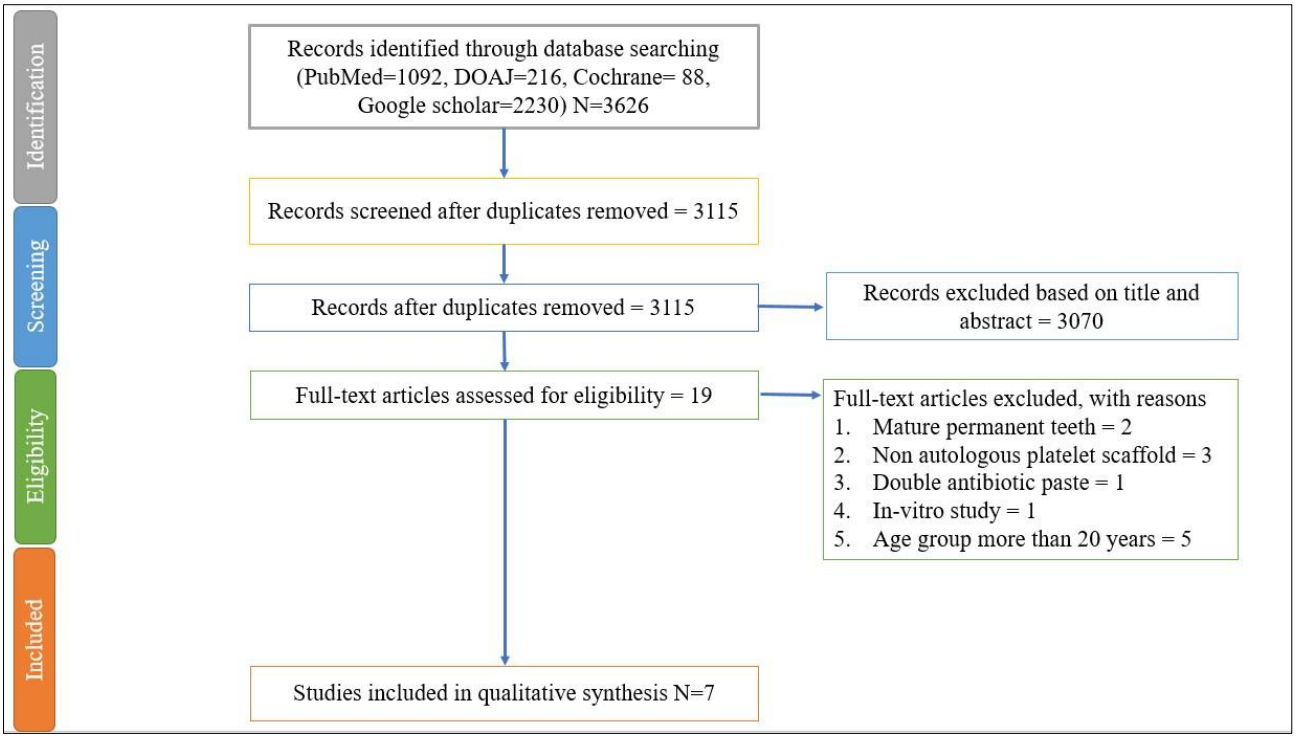

Figure 1: PRISMA flow chart

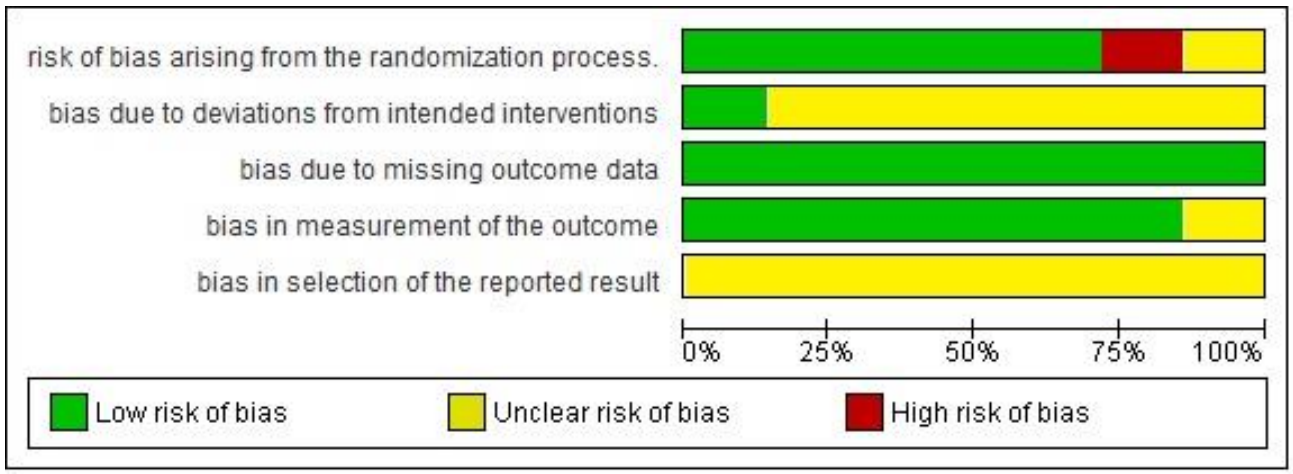

Figure 2: Risk of bias graph - Review authors' judgments about each risk of bias item presented as percentages across all included studies.

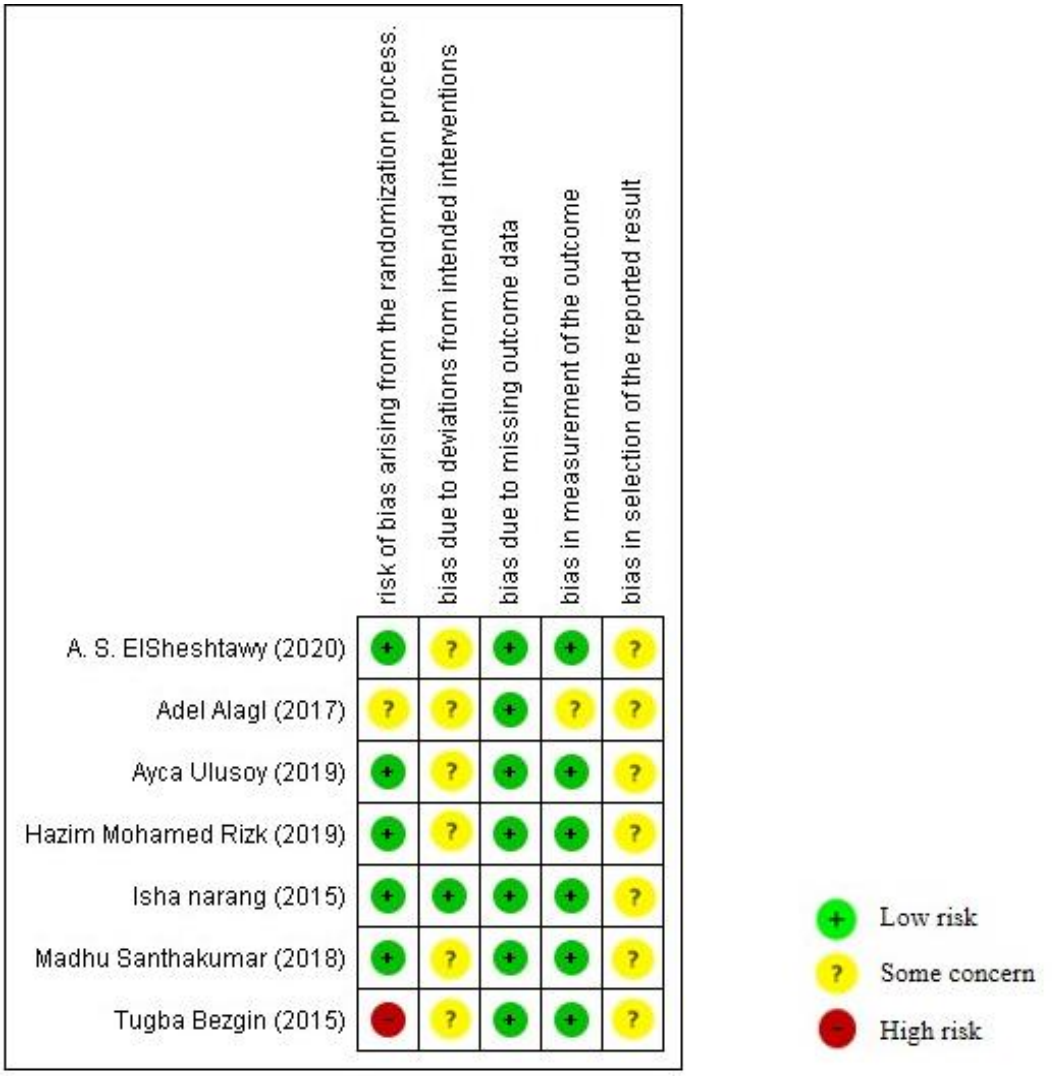

Figure 3: Risk of bias summary - Review authors' judgments about each risk of bias item for each included study.

Table 1: General characteristics of included studies

Author	Year	Country	Type of study	Age group
Bezgin et al.[8]	2015	Turkey	Randomized Clinical trial	7-13 years
Narang et al.[9]	2015	India	Randomized Clinical trial	Below 20 years of age
Alagl et al.[10]	2017	Saudi Arabia	Randomized Clinical trial	8-11 years.
Santhakumar et al.[11]	2018	India	Randomized Clinical trial	7-12 years
Ulusoy et al.[12]	2019	Turkey	Randomized clinical trial	8-11 years.
Rizk et al.[13]	2019	Egypt	Randomized controlled trial	9 ± 1 years.
ElSheshtawy et al.[14]	2020	Egypt	Randomized controlled trial	12.66 ± 4.47 years

Table 2: Details on operative protocols and a summary of included studies

Author	Scaffold used in the study (no. of sample)	Disinfectant protocol used	Intracanal medicament used	Follow up period	Summary of study
Bezgin et al.[8]	Group: PRP (n=6)	2.5% NaOCl	Equal amounts of metronidazole, ciprofloxacin, and cefaclor.	18 months	Primary outcome- all 6 teeth were clinically asymptomatic in PRP group. Secondary outcome- 3 out of 6 teeth had complete apical closure. Tertiary outcome- 3 out of 6 teeth had positive response to vitality.
Narang et al.[9]	Group A : PRP (n=5) Group B: PRF (n=5)	2.5% NaOCl	Triple antibiotic paste	18 months	Primary outcome – All 10 teeth were clinically asymptomatic. Secondary outcome – 5 out of 10 teeth had shown apical closure. Tertiary outcome - not reported.
Alagl et al.[10]	Group A : PRP (n=12)	1.5% NaOCl followed by 2.5% NaOCl.	Triple antibiotic paste - 1:1:1 mixture of metronidazole, ciprofloxacin and minocycline	12 months	Primary outcome- all teeth were asymptomatic. Secondary outcome- 10 out of 12 teeth had complete apical closure. Tertiary outcome- 9 out of 12 teeth had positive response to vitality.
Santhakumar et al.[11]	Group: PRF membrane (n=19)	3% NaOCl.	Triple antibiotic paste - 1:1:1 metronidazole, ciprofloxacin and minocycline.	12 months	Primary outcome- 18 out of 19 were found to be successful clinically. Secondary outcome- Root lengthening was achieved in 17 cases. Tertiary outcome- not reported.
Ulusoy et al.[12]	Group A : PRP (n=18) Group B : PRF (n=17)	1.25% NaOCl.	Triple antibiotic paste - equal amounts of clindamycin,ciprofloxacin, and metronidazole.	Average follow up time of 28.25 ± 1.2 months	Primary outcome- 34 out of 35 cases were clinically successful. Secondary outcome- 27 out of 35 cases had apical closure. Tertiary outcome- 28 cases had positive response to vitality.
Rizk et al.[13]	Group A : PRP (n=13) Group B : PRF (n=12)	2% NaOCl.	Triple antibiotic paste - 1:1:1 ciprofloxacin,metronidazole and minocycline.	12 months	Primary and secondary outcome - all cases showed 100% success. Tertiary outcome- all cases did not respond to vitality testing.
ElSheshtawy et al.[14]	Group: PRP (n=13)	5.25% NaOCl.	Triple antibiotic paste - 1:1:1 ciprofloxacin, metronidazole and minocycline	12 months	Primary outcome- 11 out of 13 cases were clinically successful. Secondary outcome- all cases reported with continued root development. Tertiary outcome- 100% lack of response regardless of the assessment method used.

MTA- Mineral Trioxide Aggregate, NaOCl- Sodium Hypochlorite, PRF- Platelet Rich Fibrin, PRP- Platelet Rich Plasma.

DISCUSSION

The present systematic review was carried out to assess the effect of concentration of sodium hypochlorite as a disinfectant on clinical and radiographic success in REP in immature necrotic permanent teeth. A new protocol for REP for immature permanent teeth has been suggested where three goals for REP were developed. The first requirement is the elimination of bacteria by effective canal disinfection, the second condition is the presence of a scaffold for the ingrowth of new tissue and the third prerequisite is the prevention of bacterial reinfection with creation of a bacteria-tight seal [15]. Thus, in accordance with other studies, the disinfection of the canal is an indispensable criteria for the success of REP [16].

Sodium hypochlorite is a widely used irrigant in REP as it exerts a strong antimicrobial action by reducing the surface tension of the solution by acting as a fat solvent. It disorganizes the primary protein structure by breaking the bonds between carbon atoms thus degrading the dentin collagen. Moreover, NaOCl releases chlorine which acts as a strong antioxidant and binds to amino groups to form chloramines which denatures bacterial enzymes and thus interfere with bacterial metabolism [7]. The cytotoxic effect of sodium hypochlorite on stem cells has shown that NaOCl negatively affects the dental mesenchymal stem cell survival and differentiation. This dental stem cell cytotoxicity has been directly correlated with the concentration and treatment time with NaOCl [7]. Martin et al. [5] evaluated the effect of different concentration i.e. 0.5%, 1.5%, 3% and 6% of NaOCl on survival of SCAP. The results of the study suggested similar findings that the effect of NaOCl is dose-dependent, where 0.5%, 1.5%, and 3% have showed similar reduction in survival of SCAP while 6% showed high detrimental effects on SCAP. 3% NaOCl showed 50% decreased expression of odontoblast-like cell marker dentin sialophosphoprotein (DSPP) whereas 6% completely prohibited it. Moreover, the addition of a final irrigation with 17% EDTA resulted in an increased expression of DSPP in the group treated with 1.5% NaOCl, and complete and partial reversal of DSPP-reduced expression in the groups treated with 3% and 6% NaOCl, respectively. Thus, dentin conditioning with NaOCl was found to have a profound effect on DSPP expression with the concentration of 1.5% being the

most conducive for DSPP expression [5]. Bosaid et al. [17] evaluated the structural changes of the dentin wherein 1.5% NaOCl did not alter the inorganic components or micro-hardness of dentin but had a detrimental effect on organic portion of dentin which was seen to be reversed by the use of chelating agents like 17% EDTA. A recent review article by Rai et al. [6] recommends the use of low concentration NaOCl (1%-1.5%) since it does not alter the dentinal composition and structure.

Autologous Platelet Concentrates in REP exhibit positive outcomes in the treatment of permanent teeth with root development. Murray et al[18] concluded that both platelet rich plasma (PRP) and platelet rich fibrin (PRF) induce apical closure more frequently than blood-clot revascularization. Hence, to eliminate the bias due to difference in outcome based on the scaffold system, teeth that were treated only with APCs as a scaffold from the included studies were considered as a subject in the present systematic review to render homogeneity to the data.

Seven randomized controlled trials were included and classified according to the concentration of NaOCl to evaluate the effect on clinical and radiographic success rate. Of which, 5 studies used NaOCl at high concentration (>2%) which included 60 teeth using APC as a scaffold and 2 studies used low concentration NaOCl (≤2%) which included 60 teeth using APC as a scaffold. The mean follow-up period of the included studies is 16.14 months. It is observed that the primary clinical outcome which is the resolution of pain, swelling, mobility, and sinus/fistula is seen in 98.33% out of 60 teeth in low concentration (≤2%) NaOCl and 95% teeth in high concentration (>2%) NaOCl of included studies. For the secondary outcome which is evaluated, it is observed that both the groups, low (≤2%) and high concentration (>2%) NaOCl show some degree of maturogenesis of the root. But, apical closure is seen in more number of cases when treated with low concentration (≤2%) NaOCl [12,13]. The radiographic success rate of the included cases is 86.66% out of 60 teeth in low concentration (≤2%) NaOCl and 80% out of 60 teeth in high concentration (>2%) NaOCl. Evaluation of tertiary outcome revealed that in the included study conducted by Alagl et al [10] delayed positive response was seen in 63.3% cases where 1.5% NaOCl followed by 2.5% NaOCl was used. In another included study conducted by Ulusoy et al. [12] positive pulp response for pulp vitality was observed for PRP at 4.85 ± 1.51 months and PRF at 5.27 ± 1.82 months that used 1.25% of NaOCl. On the other hand, no pulp vitality was regained in the study conducted by Rizk [13] at the end of 12 month follow-up period where 2% of NaOCl was used as an irrigant. The author attributed this absence of response to pulp sensibility testing to either presence of MTA as an insulator or the short duration of the follow-up period [13]. In a study conducted by ElSheshtawy et al. [14] 100% lack of response for pulp sensibility was observed when 5.25% of NaOCl was used as an irrigant irrespective of the valuation method used at any follow-up period. The success rate of tertiary outcome is 46.66% in low concentration (≤2%) NaOCl and 38.70% in high concentration (>2%) NaOCl.

CONCLUSION

According to this review, low concentration (≤2%) NaOCl was as effective as high concentration (>2%) NaOCl to achieve disinfection of the root canal of an immature necrotic permanent tooth due to the absence of any clinical signs and symptoms with the both. The primary and secondary outcomes might not be significantly affected by the concentration of NaOCl. However, increased success rate is associated with the use of low concentration (≤2%) NaOCl. Tertiary outcome i.e. response to pulp vitality is observed to be superior with low concentration (<2%) NaOCl according to the included studies although it might also be attributed to a longer follow-up period.

Recommendations

- Well-designed human clinical trials using different concentrations of sodium hypochlorite along with microbiological assessment should be considered for REPs.
- Clinical trials with a longer follow-up period (>12 months) should be considered, especially to assess for tertiary outcomes

Conflict of Interest

None declared.

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