

Comprehensive Review on Effectiveness of Single and Multiple Visit Regenerative Endodontics and Comparative Evaluation of Patient Reported Outcomes in Single Visit and Multiple Visit Regenerative Endodontics in Permanent Teeth: A Systematic Review and Meta-Analysis

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Abstract:- This systematic review aimed to investigate the efficacy of single visit and multiple visit regenerative endodontics and compare the patient based clinical outcome of permanent teeth treated with single visit & multiple visit regenerative endodontic therapy. The protocol was registered with Prospero registration code CRD42024505225. A comprehensive search strategy was performed in different databases—PubMed, CENTRAL, ScienceDirect, CINAHL, ERIC and PsycINFO using searching keywords and was limited to studies published till January 2024 in English.

The Inclusion criteria for the study were randomized clinical trial, prospective clinical studies, case Reports and case Series. The search found 20 eligible articles, which were included in the study. Risk of bias of clinical studies was conducted using ROBINS-I tool and JBL tool was used for quality assessment of case reports and case series included.

The conclusions of our study concluded that in terms of clinical outcome both the approaches presented success of treatment with odds were greater with multiple visits as compared to single visit REP but statistically there was no difference between both the group. Radiographically outcome - In terms of root width diameter post treatment, single visit REPs were more successful as compared to multiple visits but statistical difference was not present. However, further research and emphasis should be given on undertaking more clinical trials regeneration in endodontics to provide proper results.

I. INTRODUCTION

Immature tooth with necrosis, pertaining to trauma, dental caries or developmental anomaly could cease further root end development, resulting in thin friable root walls and blunderbuss open apices in young permanent tooth.

Endodontic management of teeth with open apex has always been a difficulty for Endodontist due to the difficulty in controlling the length of obturation at the apical end and inability to obtain a perfect hermetic seal with normal conventional obturation techniques. Calcium hydroxide has been used as a gold standard in apexification for immature permanent teeth with incomplete root formation and open apices in necrotic tissue. To encourage the induction of an apical calcific barrier, this treatment method calls for the long-term insertion of calcium hydroxide within the root canal which can weaken the root canal and ultimately can cause root fracture. Mineral trioxide aggregate (MTA) has been used as an alternative and presents better success rate than conventional apexification. But neither MTA OR calcium hydroxide-based treatment modalities shows 100% continuous root development, which makes roots that are thin prone to fracture.

Contemporary modern results show better biologically based alternative treatment methods to promote apical root end development along with closure known as Regeneration or revitalization which might take place if favorable environment is present in the absence of intra-pulpal infection and scaffold conductive environment for tissue ingrowth by keeping the apical papilla's mesenchymal stem cells and dental pulp stem cells intact. Regeneration of a partially necrotic pulp in an immature root is based on the concept that pulp-dentin complex contains vital stem cells located in the apical papilla can survive pulpal necrosis, even in the presence of a peri-radicular infection and stem cells can differentiate into secondary odontoblasts which can deposit dentin.

The regenerative procedure includes sodium hypochlorite (NaOCl) irrigation without mechanical preparation which is significantly capable to cause bacterial reduction of the root canal system and placement of triple-antibiotic paste including ciprofloxacin, metronidazole, minocycline or calcium hydroxide for the sterilization of the

root canal system in the first visit. In the subsequent second visit, induction of bleeding through perforation of apical third is done and blood clot formation occurs in the root canal system followed by placement of resorbable matrix over the blood clot and MTA as capping material after three weeks once the chief complaint of the patient like pain, swelling has subsided.

Recently, few authors^{5,6} published the reports of successful regenerative endodontics in single visit which eliminates the need for subsequent frequent appointments to disinfect the root canal system, thus reducing the possibility of further bacterial ingress and contamination of the root canal system.

A single visit regenerative endodontics with immediate blood clot formation after root canal irrigation and immediate placement of MTA is an emerging protocol in immature open apices treatment protocol to subdue limitations associated with the multiple visit regenerative therapy.

A. Follow-up for Evaluation of Successful Regenerative Therapy:

➤ *Clinical and Radiographic Examination*

- Absence of pain, positive response to tenderness to percussion & palpation, decreased swelling or no patent sinus tract (often observed in first follow up examination)
- Reduction of periapical radiolucency in follow up after treatment
- Continued root development (Increased width & length of root walls which is usually observed after 12-24 months post regeneration therapy)
- Positive Pulp sensibility test response.

The clinical and radiological successful outcome of regenerative endodontic procedures is assessed by the extent to which it is possible to accomplish primary, secondary, and tertiary goals:

- Primary goal: The absence of pain, intraoral swelling or sinus tract and tender on percussion or palpation is negative.
- Secondary goal: Evidence of increased root length & width
- Tertiary goal: Corroboration of positive responsiveness to cold, heat test and electric pulp vitality testing.
- So, the aim of our systematic review was to critically analyze the difference in the patient reported outcomes with Single visit regenerative endodontics and Multiple visit regenerative endodontics in permanent teeth.

II. METHODS

A systematic review of literature and meta-analysis was performed. This study followed the (PRISMA 2020) Preferred Reporting Items for Systematic Review 2020¹, the Cochrane Handbook for systematic reviews of interventions, version 5.1.0. and 4th Edition of the JBI Reviewer's Manual

and was registered at PROSPERO under registration code CRD42024505225.

A. Eligibility Criteria:

➤ *Inclusion Criteria:*

- *Population:*
Studies including participants with non-vital mature or immature permanent teeth requiring endodontic treatment irrespective of age, gender or socio-economic status or reason for non-vitality of tooth.
- *Intervention:*
Studies including single visit regenerative endodontic procedures irrespective of the type of materials used for the procedure.
- *Comparison:*
Studies including multiple regenerative endodontic procedures irrespective of the type of materials used for the procedure.
- *Outcome*
 - ✓ Studies giving information about success of treatment in both groups.
 - ✓ Studies giving information about radiographic parameters such as apical diameter, root length, root width after treatment.
- *Study Design*
 - ✓ Clinical trials, prospective studies, RCTs, case reports, case series were included
 - ✓ Studies published in any language where English translation is possible.
 - ✓ Studies published till 31-01-2024
 - ✓ Studies with full-text articles were included.

➤ *Exclusion Criteria:*

- ✓ Studies not fully available in the database.
- ✓ Single group studies without the control group were excluded
- ✓ Reviews, invitro studies and animal studies were excluded.
- ✓ Studies providing only abstracts are excluded
- ✓ Studies not mentioning required outcomes were excluded

B. Search Strategy

Studies were selected based on the PICOS inclusion criteria in the review protocol. Two reviewers determined whether papers would be eligible by evaluating the titles and abstracts. A third reviewer was consulted regarding any questions on inclusion or exclusion of the study.

- The preferred reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) for conducting a meta-analysis were followed.
- The database used for our detailed review used is described in table no.1

Table 1: Showing Electronic Databases Used for Detailed Search

Cochrane Central Register of Controlled Trials (CENTRAL)	MEDLINE	CINAHL	EMBASE	PsycINFO	Scopus	ERIC	ScienceDirect with controlled vocabulary and free text terms.
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- Articles published until 31/01/2024 were searched with the search strategy decided.

C. Focused Review Question:

Is there any difference in the patient reported outcomes with Single visit regenerative endodontics and Multiple visit regenerative endodontics in permanent teeth?

Table 2: Showing Search Strategy According to PICOS

Population	(mature[All Fields] AND ("dentition, permanent"[MeSH Terms] OR ("dentition"[All Fields] AND "permanent"[All Fields]) OR "permanent dentition"[All Fields] OR ("permanent"[All Fields] AND "teeth"[All Fields]) OR "permanent teeth"[All Fields])) OR (immature[All Fields] AND ("dentition, permanent"[MeSH Terms] OR ("dentition"[All Fields] AND "permanent"[All Fields]) OR "permanent dentition"[All Fields] OR ("permanent"[All Fields] AND "teeth"[All Fields]) OR "permanent teeth"[All Fields]))
Intervention	((("regenerative endodontics"[MeSH Terms] OR ("regenerative"[All Fields] AND "endodontics"[All Fields]) OR "regenerative endodontics"[All Fields] OR ("regenerative"[All Fields] AND "endodontic"[All Fields]) OR "regenerative endodontic"[All Fields]) AND ("methods"[MeSH Terms] OR "methods"[All Fields] OR "procedure"[All Fields])) AND (("single person"[MeSH Terms] OR ("single"[All Fields] AND "person"[All Fields]) OR "single person"[All Fields] OR "single"[All Fields]) AND visit[All Fields] AND ("methods"[Subheading] OR "methods"[All Fields] OR "procedures"[All Fields] OR "methods"[MeSH Terms]))
Comparison	((("regenerative endodontics"[MeSH Terms] OR ("regenerative"[All Fields] AND "endodontics"[All Fields]) OR "regenerative endodontics"[All Fields] OR ("regenerative"[All Fields] AND "endodontic"[All Fields]) OR "regenerative endodontic"[All Fields]) AND ("methods"[MeSH Terms] OR "methods"[All Fields] OR "procedure"[All Fields])) AND (multiple[All Fields] AND visit[All Fields] AND ("methods"[MeSH Terms] OR "methods"[All Fields] OR "procedure"[All Fields]))) AND (interappointment[All Fields] AND ("methods"[MeSH Terms] OR "methods"[All Fields] OR "procedure"[All Fields]))
Outcome	(((((("tooth"[MeSH Terms] OR "tooth"[All Fields]) OR "survival"[All Fields] OR "survival"[MeSH Terms])) AND (radiographic[All Fields] AND outcome[All Fields]))

Table 3: Shows Overall Search Strategy in PubMed

	Number of items obtained
(((((("dentition, permanent"[MeSH Terms] OR ("dentition"[All Fields] AND "permanent"[All Fields]) OR "permanent dentition"[All Fields] OR ("permanent"[All Fields] AND "teeth"[All Fields]) OR "permanent teeth"[All Fields]) OR ("dentition, permanent"[MeSH Terms] OR ("dentition"[All Fields] AND "permanent"[All Fields]) OR "permanent dentition"[All Fields] OR ("permanent"[All Fields] AND "tooth"[All Fields]) OR "permanent tooth"[All Fields])) AND (mature[All Fields] AND ("dentition, permanent"[MeSH Terms] OR ("dentition"[All Fields] AND "permanent"[All Fields]) OR "permanent dentition"[All Fields] OR ("permanent"[All Fields] AND "teeth"[All Fields]) OR "permanent teeth"[All Fields])))) OR (mature[All Fields] AND ("dentition, permanent"[MeSH Terms] OR ("dentition"[All Fields] AND "permanent"[All Fields]) OR "permanent dentition"[All Fields] OR ("permanent"[All Fields] AND "tooth"[All Fields]) OR "permanent tooth"[All Fields])))) AND (((("regenerative endodontics"[MeSH Terms] OR ("regenerative"[All Fields] AND "endodontics"[All Fields]) OR "regenerative endodontics"[All Fields] OR ("regenerative"[All Fields] AND "endodontic"[All Fields]) OR "regenerative endodontic"[All Fields]) AND ("methods"[MeSH Terms] OR "methods"[All Fields] OR "procedure"[All Fields])) AND (("single person"[MeSH Terms] OR ("single"[All Fields] AND "person"[All Fields]) OR "single person"[All Fields] OR "single"[All Fields]) AND visit[All Fields] AND ("methods"[Subheading] OR "methods"[All Fields] OR "procedures"[All Fields] OR "methods"[MeSH Terms])))) AND (((("regenerative endodontics"[MeSH Terms] OR ("regenerative"[All Fields] AND "endodontics"[All Fields]) OR "regenerative endodontics"[All Fields] OR ("regenerative"[All Fields] AND "endodontic"[All Fields]) OR "regenerative endodontic"[All Fields]) AND ("methods"[MeSH Terms] OR "methods"[All Fields] OR "procedure"[All Fields])) AND (multiple[All Fields] AND visit[All Fields] AND ("methods"[MeSH Terms] OR "methods"[All Fields] OR "procedure"[All Fields])))) AND (interappointment[All Fields] AND ("methods"[MeSH Terms] OR "methods"[All Fields] OR "procedure"[All Fields]))	7

Fields]) OR "regenerative endodontics"[All Fields] OR ("regenerative"[All Fields] AND "endodontic"[All Fields]) OR "regenerative endodontic"[All Fields]) AND ("methods"[MeSH Terms] OR "methods"[All Fields] OR "procedure"[All Fields]) AND (multiple[All Fields] AND visit[All Fields] AND ("methods"[MeSH Terms] OR "methods"[All Fields] OR "procedure"[All Fields])) AND (interappointment[All Fields] AND ("methods"[MeSH Terms] OR "methods"[All Fields] OR "procedure"[All Fields]))	
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The above discussed was the complete databases search history accessed till the month of January 2024.

D. Selection Of Studies

Each study's title and abstract were studied by two separate reviewers and evaluated thoroughly by both. The following techniques were employed to apply the selection criteria:

- Combining the outcome of the data to eliminate duplicate entries
- reviewing titles, abstracts to exclude articles that are clearly not relevant to the study
- retrieving the complete texts of papers that might be pertinent
- compiling several articles from the database
- reading articles in their entirety to confirm that the studies complied with the requirements
- getting in contact with researchers to discuss the study's eligibility, if needed
- selecting which study to include and moving forward with data extraction.

E. Data Extraction

Two reviewers separately removed data from the included studies. Lack of agreements were again resolved through discussion. Data was gathered using a corroboration list of articles that were considered finally for data extraction. The main items of this list were as follows:

- Authors, title and year of study
- Country
- Study design and sample size
- Single visit protocol
- Multiple visit protocol
- Clinical Outcomes
- Methods of outcome assessment
- Conclusion and other items

From all the studies included, specifics about the publication, the interventions, the comparison group, the result outcome, design of study, analysis and results and all other information (funding, conflicts of interest, etc.) were meticulously and precisely extracted. Extracted data was accessed and entered into the excel sheets for each of important clinical outcomes.

F. Critical Appraisal of Retrieved Studies (Risk of Bias Assessment)

Using the ROBINS-I technique, the risk of bias for each of the included studies was assessed. The seven disciplines that the ROBINS-I tool addresses could contribute bias into a non-RCT are as follows: Selection bias, confounding bias, miss-classification bias, bias resulting from planned interventions, missing data bias, outcome assessment bias, reporting bias.²

JBIC checklist was used for evaluating the quality of case reports and case series included in the review.³ The eight-item checklist is comprised of patient's demographics, medical history, current clinical status, description of diagnostic testing, treatment, clinical state post intervention, unforeseen events and any lessons learned.

The JBIC checklist for case series comprises of ten items that assess various critical aspects like validity of diagnostic methods, methods of condition measurement, inclusion of participants in a consecutive manner, the completeness of participant inclusion, reporting of demographic characteristics, clinical data, outcomes, the presentation of clinical demographic information and appropriateness of the statistical analysis.⁴

G. Meta-Analysis

Meta-analysis was conducted on the studies that provided information on similar outcomes.

Assessment of Heterogeneity:

Clinical heterogeneity defines how research findings differ amongst studies in terms of subjects, treatments, environments, comparators and results. The study design and the methodological quality of the studies (risk of bias) are referred to as methodological heterogeneity.

The percentage of impact estimate variability attributed to heterogeneity is expressed by I square statistics (I^2). I^2 is the percentage of observed dispersion of findings from different research that are genuine rather than erroneous when included in the meta-analysis.

If P values was less than 0.05, heterogeneity was deemed statistically significant. The Cochrane handbook's guidelines for interpreting I^2 are as follows:

- Heterogeneity may not be significant between 0 to 30 %
- Moderate Heterogeneity between 30% and 60%
- Substantial Heterogeneity between 50% to 90%
- Significant Heterogeneity between 75% and 100%.

Table 4: Showing History of Database Search with Different Keywords

History					Download history Clear history	
Search	Add to builder	Query	Items found	Time		
#13	Add	Search ((((((permanent teeth) OR permanent tooth) AND mature permanent teeth) OR mature permanent tooth)) AND ((regenerative endodontic procedure) AND single visit procedures)) AND (((regenerative endodontic procedure) AND multiple visit procedure) AND interappointment procedure)	7	12:39:48		
#12	Add	Search (((tooth survival) AND radiographic outcome) AND root length) AND root width) AND root apical diameter	247	12:38:59		
#11	Add	Search ((regenerative endodontic procedure) AND multiple visit procedure) AND interappointment procedure	15	12:37:44		
#10	Add	Search (regenerative endodontic procedure) AND single visit procedures	470	12:36:48		
#9	Add	Search (mature permanent teeth) OR immature permanent teeth	7867	12:36:02		
#8	Add	Search (((permanent teeth) OR permanent tooth) AND mature permanent teeth) OR mature permanent tooth	6478	12:35:24		

III. RESULTS

A. Study Selection

PubMed/MEDLINE, Cochrane library, CINAHL, EMBASE, PsycINFO, Scopus, ERIC, ScienceDirect were used as initial electronic database which resulted in 1593 articles, out of which 655 articles were found to be duplicates. After complete detailed search and reading the abstracts of all the articles, 91 relevant titles were selected by two independent reviewers were sought for retrieval and 757 were excluded for not being related to the inclusion criteria of our topic. Following examination and discussion by the reviewers, a total of 71 articles were chosen for full-text assessment. A manual search of the chosen studies reference lists produced no further publications to be included in our search criteria. After pre-screening, application of the criteria used in our study and handling of the PICO questions, 20 articles remained. Twenty studies were finally included in the systematic review were subjected for data extraction and statistical analysis. (Figure 1)

B. Study Characteristics

Twenty studies⁵⁻²⁴ were included in this systematic review (Table 1,2,3,4). Among the included studies, three were non-randomized clinical studies, fourteen were case reports and three were case series.

C. Characteristics of Clinical Studies

In the three clinical studies (Botero 2017, Cerqueira-Neto 2021, Karam 2023)⁵⁻⁷, a total of 88 teeth were evaluated using REP, out of which 41 teeth were treated using single visit REP and 43 teeth were treated using multiple visit REP. Overall, the participants were ranged from 6-25 years age. In the single visit protocol, root canal preparation and induction of bleeding was done in one appointment, where as in

multiple visit protocol, calcium hydroxide paste was used interim medicament between multiple visits.

The conclusions of studies indicated that both the approaches presented similar clinical and radiographic outcomes. In terms of success rate, multiple visit REPs were more successful as compared to single visit. However, the authors have emphasized the importance of undertaking more clinical trials on this topic to provide proper results.

D. Characteristics of Case Reports

Overall, six case reports mentioned single visit REP and eight reports mentioned multiple visit REPs.

➤ Single Visit Protocol

All the cases were female patients with age range of 7-12 years. One author (Shin 2009)⁸ followed pulp revascularization protocol while the rest of the reports used blood clot method by deliberate over instrumentation of the periapical area to induce bleeding in the root canal.

During the follow-up period, none of the cases showed any adverse event or failure of treatment. The conclusions of all reports indicated that single visit REP is a favorable treatment option.

➤ Multiple Visit Protocol

Among the included cases, four were females and four were males with an age range of 7-25 years. One case report (Alasqah 2020)¹⁷ used three visit protocol for REP while the remaining cases used two visit protocol. Different intracanal medicaments such as calcium hydroxide, double antibiotic paste, triple antibiotic paste, etc. were used in different cases. The inter-appointment time ranged from 1-4 weeks, based on the symptoms experienced by the patient.

E. Characteristics of Case Series

Among the three included case series, two used single visit protocol and one used multiple visit protocol. Overall, 10 patients were evaluated, of which 6 were treated by single visit REP and four were treated by multiple visit REP. The

follow-up period ranged from 12-30 months. In one case series (Sharaf 2023)²⁴, the outcome of single visit REP showed incomplete healing of peri-apical lesion after 12 months, thus implying the questionable clinical and radiographic outcomes with single visit REPs.

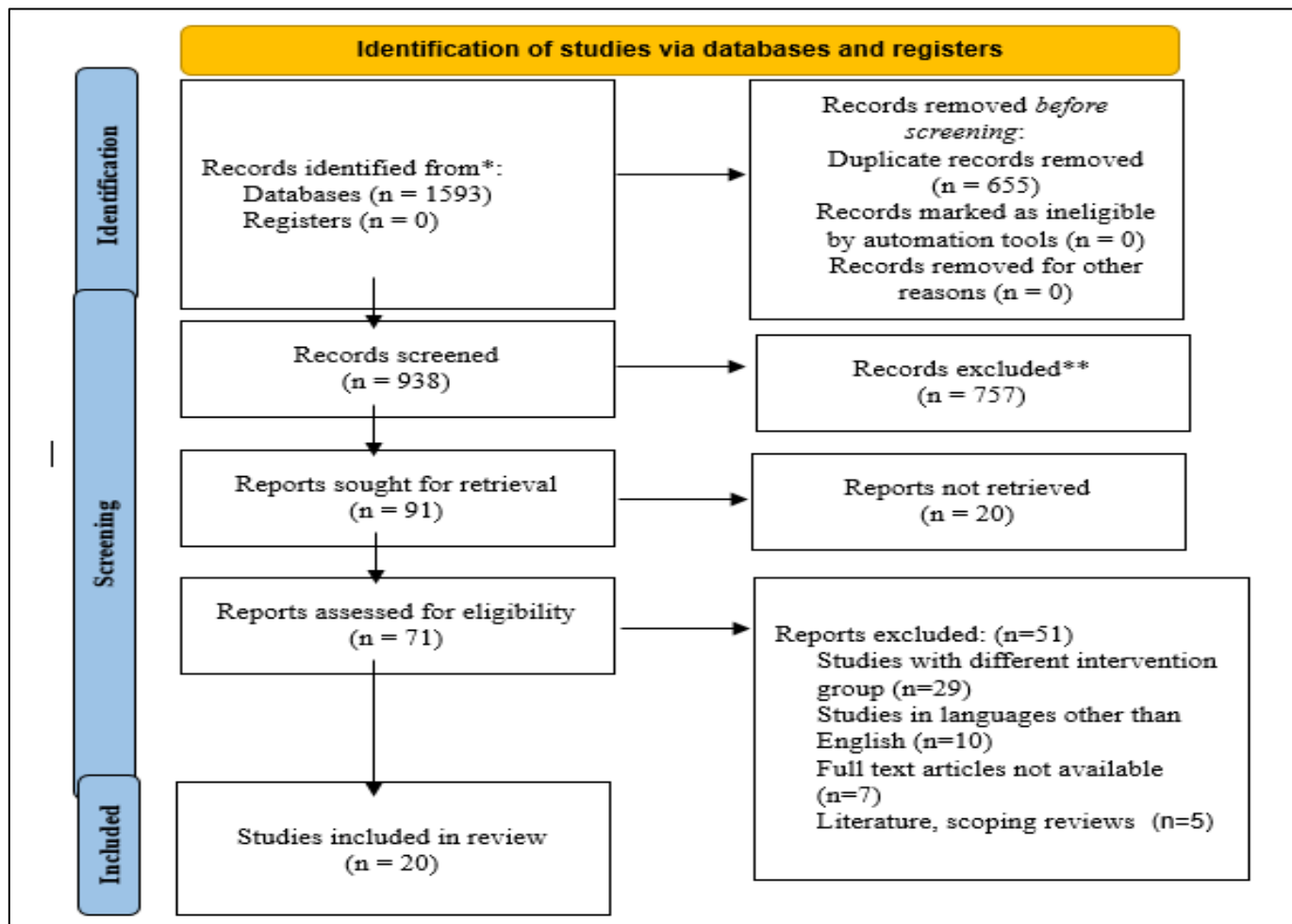


Fig 1: PRISMA 2020 Flow Diagram

IV. RISK OF BIAS ASSESSMENT

A. Clinical studies

Among the three included clinical studies, two showed low risk (Botero 2017, Cerqueira-Neto 2021)^{5,6} and one showed high risk (Karam 2023)⁷.

In study Karam 2023⁷, information related to confounders, selection of participants, classification of participants into groups was unclear.

Table 5: Showing Risk of Bias of Included Clinical Studies

Study Id	Confounding bias	Selection bias	Misclassification bias	Bias due to deviation from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias due to selective reporting of results	Risk of bias
Botero 2017 ⁵	Low	Low	Low	Low	Low	Low	Low	Low
Cerqueira-Neto 2021 ⁶	Low	Low	Low	Low	Low	Low	Low	Low
Karam 2023 ⁷	Unclear	Unclear	Unclear	Low	Low	Unclear	unclear	High

B. Case Reports

Among the included case reports, four showed high risk (Shin 2009, Alasqah 2020, Rahim 2022, Lenzi 2022)^{8,17,19,20},

one showed unclear risk (Alsharqawi 2023)²¹ and remaining ten reports showed low risk of bias. Details of quality assessment are mentioned in Table 6.

Table 6: Showing Quality Assessment of Case Reports

Study ID	Demographic characteristics	Patient history	Clinical presentation of condition	Diagnostic Tests used	Treatment procedure description	Post intervention Clinical condition	Adverse Events	Take away lesson	Overall appraisal
Shin 2009 ⁸	yes	no	Yes	yes	yes	yes	Yes	yes	High risk
Thompson 2010 ⁹	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low risk
Chen 2013 ¹⁰	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low risk
McCabe 2014 ¹¹	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low risk
Chaniotis 2015 ¹²	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low risk
Miltiadous 2015 ¹³	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low risk
Llaquet 2017 ¹⁴	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low risk
Kaval 2018 ¹⁵	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low risk
Alsofi 2019 ¹⁶	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low risk
Alasqah 2020 ¹⁷	Yes	No	Yes	Yes	Unclear	Yes	Yes	Yes	High risk
Turk 2020 ¹⁸	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low risk
Rahim 2022 ¹⁹	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	High risk
Lenzi 2022 ²⁰	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	High risk
Alsharqawi 2023 ²¹	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Unclear risk

C. Case Series

Among the included case series, two showed high risk of bias (Topcuoglu 2016 and Yoshoe 2019)^{22,23} and one showed low risk (Sharaf 2023)²⁴.

In case series by Topcuoglu²² 2016 and Yoshoe²³ 2019, information related to statistical analysis was not mentioned which led to high risk of bias in these cases.

Table 7: Showing Risk of Bias of Included Case Series

Study ID	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Overall appraisal
Topcuoglu 2016 ²²	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Unclear	No	High risk
Yoshpe 2019 ²³	Yes	No	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	No	High risk
Sharaf 2023 ²⁴	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low risk

V. META-ANALYSIS**A. Effect Measures**

In a meta-analysis, the standardized mean difference serves as a summary statistic in cases when studies evaluate the same outcome using different methods of measurement. Before the study data can be pooled in this case, they must first be standardized to a common scale. Standardized mean

difference (SMD) was therefore used as an effect metric for the quantitative assessment in this investigation.

Quantitative assessment was conducted on success rate and radiographic examination parameters.

B. Success of Treatment

Two studies were included in the evaluation of success of treatment with single and multiple visit REP. A total of 21 participants were included in single visit and 18 in multiple visits. The pooled OR obtained was 0.79[0.03, 18.70] indicating that the odds success of treatment were greater with multiple visits as compared to single visit REP. Overall,

the results were not statistically significant ($p>0.05$). Random effects model was used for assessment because of high heterogeneity ($I^2=65\%$).

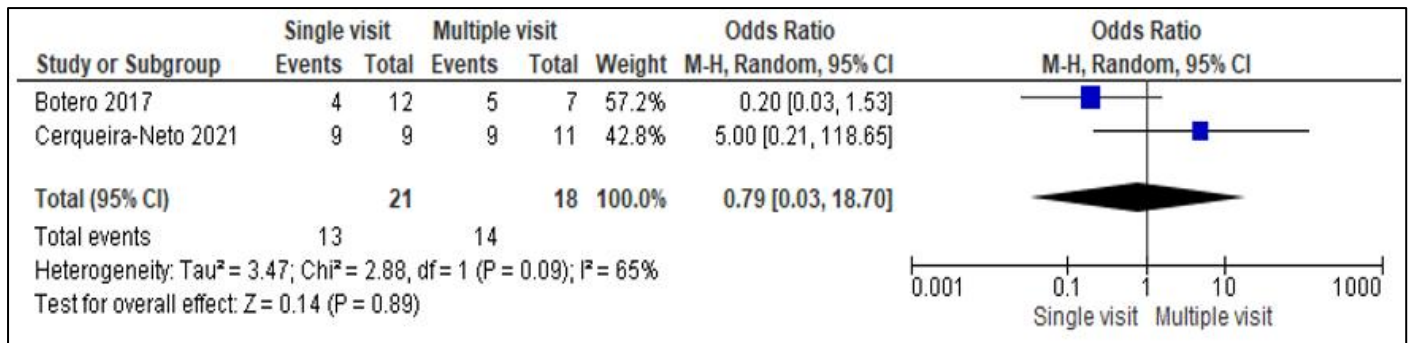


Fig 2: Showing Forest Plot Graph for Success of Treatment with Single and Multiple Visit Regeneration

C. Radiographic Outcomes

Two studies were included in the assessment of apical root diameter with single and multiple visit REP. Total 29 participants were included in single visit and 31 in multiple visits. The pooled SMD obtained was 0.28[-0.22, 0.79] indicating that the apical root diameter post treatment was greater with single visit REPs as compared to multiple visit REP. In general, the outcomes lacked statistical significance ($p>0.05$). Random effects model was used for assessment.

indicating that the root width post treatment was greater with single visit REP as compared to multiple visit REP. Overall, the results were not statistically significant ($p>0.05$). Random effects model was used for assessment.

Two studies were included in the assessment of Root width with single and multiple visit REP. A total of 29 participants were included in single visit and 31 in multiple visits. The pooled SMD obtained was 0.58[-0.19, 1.35]

Two studies were included in the assessment of root length with single and multiple visit REP. A total of 29 participants were included in single visit and 31 in multiple visits. The pooled SMD obtained was 0.36[-0.49, 1.22] indicating that the root length post treatment was greater with single visit REP as compared to multiple visit REP. The findings were not statistically significant overall ($p>0.05$). Random effects model was used for assessment.

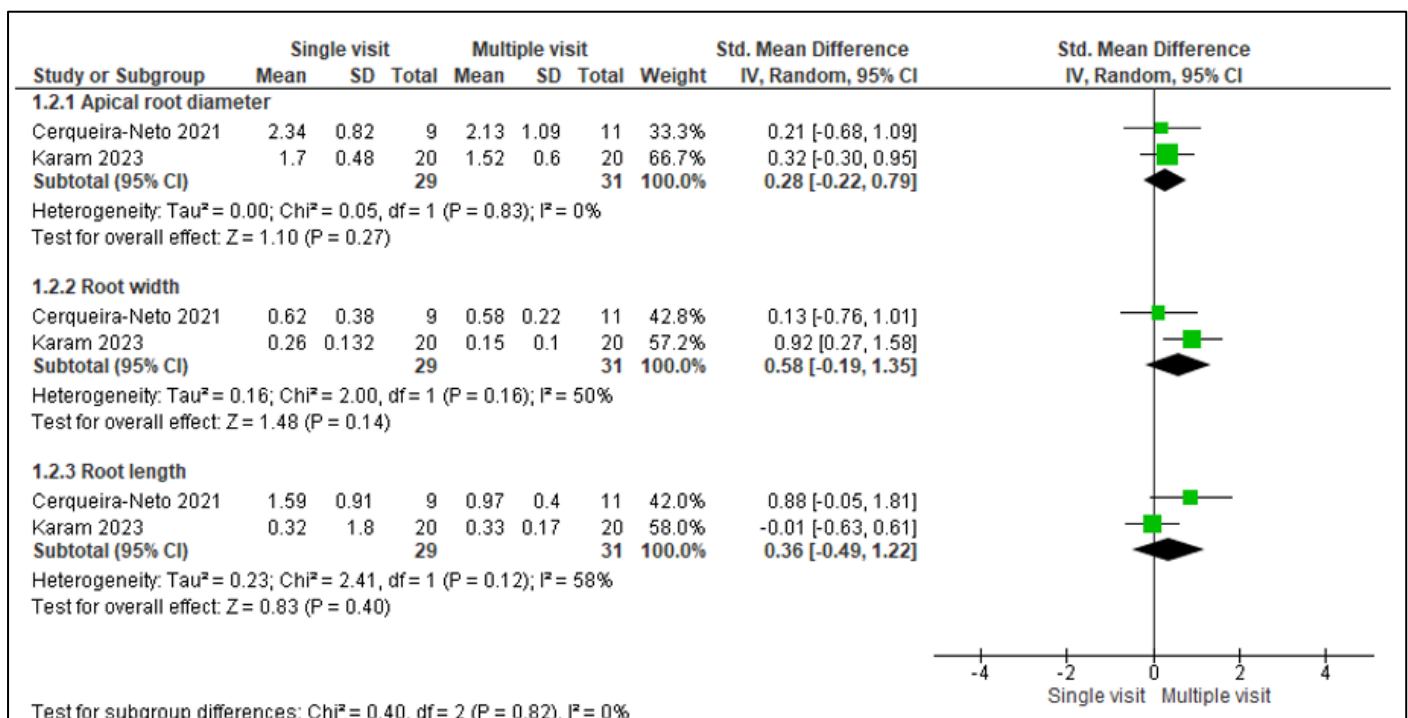


Fig 3: Showing Forest Plot Graph for Radiographic Outcome of Treatment with Single and Multiple Visit Regeneration

VI. DISCUSSION

Till date, current published data on REPs are composed of case study, prospective randomized clinical trials, case series, fewer retrospective cohort studies and very fewer systematic reviews for patient outcome in single visit and multiple visit regenerative endodontics. Our study is done to perform comprehensive review on effectiveness of single and multiple visit regenerative endodontics and compare patient reported outcomes in Single visit and Multiple visit regenerative endodontics in permanent teeth. Regenerative endodontics used tissue engineering technique and aimed to treat immature permanent teeth with pulpal necrosis by stimulating new pulpal tissue.

During REPs, the objective of stimulating intra-canal bleeding till the cemento-enamel junction is to dispense blood clot which act as a framework, thereby helping to induce stem cells and growth factors from apical third area into canal lumen to encourage tissue regeneration. In the case reports included in our review all studies have used blood clot as scaffold and which has shown tremendous positive results. The obtainable guidelines of AAE have suggested that lidocaine with vasoconstrictor should be avoided at the subsequent appointment after first visit which allows the bleeding into the root canal system. Inadequate intra-canal bleeding, violation of apical constriction during working length determination and removal of antibiotic paste and the use of local anesthesia containing vasoconstrictor are the most common probability for the failure to induce sufficient bleeding.

Platelet-rich plasma (PRP) forms a three-dimensional fibrin matrix that facilitates the extraction of growth factors even in a relatively sterile environment. PRP increases the differentiation of undifferentiated mesenchymal cells from the periapex by providing a sustained release of growth factors. PRP produces platelet concentrations that are higher than baseline, stabilizing pre-existing blood clots and encouraging angiogenesis. PRP provides the increased platelet concentration than baseline which stabilizes the already existing blood clot and promotes the angiogenesis. An increased number of platelets increases the number of growth factors secreted by them that help in the proliferation of stem cells to induce periapical healing and regeneration of tissues. The disadvantages of this procedure include withdrawal of blood in patients, the need of centrifugal machine and stimuli to prepare PRP, and the increased cost of treatment. According to systematic review and meta-analysis by Rahul²⁵ et al which concluded that different scaffolds of blood clot, PRP and PRF did not show any statistically significant difference in clinical outcome, apical root closure and pulp sensibility. Study by Thompson⁹ et al only showed the return of pulp sensibility to normal in 18 months follow up examination which was not evident in the other included studies.

Results from preliminary data from Botero⁵ comparing single visit versus multiple visit regenerative endodontics showed clinical success rate of 71% for multiple visit regenerative endodontics and a 33% success rate for single

visit regenerative endodontics with no statistically significant difference which was in harmony to our results in terms of clinical success rate showing better for multiple visit REPs but there was no statistical difference between single visit REPs and multiple visit REPs.

Comparing REPs with an interappointment dressing versus a single-visit protocol showed equivalent primary, secondary and tertiary clinical outcomes as well as quantitative radiographic outcomes according to Cerqueira-Neto⁶. On contrary our study concluded that apical root diameter, root length and root width post treatment was greater with single visit REP as compared to multiple visit REP but it was statistically not significant.

Among the eight included case reports, six studies used MTA whereas two studies used Bio dentine and Endo sequence BC RRM putty as an intra-coronal barrier. The MTA have been preferred by most clinicians as it sets even in the presence of moisture, excellent marginal adaptation & sealing ability, excellent biocompatibility and tissue-conductive properties. The disadvantage of utilizing MTA is chances of mild to moderate tooth discoloration. Conversely, the use of Biodentine was justified in study by Turk¹⁸, in order to prevent this treatment complication. Further clinical trials should be performed to understand the potential use of other bioactive endodontic cements for REPs.

Our meta-analysis demonstrated that success of treatment was greater with multiple visits as compared to single visit REP but the results were not statistically significant in terms of clinical outcome. It also concluded that root end closure, root diameter and the root length post treatment was greater with single visit REP as compared to multiple visit REP but the results were not statistically significant.

There is a lacuna of randomized clinical trial been done till now on single visit regenerative endodontics and very few done on comparison of single visit regenerative endodontics and multiple visit regenerative endodontics. Our results have shown that there is no statistical difference between clinical outcome and radiographic outcome for single visit regeneration and multiple visit regeneration, so more clinical trials should be done on performing randomized control trials to examine efficiency of different scaffolds, disinfection protocol usage in regards to measuring the clinical outcome and radiological healing assessment for single visit regeneration.

Previously already multiple systematic review has been done in recent past on randomized control trials study of multiple visit regeneration endodontics, so we have not included the same randomized control trials in our study. Since very few studies comparing the single and multiple visit regeneration endodontics are conducted and we could analyze only those studies, the results cannot be extrapolated.

In our study we have included case reports and case series for single visit & multiple visit regeneration as it was coming under our criteria of observation. However, this study opens up new possibilities for future clinical trials comparing single and multiple visit regenerative endodontics and studies on only single visit regenerative endodontic therapy evaluating the clinical outcome and radiological success rate.

VII. CONCLUSION

Clinically and radiologically regenerative endodontic procedures present favorable patient-based outcome to conventional procedures done in necrotic open apices cases. Prolonged discussions within the endodontic fraternity regarding the constraints of apical preparation, apical size and its management by different obturation materials may not be relevant to this relatively new therapeutic modality using blood clot, Platelet rich plasma and Platelet rich fibrin. In order to establish a consistent treatment regimen that would result in a more predictable clinical and radiological outcome, clinicians are encouraged to concentrate their study on the investigation of the biological basis of this unique method. Our study indicated that both the approaches presented similar clinical and radiographic outcomes in delayed induction and immediate regeneration. In terms of success rate, multiple visit REP was more successful as compared to single visit. It is imperative to do more clinical research in the field of regenerative endodontics.

ABBREVIATIONS

- MTA - Mineral trioxide aggregate
- NaOCl- Sodium hypochlorite
- REPs- Regenerative endodontic procedures
- SMD- Standardized mean difference
- PRP- Platelet rich plasma
- PRF-Platelet rich fibrin
- RCTs- Randomized controlled trials

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