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To Assess Effectiveness Between Regenerative Endodontic Procedures (REP) and Apexification Procedures (AP) with Mineral Trioxide Aggregate (MTA) and Calcium Hydroxide for Inducing Root End Apex Closure. A- SRMA

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ABSTRACT

Aim: To assess effectiveness between regenerative endodontic procedures (REP) and apexification procedures (AP) with mineral trioxide aggregate (MTA) and calcium hydroxide for inducing root end apex closure.

Methods: Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) 2020 guidelines were followed and registered in PROSPERO - CRD42024598501. Electronic databases were searched for studies evaluating effectiveness of REP and AP in terms of survival rate, success rate, increase in root length, root width and decrease in apical diameter. Cochrane risk of bias (ROB) -2 tool was used for risk of bias evaluation using Review manager (RevMan) 5.3. The risk ratio (RR) and standardized mean difference (SMD) was used as summary statistic measure with random effect model ($p<0.05$).

Results: Nine studies were included in qualitative synthesis and eight studies for meta-analysis. Quality assessment revealed moderate to low risk of bias. The pooled estimate through RR and SMD favoured REP being superior to AP for better survival rate (RR = 1.01 (0.96 – 1.06)), success rate (RR = 1.09 (0.96 – 1.24)), increase in root length (SMD = 0.25 (-0.14 – 0.63)), root width (0.66 (0.22 – 1.10)) and decrease in apical diameter (SMD =0.66 (-0.51 – 1.83)). Funnel plot did not show any heterogeneity indicating absence of publication bias.

Conclusion: REP significantly improved apical root end closure. AP are equally effective in forming calcific barrier, however it was concluded that regeneration procedures are comparably superior to apexification procedures with greater outcomes. Clinicians should consider employing the REP in cases when root development is severely deficient and where tooth's prognosis is hopeless even with an apexification procedure

Keywords: Apexification, Necrotic Pulp, Regenerative Endodontics, Revascularization, Root Canals

INTRODUCTION

The main aetiology for infected immature permanent teeth is traumatic dental injury, particularly intrusions, avulsions and combined injuries.[1-3]

Treatment of infected immature permanent teeth is a challenge for endodontists.[1] The presence of thin dentinal root walls makes teeth more susceptible to fractures.[2] In addition, chemical–mechanical preparation, working length determination and obturations are difficult to accomplish due to the presence of open apices. [4,5] In such cases, the conventional treatment is apexification with periodic changes in calcium hydroxide-based intra canal medications or placement of an apical plug with mineral trioxide aggregate (MTA).[6] Both treatments aim to form an apical calcific barrier.[6] Although these procedures result in the resolution of the infection and the remission of signs and symptoms, they do not allow continued root development, and the teeth persist with thin and fragile dentinal walls.[7]

There are numerous challenges that the clinician faces when treating infected pulp in immature permanent teeth. The cleaning and shaping of the root canal system is challenging because of the thin dentinal walls. Obturation is also complicated because the apex is not fully developed and has a blunderbuss shape. Moreover, these teeth may be susceptible to fracture during or after treatment.[8] Traditionally, a calcium hydroxide–based apexification procedure has been advocated for treating an immature permanent tooth with an open apex.[9] Teeth treated with this

apexification procedure require a long-term application of calcium hydroxide in order to create an apical barrier to prevent the extrusion of obturation materials.[10] However, there are several drawbacks to this traditional apexification procedure, including a potential calcium hydroxide–mediated reduction in root strength and the requirement for excellent patient compliance because of the need for multiple visits scheduled over many months.[10] Thus, the traditional calcium hydroxide treatment approach for these cases may be less than ideal for many patients.[11]

Alternative apexification methods have recently been proposed. Mineral trioxide aggregate (MTA), used in a 1- or 2-step apexification procedure, has been shown to create an artificial apical barrier that permits the compaction of obturating material and the placement of coronal restoration.[5]

In contrast, RET or Regenerative Endodontic Surgery (REPS) is a biological procedure designed to replace damaged structures such as roots and dentin, as well as cells in the pulp- dentin complex.[11] The main purpose of REPS is to stimulate mesenchymal stem cells such as bone/dental progenitor stem cells, dental pulp tissue in the root canal and to create a suitable environment for the continuous development of root and to avoid any deficient root development. [12]

Some studies compared the treatment outcomes of apexification and regenerative endodontic procedure; both procedures promote satisfactory success rates ranging from 68% to 100%, with the infection being resolved as well as remission of signs and symptoms.[13-15] Concerning the continuation of root development, the results found in the literature vary, showing rates of increase in root length from 8.55% to 14.9% and increased width of dentin walls ranging from 1.4% to 28.2%, in addition to involving different aetiologies for pulp necrosis.[14,15]

Studies has been conducted on clinical comparison of REP and AP, but no study to date has provided a comprehensive analysis of the comparison between REP and AP. Therefore, we conducted the current study by including relevant data and perform a qualitative analysis in order to compare and evaluate the effectiveness of the two treatments modality through a meta- analysis.

METHODOLOGY

Protocol development

Review was performed in according to PRISMA 2020 guidelines [16] and registered in PROSPERO (prospective registration of systematic review) – CRD42024598501.

Study design

Participants (P), Intervention (I), Comparison and Outcome (O) format was used for proposed focused research question "Is there any difference in the effectiveness of regenerative endodontics (C) and apexification procedures (I) in patients with necrotic permanent tooth (P) with regards to (O) survival rate, success rate, increase in root length, root width and decrease in apical diameter"?

Eligibility Criteria: Inclusion Criteria:

1. Articles in English language and having sufficient data on effectiveness of REP and AP and reporting outcome in terms of survival rate, success rate, increase in root length, root width and decrease in apical diameter
2. Studies published between January 2000 till April 2024 and as free available full text articles and from open access journals
3. Comparative studies and clinical studies were taken into consideration
4. Study involving assessing the study outcome in terms of mean and standard deviation

Exclusion criteria:

a. Articles in other than English language Reviews, abstracts, letter to the editor, editorials, animal studies and in vitro studies will be excluded
b. Articles not from open access journals
c. Articles not reporting the study outcomes in terms of mean and standard deviation

Search Strategy
An electronic search was performed from January 2000 till April 2024 for the studies published within the last 24 years using the following databases: PubMed, google scholar and EBSCOhost. Cross-referencing were explored and grey literature search were conducted using Google Scholar, Greylist, and OpenGrey.

Search Strategy according to PICO Format:

	Strategy
Population	(("immature teeth"[MeSH Terms] OR "open apices" OR "tooth injury" OR ("necrotic pulp"[MeSH Terms] OR "immature root" OR ("traumatic tooth injury"[MeSH Terms] OR ("root canal treatment"
Intervention	((("apexification"[MeSH Terms] OR ("apical periodontitis" AND "calcium hydroxide" AND "mineral trioxide aggregate" OR "revascularization" OR "regeneration" OR ("tooth vitality"[MeSH Terms] OR ("dentinal wall width" AND "minimal instrumentation" OR "blood induction" OR ("canal healing")[MeSH Terms]
Comparator	(("regenerative endodontics" OR "revascularization"[MeSH Terms] OR ("artificial neural network" AND "treatment" OR "increase in root length" OR ("increase in root width" AND "decrease in apical diameter" OR "apical plug"
Outcome assessed	((("periapical healing"[MeSH Terms] OR "clinical outcome" OR ("clinical success"[MeSH Terms] OR ("endodontics" AND "maturogenesis" OR "success rate"OR ("survival rate"AND "randomized controlled trial" AND "clinical study" OR "prospective study"

Screening Process
A rigorous two-phase screening process was conducted by two authors to select relevant articles. Initially, titles and abstracts were reviewed, and non-relevant articles were excluded. Same reviewers independently performed the review of full text articles, with disputes resolved through discussion. A third reviewer was consulted when necessary to ensure consensus.

Data extraction
The descriptive study details were extracted with the following headings: author(s), country of study, year of study, sample size, reason for pulp necrosis, irrigation material used, intracanal medicament used, follow up duration, intervention and comparator group.

Quality assessment of studies
Quality assessment was performed by using Cochrane collaboration risk of bias (ROB) -2 tool [17] through its various domains in Review Manager (RevMan) 5.3 software.

Statistical analysis
Statistical analysis was performed with standardized mean difference (SMD) serving as the summary measure. Significance was determined at the threshold of $p<0.05$.[18]

Assessment of heterogeneity
The Cochranes test for heterogeneity was employed to assess the significance of any differences in treatment effect estimations among trials. Heterogeneity was deemed statistically significant if the P-value was <0.01.[19]

Investigation of publication bias
The study assessed publication bias using Begg's funnel plot, which plots the effect size against standard error. Asymmetry in the funnel plot may indicate potential publication bias.[20]

RESULTS

Study Selection

After duplicates removal, reference list of included studies was screened. Of which 116 studies were excluded. After this full text articles were assessed for eligibility and articles that did not meet inclusion criteria were excluded. Nine studies fulfilled eligibility criteria and were included in qualitative synthesis and eight studies for in meta – analysis. A flowchart of identification, inclusion and exclusion of studies is shown in **Figure 1 below**

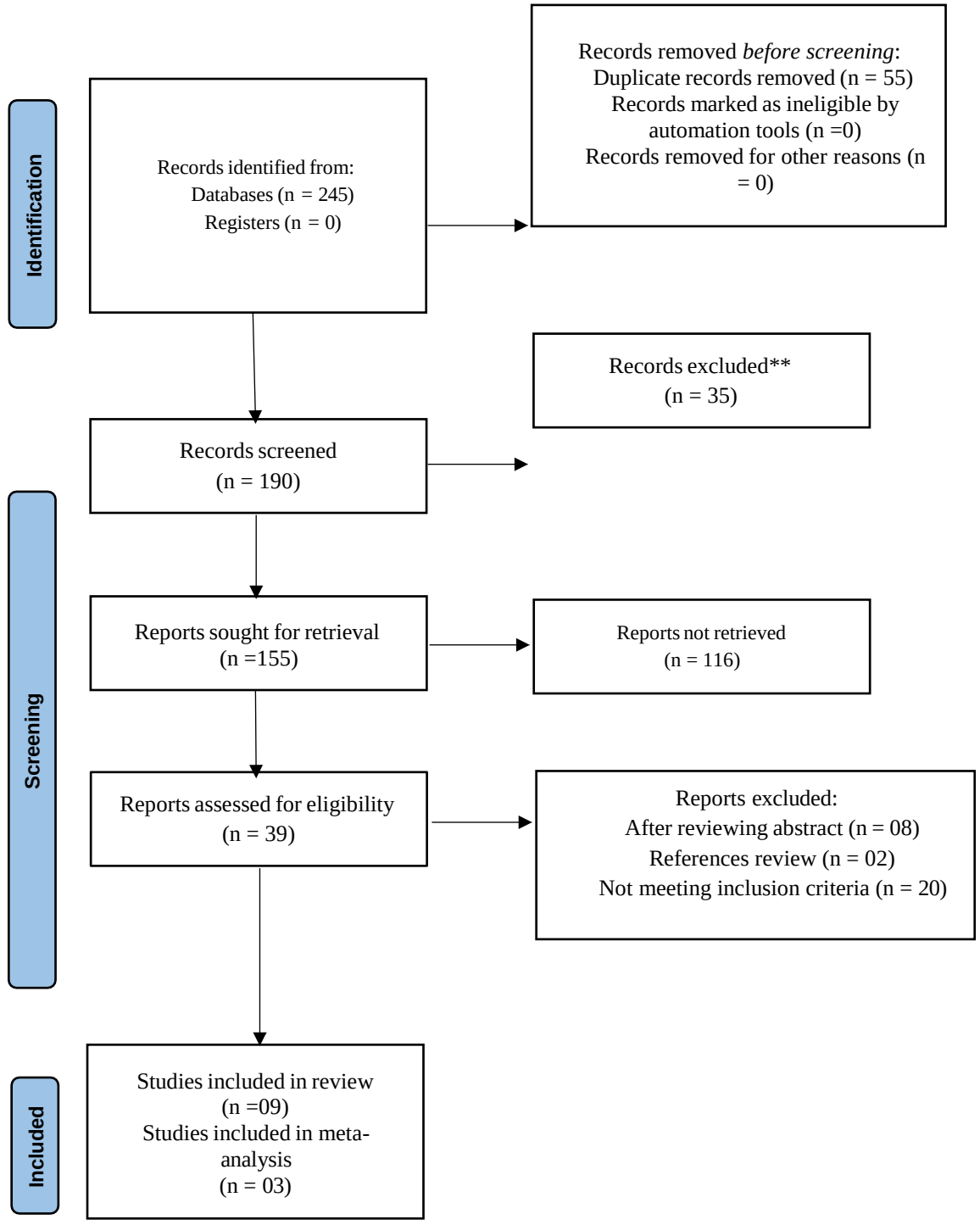

Figure 1. PRISMA 2020 Flow Diagram

Study Characteristics

A summary of qualitative study characteristics all included studies is shown in **Table 1.** Data was evaluated from nine studies[21-29] from a total of 671 teeth with pulp necrosis having undergone the endodontic treatment. Trauma and caries were the common reason for pulp necrosis with presence of periapical pathology. All the included studies had randomized controlled trial (RCT) study design. EDTA and NaOCL were the most commonly used irrigants with placement of triple antibiotic paste (TAP) and calcium hydroxide as intracanal medicament. All the included studies had regenerative endodontic procedure (REP) compared against the apexification procedure with MTA and $Ca(OH)_2$ with a mean follow up duration of 15 months for inducing incomplete root formation and proper apical closure. Assessment of outcomes like survival rate, success rate, increase in root length, root width and decrease in apical diameter were assessed quantitatively.

Table 1: Showing Descriptive Characteristics Of Included Studies

Author, years of study	Study type	mple size	Pulp necrosis reason	Irrigation method	Intracanal medicament	Follow up (months)	Intervention	Comparator group
Alobaid et al. 2014[21]	RCT	31	Trauma	17% EDTA	TAP	15-22	REP	AP
Awies et al. 2017[22]	RCT	22	Trauma/Caries	5.25% NaOCL	TAP	12	REP	AP
Chen et al. 2015[23]	RCT	38	Trauma/Caries	2.5% NaOCL	-	12	REP	AP
Felippe et al. 2006[24]	RCT	20	Caries	1.5% NaOCL	$Ca(OH)_2$	5	REP	AP
ruphan et al. 2012[25]	RCT	61	Trauma/Caries	5.25% NaOCL	TAP	24	REP	AP
Lin et al. 2017[26]	RCT	103	Trauma	1.5% NaOCL, 17% EDTA	TAP	12	REP	AP
Pereira et al. 2020[27]	RCT	44	Trauma	1.5% NaOCL, 17% EDTA, saline and CHX	TAP	12-30	REP	AP
Silujjal et al 2016[28]	RCT	43	Trauma/Caries	1.5% NaOCL, 17% EDTA	$a(OH)_2$ / TAP	12-96	REP	AP
Xuan et al. 2018[29]	RCT	30	Trauma	-	-	12	REP	AP

AP- apexification procedure; CHX- chlorhexidine; EDTA- ethylene dioxide tri-aggregate; REP- regenerative endodontics procedure; Tap- triple antibiotic paste

Quality assessment of included studies

The highest risk of bias was seen for allocation concealment followed by selective reporting. All of the included studies reported moderate to lowest risk of bias. Domains of rando sequence generation, blinding pf participants and personnel, blinding of outcome assessment, incomplete outcome data and other bias were given lowest risk of bias as depicted in **Figure 2 and 3** as

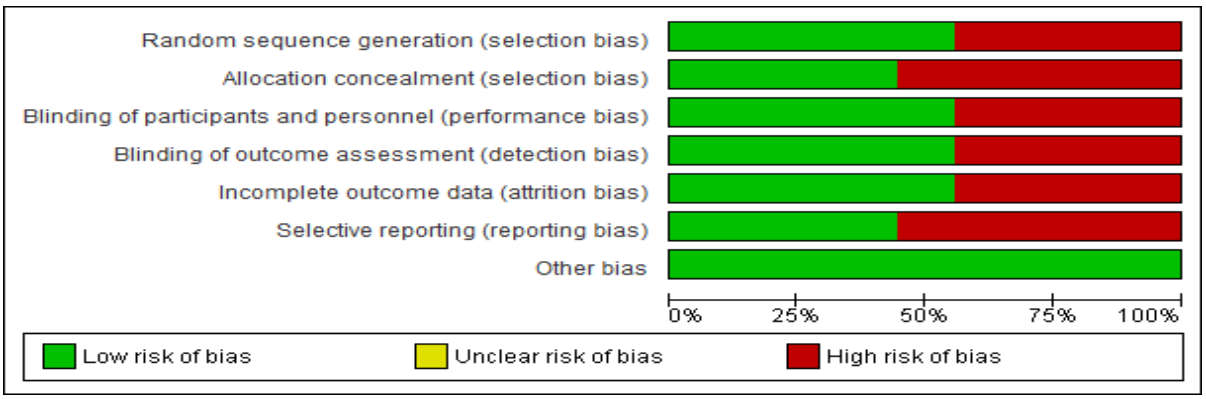

Figure 2: Showing Risk Of Bias Graph: Presented As Percentages Across All Included Studies.

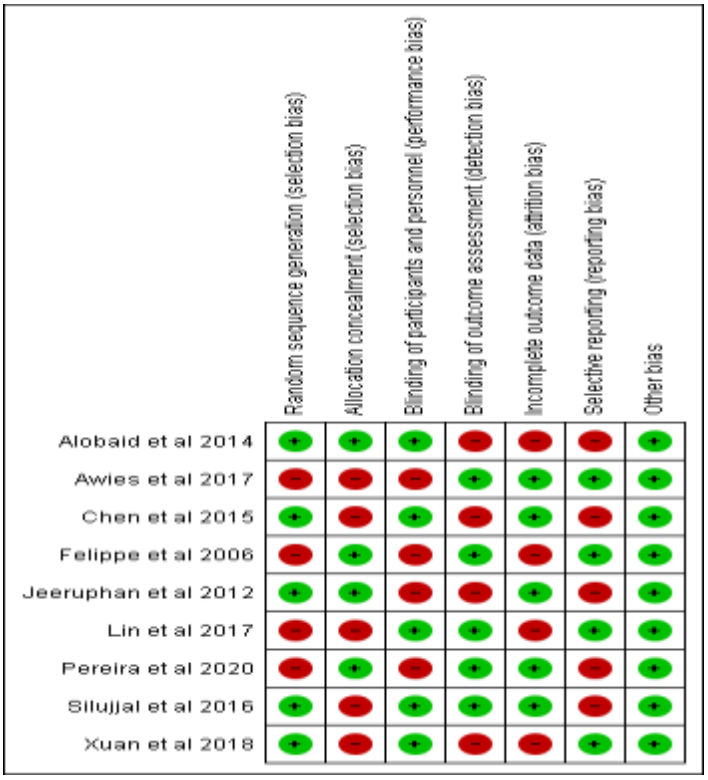

Figure 3: Showing Risk Of Bias Summary: For Each Included Study

Synthesis of Result

The meta-analysis was performed for assessing the outcome in terms of survival rate, success rate, increase in root length, root width and decrease in apical diameter **as shown below in figures 4-10**.

Survival rate

Three studies[21,25,26] containing data on 174 teeth, of which (n=101) teeth were evaluated by regenerative endodontic procedure (REP) and (n=73) teeth by apexification (AP) for the evaluation of the better effectiveness between the two in terms of better survival rate.

As shown in **Figure 4.** the RR is 1.01 (0.96 – 1.06) and the pooled estimates favours REP. This signifies that survival rate on an average was 1.01 times more in REP compared to AP. (p>0.05).

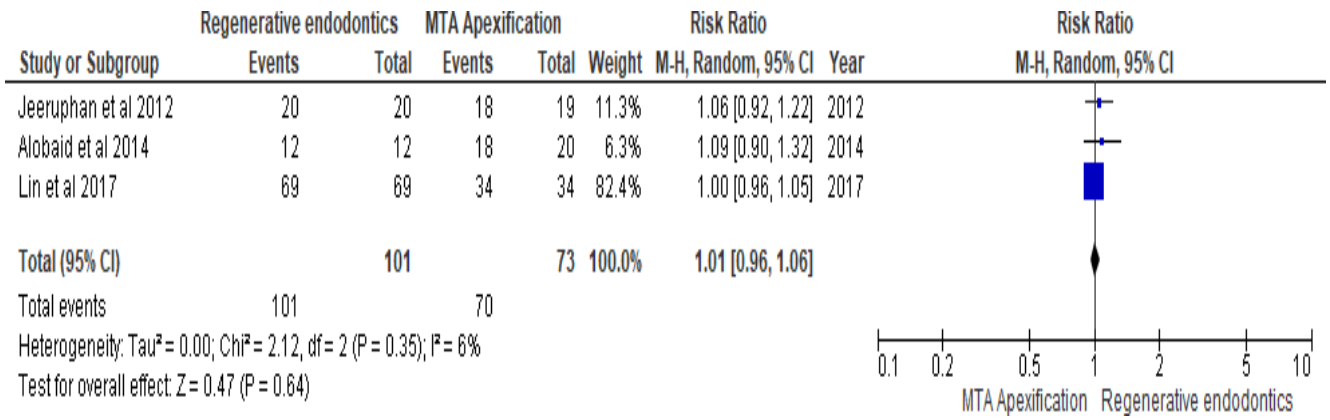

Figure 4: Survival Rate Comparison With REP Or Apexification Procedure

Success Rate

Five studies[21,23,25,27,28] containing data on 195 teeth, of which (*n*=87) teeth were evaluated by regenerative endodontic procedure (REP) and (*n*=108) teeth by apexification for the evaluation of the better effectiveness between the two in terms of better success rate.

As shown in **Figure 5.** the RR is 1.09 (0.96 – 1.24) and the pooled estimates favours REP. This signifies that success rate on an average was 1.09 times more in REP compared to AP. (*p*>0.05).

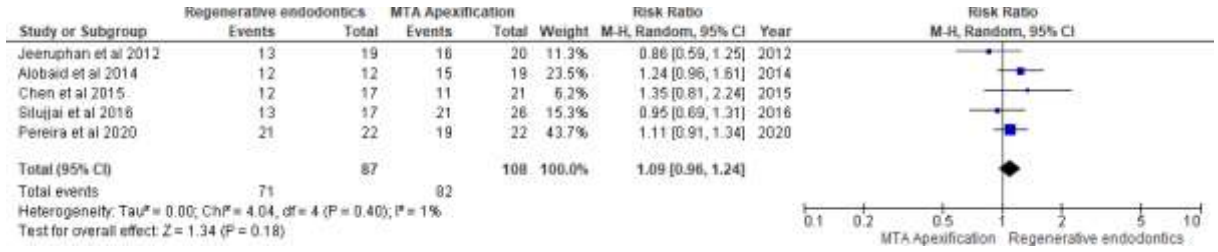

Figure 5: Success rate comparison with REP or apexification procedure

Increase in Root Length

Three studies[22,27,28] containing data on 109 teeth, of which (*n*=50) teeth were evaluated by regenerative endodontic procedure (REP) and (*n*=59) teeth by apexification for the evaluation of the better effectiveness between the two in terms of increase in root length.

As shown in **Figure 6.** the SMD is 0.25 (-0.14 – 0.63) and the pooled estimates favours REP. This signifies that increase in root length on an average was 0.25 times more in REP compared to AP. (*p*>0.05).

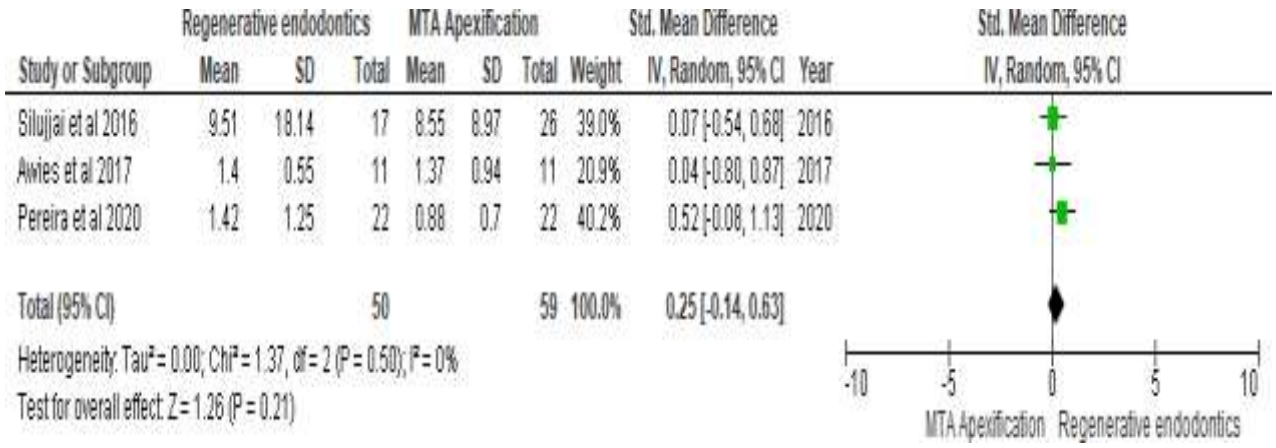

Figure 6: Increase in root length comparison with REP or apexification procedure

Increase in Root Width

Two studies[27,28] containing data on 87 teeth, of which (*n*=39) teeth were evaluated by regenerative endodontic procedure (REP) and (*n*=48) teeth by apexification for the evaluation of the better effectiveness between the two in terms of increase in rot width.

As shown in **Figure 7.** the SMD is 0.66 (0.22 – 1.10) and the pooled estimates favours REP. This signifies that increase in root width on an average was 0.66 times more in REP compared to AP. (*p*>0.05).

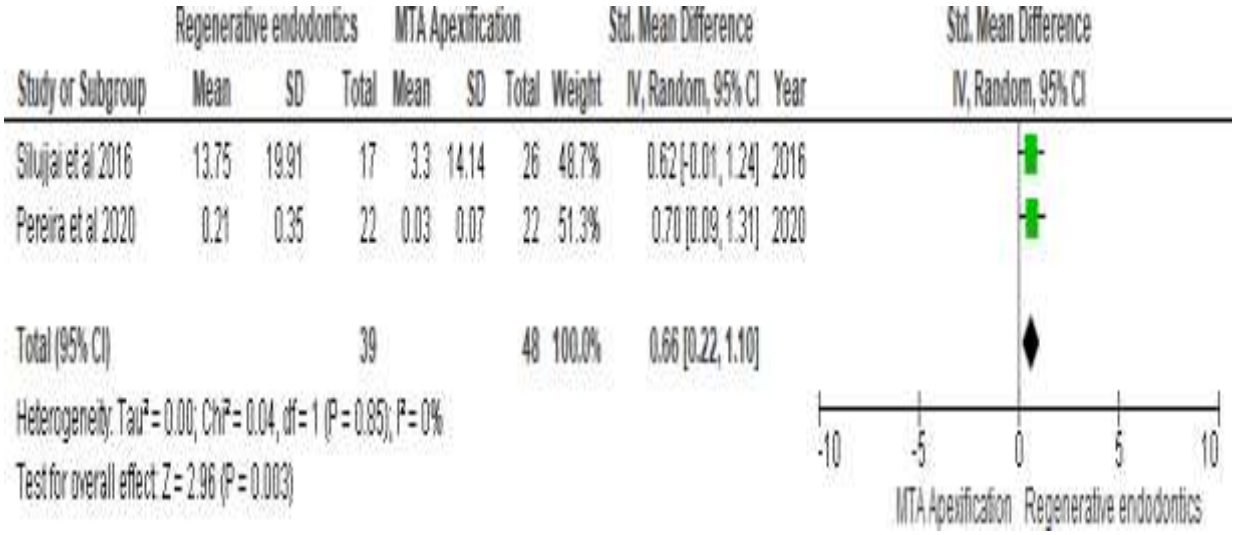

Figure 7: Increase in root width comparison with REP or apexification procedure

Decrease in apex diameter

Four studies[22,26,27,29] containing data on 244 teeth, of which (*n*=132) teeth were evaluated by regenerative endodontic procedure (REP) and (*n*=112) teeth by apexification for the evaluation of the better effectiveness between the two in terms of decrease in apex diameter.

As shown in **Figure 8.** the SMD is 0.66 (-0.51 – 1.83) and the pooled estimates favours REP. This signifies that decrease in apex diameter on an average was 0.66 times more in REP compared to AP. (*p*>0.05).

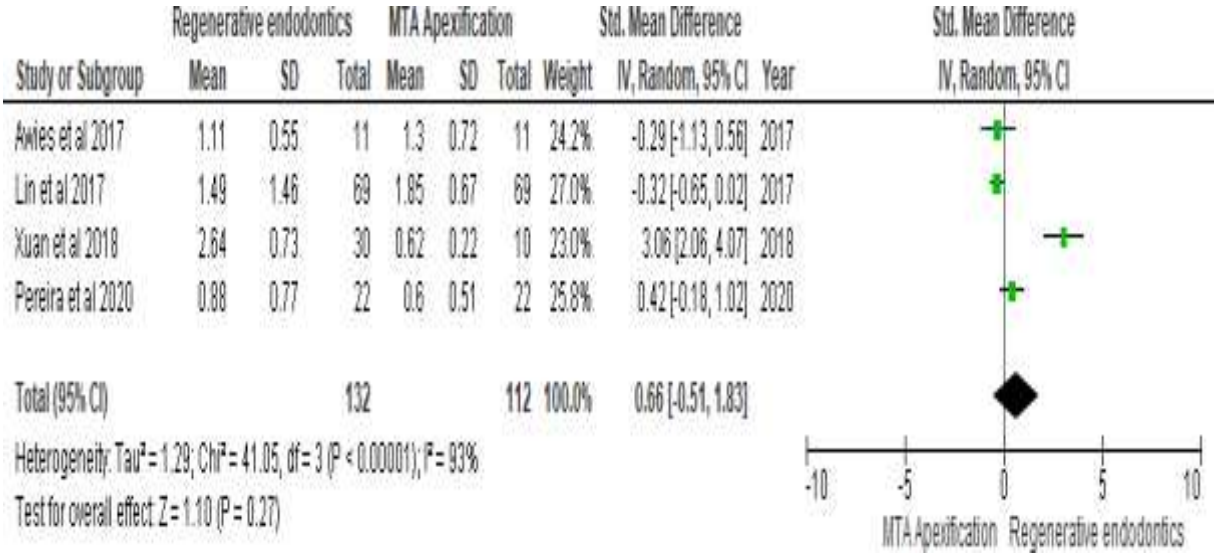

Figure 8: Decrease in apex diameter comparison with REP or apexification procedure

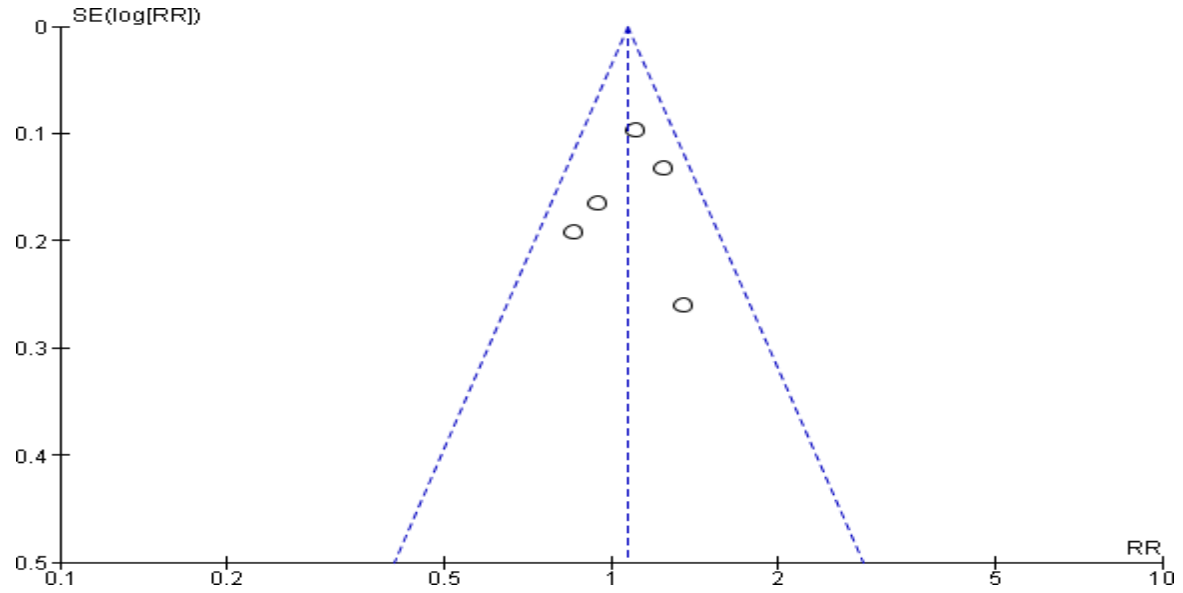

Figure 9: Showing Begg's Funnel Plot With 95% Confidence Intervals Demonstrating An Absence Of Publication Bias.

DISCUSSION

RET and apexification are 2 treatment modalities for an immature tooth with pulp necrosis and apical periodontitis. The success rate of RET and apexification have been reported in several clinical studies.[12,14] Calcium hydroxide and MTA have been used for apexification. One- session apexification using MTA could build an artificial barrier without any change of the root, whereas apexification with calcium hydroxide could achieve a calcification barrier, which may contribute to an increased root length. To better evaluate the effect on root development of RET, we chose the apexification technique (calcium hydroxide) as the control group in the present study.

Regeneration was proposed by the literature as technique to provide the proper environment for continuing the root formation thus increasing root length and dentin thickness and decreasing the apical foramen diameter.[1,8] The concept of the revascularization techniques is based on the differentiation of the vital stem cells into secondary odontoblasts, ultimately allowing dentin deposition (9) . Jeeruphan et al.[22] have found that the MTA apical plugging and the regenerative procedure were successful treatment options regarding the apical closure.

REP can be a significant clinical benefit, especially for immature teeth. However, there are still drawbacks that needs to be addressed to improve the quality and efficiency of the treatment.

This systematic review was conducted to provide a quantitative comparative analysis between regenerative endodontics and apexification procedures with mineral trioxide aggregate and calcium hydroxide for inducing incomplete root formation and proper apical closure. Both the interventions are aimed at saving immature necrotic teeth. The outcomes assessed were better survival rate, success rate, increase in root length, root width and decrease in apical diameter. Based on eligibility criteria's nine studies were included in review. Included studies had moderate to low level of bias. The results of meta-analysis revealed that REP was overall superior to AP with regards to better survival rate (RR = 1.01 (0.96 – 1.06)), success rate (RR = 1.09 (0.96 – 1.24)), increase in root length (SMD = 0.25 (-0.14 – 0.63)), root width (0.66 (0.22 – 1.10)) and decrease in apical diameter (SMD =0.66 (-0.51 – 1.83)).

However, the results of this systematic review are consistent with the systematic review and review by Panda et al. 2022 [27] to compare clinical outcomes using endodontic therapy (RET) and apexification in the treatment of young, immature teeth. Clinical outcomes such as dentin wall thickness (DWT), root length increase (RL), apical closure (AC), viability response (VR) and success rate (SR) were evaluated. The survival rate was found to be similar in both interventions; However, if root development is poor, dentin is insufficient, and the prognosis of the tooth is hopeless even with apical treatment, RET should be preferred.

Systematic review [28] evaluated the clinical` and functional outcomes of immature teeth treated with endodontic revascularization or apexification after at least three months of follow up to determine which was most effective. The authors concluded that although endodontic revascularization surgery can make roots longer and wider, trials are needed to measure the "true increase" in root growth using the standard model because some electronic interventions may exaggerate the gain. It is also concluded that appropriate root canal medications should be considered to improve

SCAP survival while reducing microbial infection and infection risk. According to their meta-analysis, the results did not favour one treatment over the other.

Another review [29] evaluated the clinical and radiographic outcomes of non-vital permanent teeth treated with RET, and the authors found positive tooth survival and periapical pathology after RET. However, results regarding better outcomes such as continued root growth are unclear. This study also follows up on the results of our review.

The systematic review adhered to PRISMA guidelines, employing a comprehensive literature search and rigorous methodology, including Cochrane tool ROB assessment. This resulted in high-quality studies with minimal bias, providing a robust evidence base for therapeutic recommendations on optimizing the usage of using silver nanoparticles and calcium hydroxide as an intracanal medicaments.

Systematic reviews and meta-analyses are considered the highest level of evidence, offering transparency and reproducibility in addressing specific research questions. However, the quality of included studies impacts the strength of evidence. This review included sufficient studies with brief observation periods and known risk of bias.

CONCLUSION

Clinicians should consider REP in cases with root growth defects, inadequate dentin, and where the dental outcome is hopeless. REP improved apical closure. MTA and $Ca(OH)_2$ have similar effects in creating a calcification barrier, but it can be concluded that regenerative endodontics is better than apexification surgery and has better results.

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