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To evaluate and assess the anti-bacterial effect and the incidence of post-operative pain using silver nanoparticles (AgNPs) and calcium hydroxide $(CaOH)_2$ as an intracanal medicaments

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ABSTRACT

Aim: To evaluate and assess the anti-bacterial effect and the incidence of post-operative pain using silver nanoparticles (AgNPs) and calcium hydroxide $(CaOH)_2$ as an intracanal medicaments.

Methods: Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) 2020 guidelines were followed and registered in PROSPERO-CRDXXXXXX. Electronic databases were searched for studies assessing and evaluating effectiveness of silver nanoparticles and calcium hydroxide on of reduction of post-operative pain and antibacterial effect on overall reduction in colony forming units (CFU) and total bacterial count. 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: Six studies were included in qualitative synthesis and four studies for meta-analysis. Quality assessment revealed moderate to low risk of bias. The pooled estimate through RR and SMD indicated that incidence of post-operative pain at 4hrs was RR 1.75 (1.11 – 2.76) more in $Ca(OH)_2$ while reduction in CFU with SMD 2.46 (1.27 – 3.65) more in AgNPs ($p<0.05$) and reduction in total bacterial count SMD -78.27 (-119.95 – -36.60) more in AgNPs group compared to $Ca(OH)_2$ group ($p<0.05$). Meta-analysis did not show any significant asymmetry with absence of potential publication bias.

Conclusion: silver nanoparticles alone or incorporated with calcium hydroxide compared to calcium hydroxide alone had shown greater reduction in incidence of post-operative pain and antibacterial efficacy on basis of overall reduction in colony forming units and total bacterial counts. Furthermore, RCTs or comparative studies with larger follow up period and greater sample size should be carried out to validate study findings

Keywords: calcium hydroxide, intracanal medicament, root canal treatment, silver nanoparticles, systematic review

INTRODUCTION

Post-operative pain after endodontic treatment is an undesirable occurrence for both patients and clinicians. Although several factors have been suggested, microbial injury has been considered the most common cause.[1] Bacteria residing in areas of the root canals such as isthmuses, apical ramifications, deltas, and dentinal tubules may be left unaffected by disinfection procedures.[2] Inadequate elimination of this bacteria allows for bacterial growth which can gain access to the periapical tissues and cause inflammation.[3]

Lately, silver nanoparticles (AgNPs) have gained much attention due to their unique characteristics, which lead to being incorporated in various dental materials.[4] AgNPs seem to be potential antibacterial agents due to their large surface-to-volume ratios and surface structure which can be a valuable additive to endodontic materials[8], and specifically as an intracanal medication alone or in combination with $Ca(OH)_2$.[5]

Calcium hydroxide ($Ca(OH)_2$) is a widely applied intracanal medicament between appointments to reduce canal bacteria.[6] It is antibacterial, and during apexogenesis, or pulp capping, it stimulates hard tissue formation, dissolves the tissues, and promotes apical exudate elimination.[7]

Calcium hydroxide NPs (nano-CH) have been synthesized as active catalysts in chemical reactions.[8] Their application as ICM might overcome the limitations of regular calcium hydroxide which are culture reversal, limited penetration inside the dentinal tubules, and bacterial resistance. However, this is not yet explored clinically.[9]

Nowadays, AgNPs are being incorporated in various medical and dental materials and devices because of its inhibitory effects on the growth of microorganisms.[10] The specific antibacterial mechanism of AgNPs is not yet clear; however, several mechanisms were proposed including interacting with cell wall and membrane causing lysis, disturbing protein synthesis, or inhibiting DNA replication.[11]

The antibacterial effect of the mixture of $Ca(OH)_2$ + AgNPs is comparable to that found in several studies. The exact mechanism of the antibacterial activity of the mixture of $Ca(OH)_2$ + AgNPs is yet to be fully understood.[12] Researchers related the antibacterial effect of AgNPs to the concentration used and mode of application. The application of a 0.02% AgNPs gel as a medication resulted in a significant disruption of E. faecalis biofilm compared to $Ca(OH)_2$..[13]

Post-operative pain and flare ups which are occasionally associated with root canal treatment procedures represent a relevant concern for both patients and clinicians.[13] The origin of post-operative pain is multifactorial and the development is mostly influenced by mechanical, chemical, and microbial factors.[14]

Lately, nanotechnology in dentistry has promoted the development of excellent biomaterials with unique physical, chemical, and biological properties.[11] The nanoparticles (NPs) have superior antibacterial effects due to their higher volume-to-surface area ratio and lesser particle dimension, which results in higher effective contact and larger reaction surface. Subsequently, they penetrate the dentinal tubules and produce a prolonged antibacterial impact at the infection site at reduced doses.[15]

Therefore, this review was conducted to assess, evaluate and compare the anti-bacterial effect and the incidence of post-operative pain using silver nanoparticles and calcium hydroxide as an intracanal medicaments in adults through a novel meta-analysis.

METHODOLOGY

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

Study design
Focused research question in the Population (P), Intervention (I), Comparison (c) and Outcome (O) format was proposed "Is there any difference in the effectiveness of silver nanoparticles and calcium hydroxide as an intracanal medicament on post-operative pain?"

P – Teeth with necrotic pulp, irreversible pulpitis, symptomatic apical periodontitis, asymptomatic vital/ non vital pulp
I – silver nanoparticles
C – calcium hydroxide
O –reduction of post-operative pain and colony forming unit (CFU) and total bacterial count

Eligibility Criteria-

a) Inclusion Criteria:

1) Articles published in English language
2) Articles from open access journals
3) In Vitro Studies, randomized controlled trials, comparative study, clinical trials, in-vivo studies were included
4) Article assessing effectiveness of silver nanoparticles and calcium hydroxide and reporting outcomes in terms of reduction of post-operative pain among teeth with necrotic pulp, irreversible pulpitis, symptomatic apical periodontitis, asymptomatic vital/ non vital pulp
5) Articles available as free available full text articles
6) Articles published between January 2000 to April 2024
7) Articles reporting outcomes in terms of mean and standard deviation

1) **Exclusion Criteria:** Any studies conducted before 2000

2) Articles in other than English language
3) Reviews, abstracts, letter to the editor, editorials, animal studies were excluded
4) Articles not from open access journals
5) Studies showing teeth with periapical lesions
6) Studies including teeth with developmental anomalies (e.g., dens invaginatus), transplanted teeth as well as avulsed and re-implanted teeth
7) Medically compromised patients or pregnant females with presence of facial swelling

Search Strategy
Database search was performed till September 2024 for studies published within the last 24 years: PubMed, google scholar and EBSCOhost.

Key words and Medical Subject Heading (MeSH) terms were selected and combined with Boolean operators like AND/OR as shown below
Search Strategy according to PICO Format:

	Strategy
Population	(("periapical infection"[MeSH Terms] OR "necrotic pulp" OR "endodontic treatment") OR ("intracanal medicament"[MeSH Terms] OR "bacterial infection" OR ("bacterial load reduction"[MeSH Terms] OR ("root canal treatment"
Intervention	((("silver nanoparticles"[MeSH Terms] OR ("periapical infection" AND "calcium hydroxide" AND "bacterial count" OR "apical periodontitis" OR "periapical infection" OR ("periapical healing"[MeSH Terms] OR "bactericidal" AND "bacteriostatic"
Comparator	(("calcium hydroxide" OR "nanotechnology"[MeSH Terms] OR ("post endodontic pain" AND "bacterial infection" OR "bacterial load reduction" OR ("periapical healing" AND "decrease in root canal infection" OR "necrotic pulp"
Outcome assessed	((("post operative pain"[MeSH Terms] OR "visual analogue scale" OR ("swelling"[MeSH Terms] OR ("decrease in infection" AND "periapical healing" OR "asymptomatic" OR ("tooth survival" 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, medicaments used, parameters assessed and conclusion.

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 eliminating duplicate entries, the reference list of included studies underwent screening, resulting in the exclusion of 116 studies. Following, this full text articles were assessed for eligibility and those that did not meet the inclusion

criteria were excluded. Six studies were included in the qualitative synthesis and four studies in meta-analysis as illustrated in **Figure 1 below**

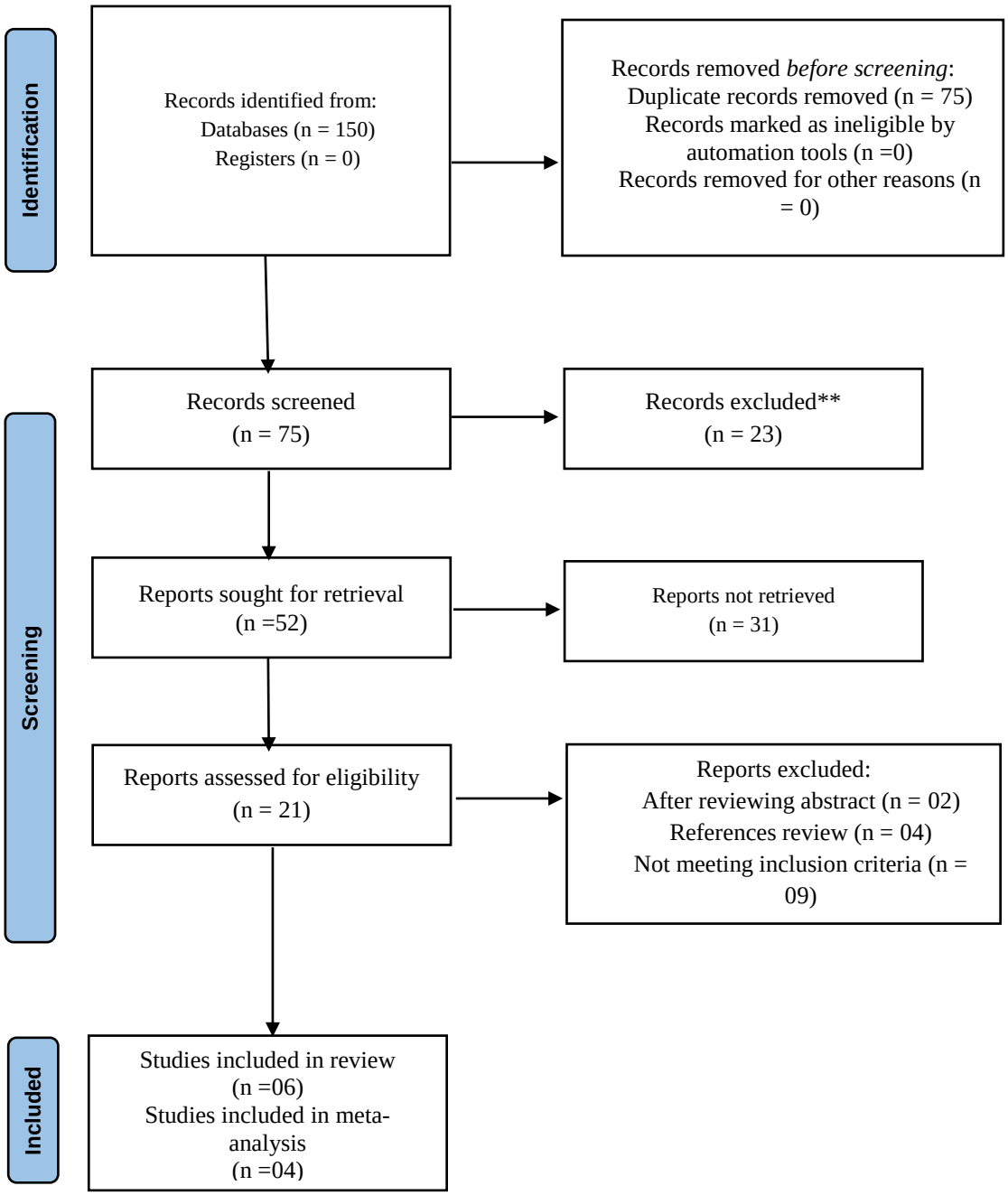

Figure 1. PRISMA 2020 Flow Diagram Assessment

Study Characteristics

As shown in **Table 1,** data was evaluated from six studies[21-26] from an aggregate of total of 658 specimens (permanent maxillary and mandibular single rooted teeth) on which the effectiveness of various intracanal medicaments like calcium hydroxide and silver nanoparticles combined with other medicaments (2% chlorhexidine and 2% chitosan) was assessed and evaluated against *Enterococcus faecalis* in terms of overall reduction in post-operative pain and anti-microbial/bacterial efficacy in terms of (reduction in colony forming units (CFU), zone of inhibition, zone of bacterial colonies and number of viable bacteria). All the included studies had randomized controlled trial (RCTs) study design. Among the included studies, five studies were conducted in India [18-21,25], two studies in Egypt [22,23] and one study in Yemen [24] and one study in Israel [26]

Table 1: showing descriptive study details of included studies

Author, years of study	Country	Study design	Sample size	Medicaments used	Parameters assessed (follow up duration)	Outcome
Afkhami et al., 2015 [21]	Iran	RCT	54 (permanent molars)	$Ca(OH)_2$, $Ca(OH)_2$ + CHX, $Ca(OH)_2$ + AgNPs	Antibacterial efficacy (reduction in CFU)	AgNPs were more effective than other medicaments
Alabdulmohsen et al., 2017 [22]	Saidi Arabia	RCT	110 (single rooted teeth)	$Ca(OH)_2$, AgNPs and $Ca(OH)_2$ + AgNPs	Antibacterial efficacy (bacterial reduction, CFU) (1 & 2 weeks)	Antibacterial effect of $Ca(OH)_2$ was superior to AgNPs
El Abbasy et al., 2018 [23]	Egypt	RCT	34 Single rooted maxillary & mandibular teeth)	$Ca(OH)_2$ and AgNPs	Post-operative pain (4,12,24 & 48 hrs)	Greater pain reduction was shown by AgNPs group
Hassan et al., 2021 [24]	Egypt	RCT	30 (Mandibular anteriors) (Maxillary central incisors)	$Ca(OH)_2$ + 0.1% AgNPs and $Ca(OH)_2$	Post-operative pain (4,24,48,72,96 hrs) and bacterial count through reduction in CFU	No significant difference was seen between 2 groups while $Ca(OH)_2$ with AgNPs reduced more intracanal bacterial count
Riaz et al., 2022 [25]	Pakistan	RCT	30 (premolars)	$Ca(OH)_2$ + 0.1% AgNPs and $Ca(OH)_2$	Zone of inhibition, Zone of bacterial colonies, No. of viable bacteria	$Ca(OH)_2$ with AgNPs showed greater elimination of *E.faecalis*
Teja et al.,2023 [26]	India	RCT	400 (Mandibular premolars)	$Ca(OH)_2$, $Ca(OH)_2$ +2% CHX, $Ca(OH)_2$ + 2% chitosan gel,($Ca(OH)_2$ + 0.2% AgNPs, $Ca(OH)_2$ + bioactive glass	Antimicrobial efficacy	Addition of $Ca(OH)_2$ had shown a synergistic effect on bacterial elimination

AgNPs: silver nanoparticles; $Ca(OH)_2$; calcium hydroxide; CFU: colony forming units; CHX: chlorhexidine; RCT: randomized controlled trial; REP: regenerative endodontic procedures

Quality assessment

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

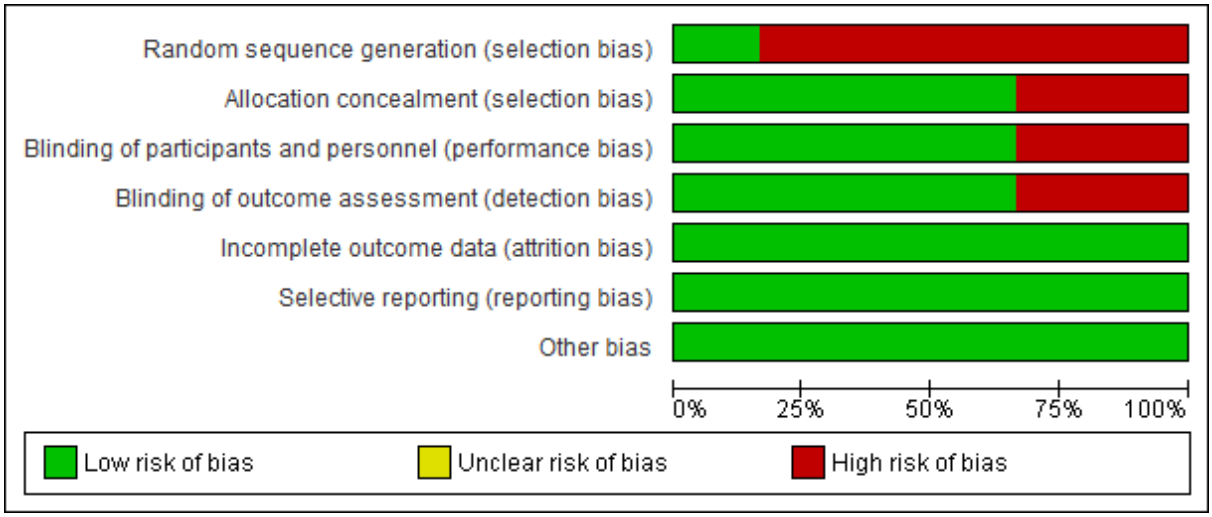

Figure 2: ROB: shown as percentages across all included studies.

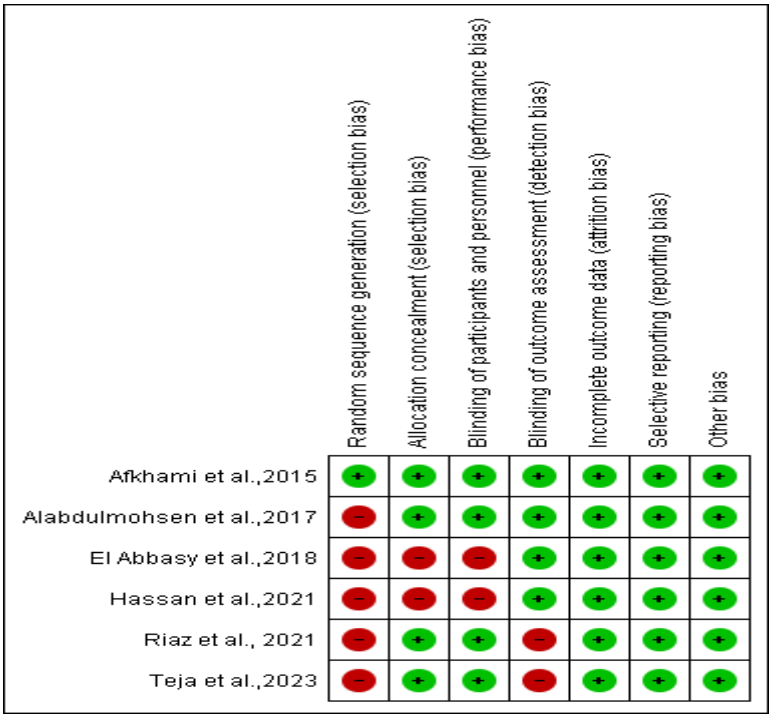

Figure 3: ROB summary: for each study

Synthesis of Result

The meta-analysis was performed for assessing the effectiveness between the intracanal medicament in terms of decrease in post-operative pain (4 and 24 hrs) and anti-microbial effect in terms of reduction in CFU and total bacterial count **as shown below in figures 4-11**

A) Incidence of post-operative pain at 4 hrs

Two studies[23,24] containing data on 54 teeth, of which (*n*=27) teeth were evaluated by $Ca(OH)_2$ and (*n*=27) teeth by AgNPs for the evaluation of the better effectiveness between the two medicaments in terms of reduction in incidence of post-operative pain at 4hrs. As shown in **Figure 4.** the RR is 1.75 (1.11 – 2.76) and the pooled estimate signifies that incidence of post-operative pain at 4hrs on an average was 1.75 times more in $Ca(OH)_2$ compared to AgNPs. (p>0.05).

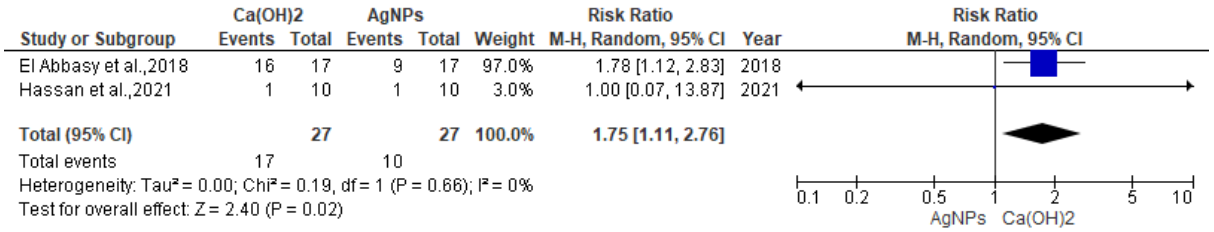

Figure 4: Incidence of post-operative pain at 4 hrs

The funnel plot did not show significant asymmetry, indicating absence of publication bias as shown in **Figure 5.**

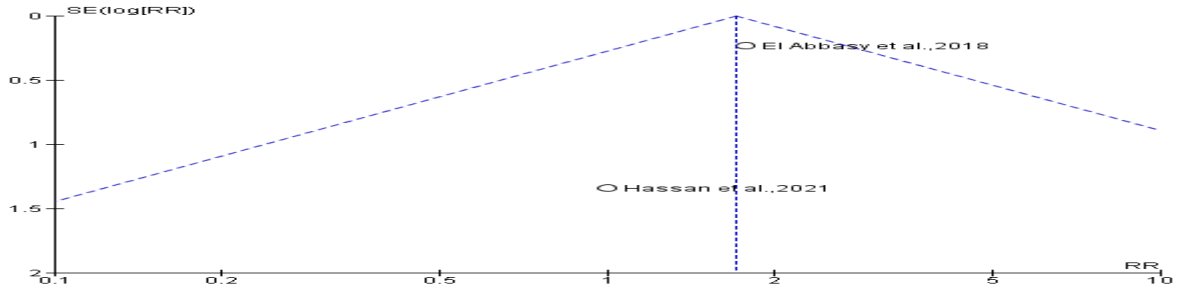

Figure 5: showing Begg's Funnel plot with 95% confidence intervals demonstrating an absence of publication bias.

B) Incidence of post-operative pain at 24 hrs

Two studies[23,24] containing data on 54 teeth, of which (*n*=27*)* teeth were evaluated by $Ca(OH)_2$ and (*n*=27) teeth by AgNPs for the evaluation of the better effectiveness between the two medicaments in terms of reduction in incidence of post-operative pain at 24hrs. As shown in **Figure 6.** the RR is 0.98 (0.11 – 8.89) and the pooled estimate signifies that incidence of post-operative pain at 24hrs on an average was mor or less equal in both the groups (p>0.05).

Figure 6: Incidence of post-operative pain at 24 hrs

The funnel plot did not show significant asymmetry, indicating absence of publication bias as shown in **Figure 7.**

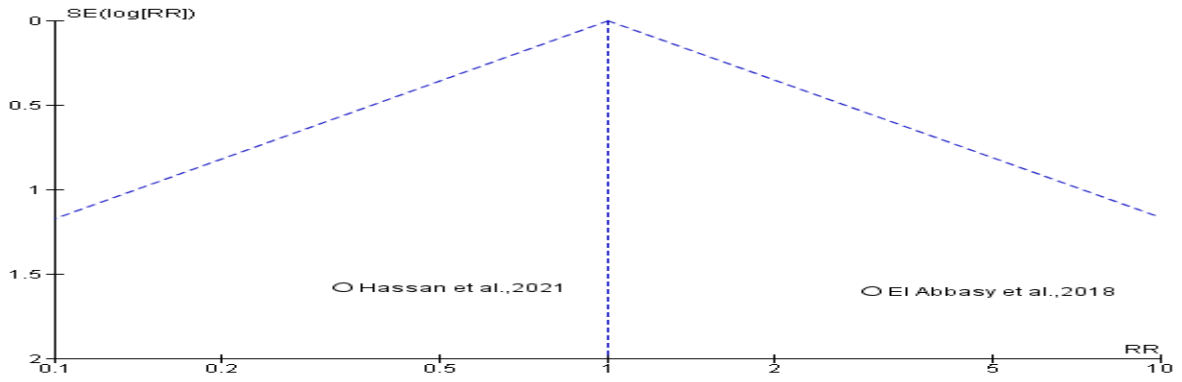

Figure 7: showing Begg's Funnel plot with 95% confidence intervals demonstrating an absence of publication bias.

C) Reduction in colony forming units (CFU)

Two studies[24,26] containing data on 52 teeth, of which (*n*=26*)* teeth were evaluated by $Ca(OH)_2$ and (*n*=26) teeth by AgNPs for the evaluation of the better effectiveness between the two medicaments in terms of reduction in CFU. As shown in **Figure 8.** The SMD is 2.46 (1.27 – 3.65) and the pooled estimate signifies that reduction in CFU on an average was 2.46 times more in AgNPs group compared to $Ca(OH)_2$ (*p*<0.05).

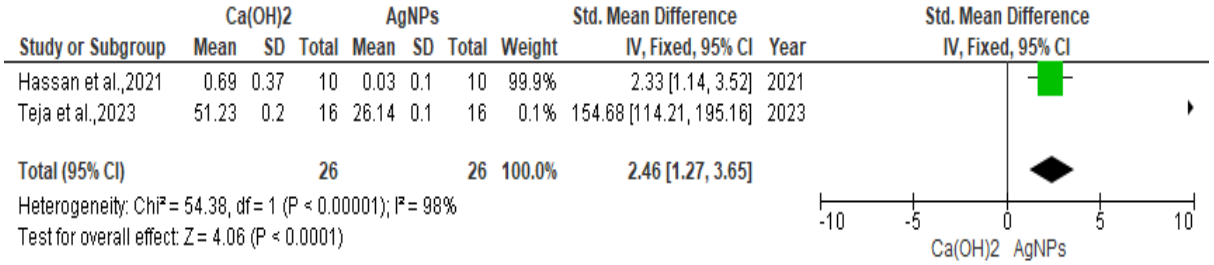

Figure 8: Reduction in total CFU

The funnel plot did show significant asymmetry, indicating presence of publication bias as shown in **Figure 9.**

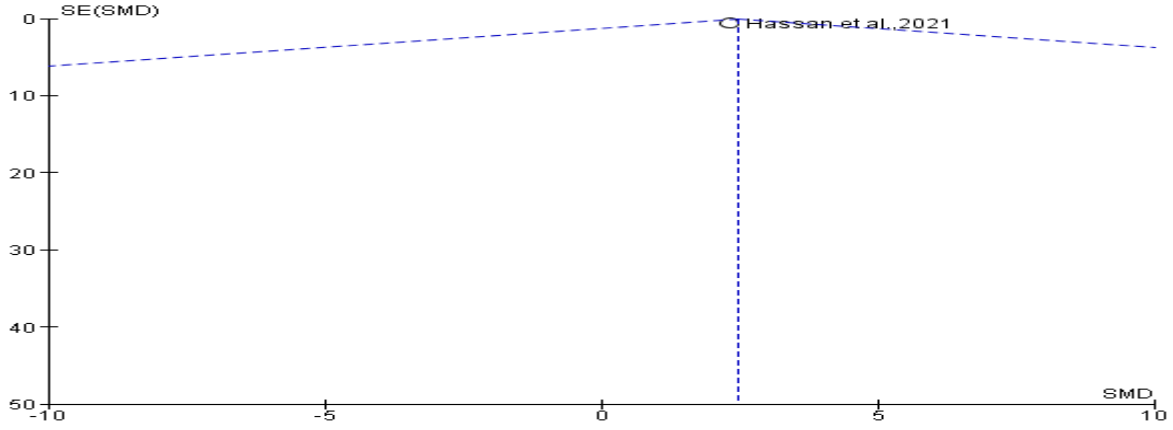

Figure 9: showing Begg's Funnel plot with 95% confidence intervals demonstrating presence of publication bias.

D) Percentage reduction in bacterial counts

Two studies[24,26] containing data on 54 teeth, of which (*n*=27*)* teeth were evaluated by $Ca(OH)_2$ and (*n*=27) teeth by AgNPs for the evaluation of the better effectiveness between the two medicaments in terms of reduction in total bacterial count. As shown in **Figure 10.** The SMD is -78.27 (-119.95 – -36.60) and the pooled estimate signifies that reduction in total bacterial count on an average was -78.27 times more in AgNPs group compared to $Ca(OH)_2$ group (*p*<0.05).

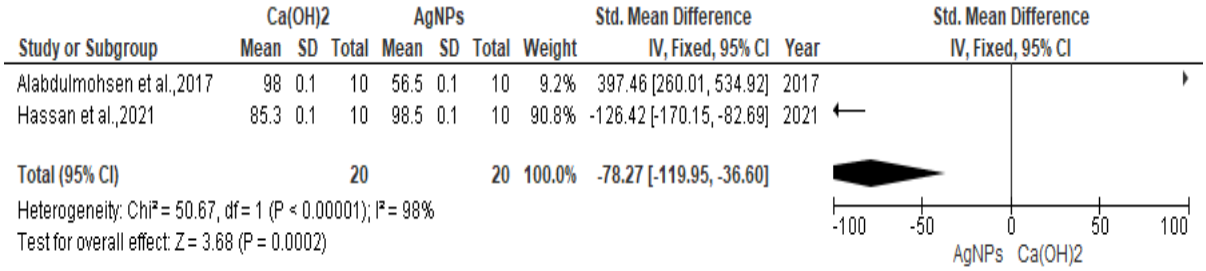

Figure 10: Reduction in total bacterial count

The funnel plot did show significant asymmetry, indicating presence of publication bias as shown in **Figure 11.**

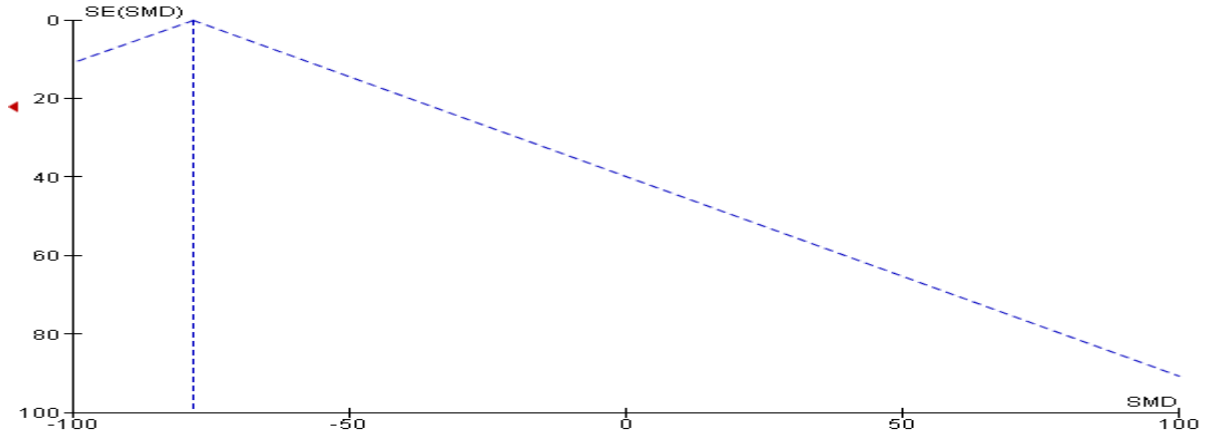

Figure 11: showing Begg's Funnel plot with 95% confidence intervals demonstrating presence of publication bias.

DISCUSSION

Effective control of intra-canal microbial load before obturation is the key element to the high success of root canal treatment.[8] Bacteria can be eliminated from the root canal space by mechanical instrumentation of the root canal which resulted in 50% reduction[9,10]

Although Ca(OH)2 is a widely used intracanal medication, it does not affect all bacteria found in the root canal uniformly. Several studies have reported that $Ca(OH)_2$ failed to effectively eliminate enterococci, due to their tolerance to high pH values, ranging from 9 to 11 compared to that of other bacterial species. They attributed the low antibacterial activity of $Ca(OH)_2$ to its affection to the buffering property of dentine.

Pain is a challenging outcome to assess due to its complex and subjective nature, however, patients' self-assessment reports provide the most valid measure of pain experience.[10] Several pain scales; numerical, verbal, and VAS are used in clinical studies.

To gain a successful endodontic treatment of teeth with apical periodontitis, an effective control of the root canal infection must be achieved. [3,4] Chemo-mechanical cleaning and shaping of the infected root canal results in the reduction of microorganism counts, but cannot eliminate it completely. This is mainly because of anatomical complexity and access limitations to the root canal system by instruments and irrigants. In some cases where microorganisms are resistant to regular therapy and present with pain and exudation, the need for intracanal medication is increased. Although $Ca(OH)_2$ is widely used, it cannot be considered a universal intracanal medicament, since it is not equally effective against all bacteria found in the root canal. Indeed, several studies have reported the failure of $Ca(OH)_2$ to eliminate Enterococci effectively, as they tolerate high pH values, varying from 9 to 11.

This systematic review was conducted to assess and evaluate the better effectiveness between calcium hydroxide and silver nanoparticles as an intracanal medicaments in terms of reduction in post-operative pain and total reduction in colony forming units (CFU) and bacterial count. Databases were searched from January 2000 to April 2024 from RCTs and comparative studies evaluating these two medicaments on basis of reduction of post-operative pain, CFU and total bacterial count. Six studies were included in qualitative review and four for meta-analysis. ROB assessment revealed presence of low to moderate risk of bias. From the results of review, it was found that $Ca(OH)_2$ with AgNPs or AgNPs alone had shown greater reduction in incidence of post-operative pain than $Ca(OH)_2$ alone ($p<0.05$) while at 24^{th} hrs the incidence of pain was equal in both groups ($p>0.05$).

Post-operative pain at 4^{th} and 24^{th} hrs and reduction in CFU with total bacterial count was evaluated through meta-analysis. It was found that incidence of post-operative pain at 4hrs on an average was 1.75 times more in $Ca(OH)_2$ while reduction in CFU on an average was 2.46 times more in AgNPs ($p<0.05$) and reduction in total bacterial count was -78.27 times more in AgNPs group compared to $Ca(OH)_2$ group ($p<0.05$). Meta-analysis did not show any significant asymmetry with absence of potential publication bias.

Gupta et al.,[23] carried out scoping review of existing literature on evaluating the effect of silver nanoparticles (AgNPs) as an intracanal medicament. Databases were searched till April 2022. Ten in-vitro studies were included in the review. AgNPs were compared to other medicaments like bioactive glass, chitosan-propolis, zinc oxide and calcium hydroxide. From the results of the study, it was found that overall antibacterial efficacy of AgNPs was superior to other medicaments.

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

It was concluded that silver nanoparticles alone or incorporated with calcium hydroxide compared to calcium hydroxide alone had shown greater reduction in incidence of post-operative pain and antibacterial efficacy on basis of overall reduction in colony forming units and total bacterial counts. Furthermore, RCTs or comparative studies with larger follow up period and greater sample size should be carried out to provide an overall good quality of evidence and to validate our study findings.

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