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Review Article

Evidence on pharmacological agents for treating bony defects in chronic periodontitis: A network meta-analysis

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ABSTRACT

Background: Chronic periodontitis is an infectious disease of the oral cavity that causes progressive destruction of periodontal tissues, leading to structural changes like attachment loss, bone resorption, resulting in bony defects, and potential tooth loss if left untreated. Effective drugs, such as alendronate, rosuvastatin (RSV), atorvastatin, melatonin, and metformin (MF), have been used as adjuncts to scaling and root planning and require evaluation for their comparative effectiveness in treating bony defects in patients with chronic periodontitis. This study aims to compare the effectiveness of these drugs for treating such defects.

Materials and Methods: This network meta-analysis (NMA) was conducted following Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines and registered in PROSPERO (CRD42024600432). A comprehensive search of PubMed, Scopus, and Cochrane Library identified 11 eligible randomized clinical trials reporting changes in clinical attachment level (CAL) and bone fill (BF) at 6 months posttreatment. The NMA systematically compared treatment outcomes across different intervention groups.

Results: MF was the most effective treatment for CAL and BF at 6 months. Ranking probabilities indicated that MF and RSV had the highest likelihood of being the most effective treatments.

Conclusion: These findings from the NMA suggest that MF may be an effective option for CAL improvement and BF. Further research is needed to validate these results and optimize treatment strategies for bony defects in chronic periodontitis.

Key Words: Alendronate, bone regeneration, chronic periodontitis, intrabony defects, melatonin, metformin, network meta-analysis, rosuvastatin

INTRODUCTION

Periodontitis, a chronic inflammatory disease of the supporting structures of the teeth, affects approximately 47% of U. S. adults aged 30 years and above (Eke *et al*., 2012), with European estimates ranging from 20% to 50% depending on disease severity and diagnostic criteria (Sanz *et al*., 2010).[1,2] It compromises the structural integrity of the periodontium contributing to progressive attachment loss, bone loss, and development of various types of intrabony and interradicular defects, ultimately leading to tooth loss, if left untreated.[3] This can negatively impact self-esteem, chewing ability, appearance, and overall quality of life.[4,5]

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According to the American Academy of Periodontology, an intrabony defect is defined as a "periodontal defect within the bone surrounded by one, two, or three bony walls, or a combination thereof."[6] Similarly, furcation involvement (interradicular defect) is defined as bone resorption into the bi-or trifurcation area of a multi-rooted tooth as a result of periodontal disease. Teeth with deep pockets associated with intrabony or interradicular defects present significant clinical challenges and are often categorized by most authors as having a questionable or hopeless prognosis.[7]

The goal of an effective periodontal treatment is to restore both the structural integrity and functional capacity of the affected periodontium. While scaling and root planning (SRP) is the primary treatment for periodontal disease, it may not fully eliminate pathogens in deep intrabony and interradicular defects, allowing infection to persist. To enhance clinical outcomes, adjunctive therapies such as local drug delivery (LDD) systems are often used in conjunction with SRP. Various pharmacological agents have been investigated for this purpose, including alendronate (ALN), rosuvastatin (RSV), atorvastatin (ATV), melatonin (ML), and metformin (MF), each offering distinct mechanisms of action that modulate the host response in periodontitis.

The host response in periodontal disease, while protective, can also cause tissue damage and bone resorption. Bisphosphonates such as ALN inhibit osteoclast-mediated bone resorption by disrupting the RANK/RANKL/OPG signaling pathway, which is essential for osteoclast differentiation and activation. ALN binds to hydroxyapatite in alveolar bone and is internalized by osteoclasts, where it inhibits farnesyl pyrophosphate synthase in the mevalonate pathway, leading to impaired GTPase prenylation and osteoclast apoptosis. It also reduces RANKL expression and enhances osteoblast activity, thereby promoting bone formation and maintaining alveolar bone integrity.[8] MF is a widely prescribed oral hypoglycemic agent for the management of type II diabetes mellitus. Research has also indicated that it enhances osteoblast proliferation and inhibits osteoclast activity by activating AMPK and Wnt/β-catenin pathways, promoting osteogenic differentiation and bone mineralization. It also modulates the RANKL/OPG ratio and suppresses AGE-RAGE and NLRP3 inflammasome pathways, thereby reducing bone resorption and inflammation in periodontitis.[9] ML, chemically known as N-acetyl-5-methoxytryptamine, primarily regulates circadian rhythms (day-night cycles) and serves anti-inflammatory, anti-oncotic, and immunomodulatory functions. It acts as a free radical scavenger by interacting with cell membrane and intracellular proteins.[10]

Statins (e.g., RSV and ATV) are the competitive inhibitors of HMG-CoA reductase, primarily used for lipid-lowering therapy. They significantly reduce serum cholesterol levels and thereby lowers the risk of cardiovascular diseases. Beyond their lipid-lowering effects, they also exhibit notable anti-inflammatory properties and promote osteoblastic differentiation, and increase alkaline phosphatase activity, a recognized marker of osteoblastic function, indicating a potential role in bone health and regeneration.[11] These agents were incorporated into gel formulations and delivered subgingivally via a syringe with a blunt cannula into the deepest interproximal pocket (probing depth [PD] ≥5 mm) following Phase I therapy.

The addition of these pharmacological agents with host modulatory and potential antimicrobial effects as adjuncts notably enhanced periodontal status following nonsurgical periodontal treatment when compared to SRP alone.[12-16]

Earlier meta-analyses have been carried out to identify the therapy with the highest efficacy using direct evidence. However, these analyses were limited by their narrow scope of comparisons and inadequate statistical power, primarily due to the small number of head-to-head trials available. In addition, they were unable to compare multiple interventions simultaneously or incorporate indirect comparisons, which restricted the comprehensiveness of their findings. Based on this background, conducting a network meta-analysis (NMA) to assess efficacy outcomes holds significant clinical relevance. NMA in oral health research has been implemented as a method capable of integrating both direct and indirect comparisons among the studies included, the latter being comparisons not directly conducted within individual trials.[17] Furthermore, NMA provides clear insights into the overall ranking of different therapeutic interventions in a single analytical framework and facilitates effective communication of results to both clinicians and the general public. Hence, we proceeded to perform an NMA of randomized controlled trials (RCTs) to compare the efficacy of adjunctive agents: ALN, RSV, ATV,

ML, and MF in chronic periodontitis patients with intra-bony and inter-radicular defects.

MATERIALS AND METHODS

Protocol registration and reporting format

The manuscript of this NMA has been prepared following the Cochrane Collaboration guidelines[18] and implemented based on Preferred Reporting Items for Systematic Reviews and Meta-analyses Extension (PRISMA) statement for Systematic Reviews incorporating network meta-analyses for healthcare interventions.[19-21] This study is registered in the PROSPERO database (CRD42024600432). Registration and was completed prior to data extraction.

Objectives

The goal of this review was to address the following focused questions regarding the use of 1% ALN, 1% RSV, 1.2% ATV, 1% ML, and 1% MF as locally delivered adjunctive drug agents in chronic periodontitis:

1. What is the comparative efficacy of these agents in improving clinical attachment levels (CALs) in chronic periodontitis patients?
2. How do these agents compare in promoting bone fill (BF) at 6 months post-treatment?

Population, intervention, comparison, outcome, and time question

The following PICOT framework was used to guide the inclusion and exclusion of studies for the aforementioned focused questions.[22]

- Population (P): Patients undergoing treatment for chronic periodontitis exhibiting intrabony or interradicular defects
- Intervention (I): Use of locally delivered adjunctive drugs (e. g., ALN, RSV, ATV, ML, and MF) in conjunction with SRP
- Comparison (C): Adjunctive drugs were compared with each other and with placebo gel
- Outcome (O): Improvement in clinical and radiographic parameters, including BF and gain in CAL around the treated teeth
- Time (T): Follow-up duration of 6 months' posttreatment.

Information sources and search strategy

The PubMed/MEDLINE, Wiley Online Library, Google Scholar, Scopus, Embase, and Cochrane Central Register of Controlled Trials (CENTRAL) databases were searched up to October 2023, with articles taken after publication year 2016. The outcomes of interest were CAL and BF reported at 6 month post-treatment.

Search strategy

Three authors performed a literature search of titles and abstracts relevant to the PICOT question across the following databases: PubMed/MEDLINE, Wiley Online Library, and Google Scholar and included articles published after 2016. A combination of keywords, Mesh terms, and Boolean operators (AND, OR, and NOT) were used in the search.

The terms included:

(1) Periodontitis AND Alendronate/Rosuvastatin/Atorvastatin/Metformin/Melatonin
(2) Alendronate/Rosuvastatin/Atorvastatin/Metformin/Melatonin AND Adjunctive periodontal therapy
(3) Alendronate/Rosuvastatin/Atorvastatin/Metformin/Melatonin AND interradicular defects OR furcation involvement
(4) Alendronate/Rosuvastatin/Atorvastatin/Metformin/Melatonin AND Intrabony defects.

The following key terms were utilized for searching the remaining electronic databases.

bone regeneration; NMA; alendronate; metformin; melatonin; rosuvastatin; atorvastatin; synonyms for these terms.

Eligibility criteria

Inclusion criteria

(1) Randomized clinical trials (RCTs) performed on humans
(2) Patients presenting with Grade II furcation and intrabony defects confirmed by radiographic and clinical evidence and treated with locally delivered ALN, RSV, ATV, ML, MF, and placebo with articles after publication year 2016
(3) Articles with a follow-up period of 6 months
(4) Only studies published in English were included
(5) Studies reporting clinical parameters: CAL and BF.

Exclusion criteria

(1) *In vitro* studies
(2) Non-English
(3) Animal studies
(4) Case reports
(5) Case series
(6) Reviews
(7) Conference abstracts
(8) Patients undergoing systemic treatment with any of the following agents: ALN, RSV, ATV, MF, or ML.

Categorization of drug interventions

For clarity and ease of interpretation in network geometry and result presentation, each drug intervention included in this review was assigned a group label. These labels were consistently used in subsequent network diagrams and statistical analyses.

To facilitate clarity in the presentation of network geometry and treatment comparisons, each drug intervention was assigned a group label. ALN was designated as Group A, RSV as Group B, ATV as Group C, ML as Group D, MF as Group E, and Placebo as Group F. These group labels were used consistently throughout the NMA for ease of interpretation in figures and statistical comparisons.

Data extraction

Essential information regarding title, authors, published year, interventions, comparators, time periods, and no. of studies was extracted. The outcomes of interest were CAL, BF. Data extraction was performed independently by two authors (S. K. and S. R.), with discrepancies resolved through discussion with a third reviewer (P. B). CAL was assessed using a periodontal probe, typically a UNC-15 probe, by measuring the distance from the cementoenamel junction to the base of the periodontal pocket, while BF was evaluated radiographically, with several studies employing cone-beam computed tomography for quantitative analysis at baseline and 6-month follow-up period.

Quality assessment and bias evaluation

Two independent observers independently scanned the abstracts and later the preselected full-text articles.

For the risk of bias across studies:

The included studies were evaluated for bias following the Cochrane Handbook of Systematic Reviews (SR) guidelines[23,24] for assessing randomized-controlled trials by two reviewers (S. K. and S. R). The assessment focused on selection bias, performance bias, detection bias, attrition bias, and reporting bias. Each study was classified as having a "Low risk," "Medium risk," "High risk," or "Unclear risk" of bias based on established methodology. Data were then extracted carefully from the selected studies, with appropriate adjustments made to account for differences in study design and reported outcomes.

Statistical analysis

A frequentist random-effects model was used for the NMA to estimate relative treatment effects and generate SUCRA values. A network plot was constructed to depict relationships among treatment methods, with nodes representing treatments and connecting lines indicating direct comparisons. Node size reflected the number of studies, and line thickness denoted data volume for each comparison. Inconsistency between direct and indirect evidence was assessed using overall inconsistency and node-splitting analyses; a $P > 0.05$ indicated no significant inconsistency, and a consistency model was applied. Loop inconsistency was explored using side-splitting models. Forest plots presented point estimates and 95% confidence intervals (CIs) for direct evidence by study design, along with pooled effects under both consistency and inconsistency models. Marker size indicated study weight, and CI length reflected uncertainty. Consistency was visually assessed by comparing the pooled estimates from each design with the overall effect–overlapping CIs suggested consistency, while divergence indicated possible inconsistency. Treatments were ranked using the estimated probabilities (%) of each achieving a given rank, assuming the highest rank indicates the best performance. Rankings were derived from 10,000 draws to account for parameter uncertainty. The analysis was based on 10,000 draws, accounting for parameter uncertainty. Statistical analysis was performed using the Statistical analysis was performed using the Stata (version 14.2) software (StataCorp LP, College Station, Texas, USA) with $P < 0.05$ considered as statistically significant.

RESULTS

Study characteristics

Following an extensive electronic search, a total of 151 articles were identified, specifically 78 from Pubmed/ Medline, 26 from Wiley Online Library and 47 from Google Scholar. After removing 53 duplicates and excluding 98 articles for other reasons, 45 records were screened on the basis of titles and abstracts. Full-text assessment was performed on 24 articles based on the inclusion criteria and 11 articles were finally selected for this present NMA [Figure 1].

The included studies compared ALN vs placebo ($n = 3$);[25-27] RSV versus placebo ($n = 3$);[28-30] ATV versus placebo ($n = 3$);[27,29,30] ML versus placebo ($n = 1$);[31] MF versus placebo ($n = 1$);[32] ATV versus ALN ($n = 2$);[27,33] MF versus ALN ($n = 1$);[34] MF versus RSV ($n = 1$)[35] [Table 1].

Risk of bias assessment of included studies

Eleven of the included RCTs were considered to have a low risk of bias,[20-30] while one[28] was assigned a moderate risk of bias [Figure 2].

Pooled estimates, individual study outcomes, and clinical recommendation for regenerative procedures (RPs).

Results of the mixed-model network meta-analysis

A total of 11 eligible RCTs were included in the study. The drugs were categorized as A, B, C, and so on. Networks were created for each outcome: CAL and BF which included only adjunctive drugs compared with other drugs or placebo.

We conducted a NMA comparing the effectiveness of 6 treatments for CAL and BF using mean differences observed at 6 months of treatments.

Clinical attachment level as individual components of regenerative procedure

Network plot

Figure 3 (I) illustrates the network of included studies, highlighting both direct and indirect comparisons among treatments. Node size reflects the number of studies per treatment, while line thickness indicates the data volume for each comparison.

Inconsistency in the network (network split)

To explore the loop inconsistency, we fit the side-splitting models. Supplementary Table 1 shows the estimated direct and indirect treatment effects and along with the *P* value representing the statistical difference. Indirect comparisons were consistent with direct comparisons supporting the robustness of the findings.

Results under consistency model

Using the frequentist consistency model, MF, ALN, RSV, and ATV demonstrated statistically significant improvements in CAL, with *P* values ranging from 0.012 to 0.038 [Supplementary Table 2]. MF showed the highest effect size (Coef: 1.78, 95% CI: 0.65–2.92), followed by RSV (Coef: 1.67, 95% CI: 0.74–2.59).

Forest plot

Figure 4 presents the point estimates and 95% CIs for each study contributing direct evidence, categorized by the study design. Both pooled within-design estimates (blue diamonds) and pooled overall network estimates (red diamonds) are presented for each comparison. In both panels (I and II), the overlap between pooled within-design and overall pooled estimates generally indicates consistency between direct and indirect evidence, with no notable

Table 1: Study characteristics

Study number	Author	Year	Population/ defect type	Intervention	Control	Outcome	Follow up (months)
5	Ipshita *et al.*[25]	2018	Interradicular LDD	1% ALN	Placebo	Significant improvement in HCAL, VCAL and greater defect depth reduction	6
6	Sheokand *et al.*[26]	2019	Intrabony LDD	1% ALN	Placebo	Significant gain in CAL and defect fill	6
9	Pradeep *et al.*[27]	2017	Intrabony LDD	1% ALN 1.2% ATV	Placebo	Significant improvement in CAL and IBD reduction	6
10	Sharma and Prasad[33]	2022	Intrabony LDD	1.2% ATV 1% ALN		Significant improvements in CAL gain, and bone fill	6
13	Chatterjee *et al.*[28]	2019	Intrabony LDD	1.2% RSV	Placebo	Significantly greater gain in CAL and bone fill	6
14	Pradeep *et al.*[29]	2016	Intrabony LDD	1.2% RSV 1.2% ATV	Placebo	Greater CAL gain and DDR	6
15	Garg and Pradeep[30]	2017	Interradicular LDD	1.2% RSV 1.2% ATV	Placebo	Significant improvement in RVCAL, RHCAL and greater DDR%	6
20	Pradeep *et al.*[32]	2017	Intrabony LDD	1% MF	Placebo	Greater CAL gain, and IBD depth reduction	6
21	Mitra *et al.*[34]	2023	Intrabony	1% MF 1% ALN		Significant DDR, and RAL gain in both groups. No difference between the groups	6
22	Pankaj *et al.*[35]	2018	Intrabony LDD	1.2% RSV 1% MF		Marked CAL improvement, and enhanced bone fill	6
24	Gonde *et al.*[31]	2022	Intrabony LDD	1% Melatonin	Placebo	Significant gain in IBD defect fill and CAL gain	6

LDD: Local drug delivery; CAL: Clinical attachment level; HCAL: Horizontal CAL; VCAL: Vertical CAL; RVCAL: Relative vertical CAL; RHCAL: Relative horizontal CAL; ALN: Alendronate; ATV: Atorvastatin; RSV: Rosuvastatin; MF: Metformin; IBD: Infrabony defect depth; DDR: Defect depth reduction; RAL: Relative attachment level

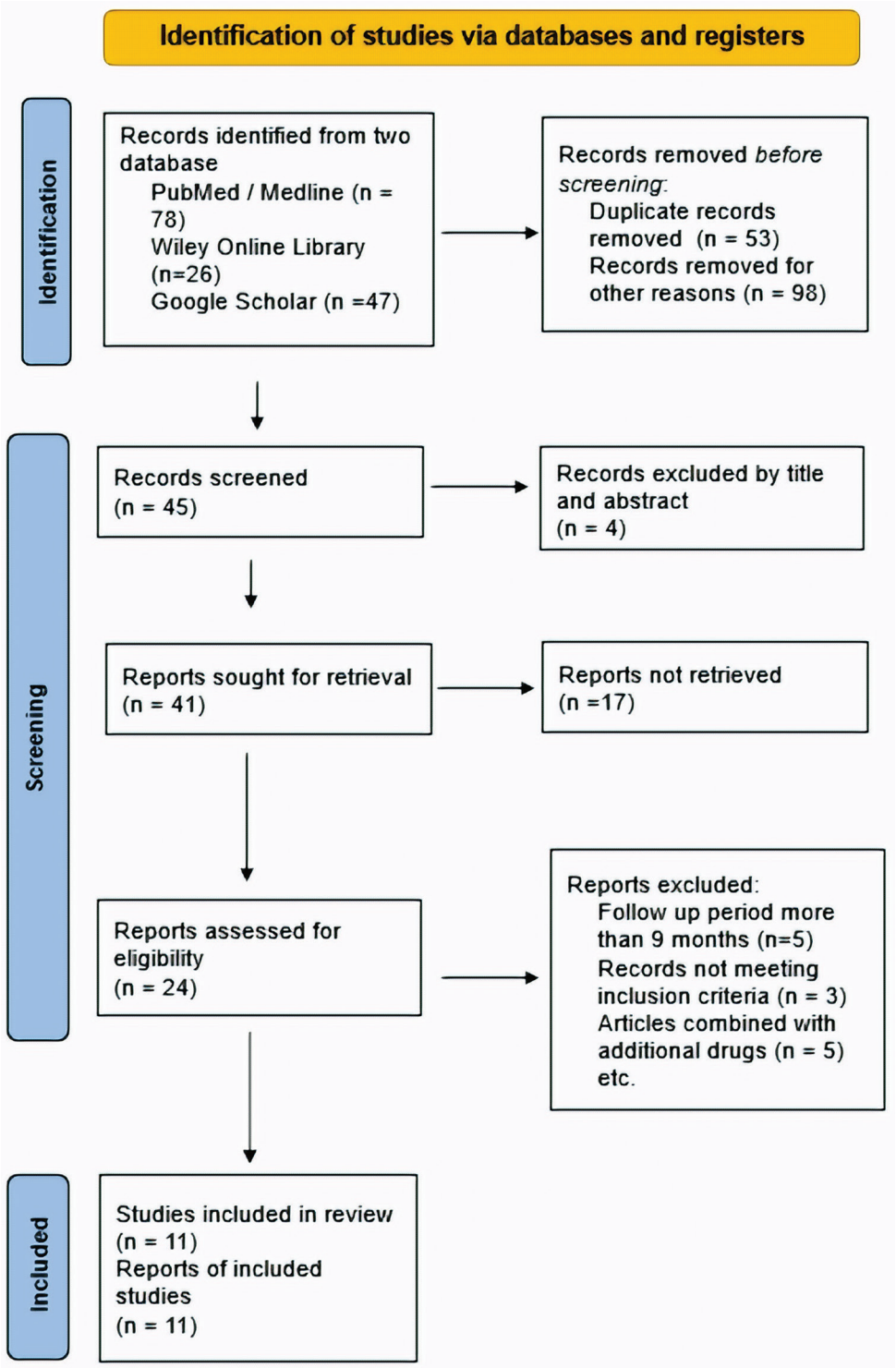

Figure 1: Flowchart (Preferred Reporting Items for Systematic Reviews and Meta-analyses format) of the screening and selection process.

divergences suggesting major inconsistency. The variation in CI length reflects differences in precision, with larger markers representing studies contributing greater weight to the analysis.

Ranking of the treatments for clinical attachment level

Treatments were ranked after the NMA using estimated probabilities (%) of each treatment achieving each rank, assuming the maximum parameter indicates the best performance. The analysis was based on 10,000 draws, accounting for parameter uncertainty.

Table 2 (I) demonstrated the ranking of treatments for CAL. Based on SUCRA values, MF demonstrated the highest probability of being the most

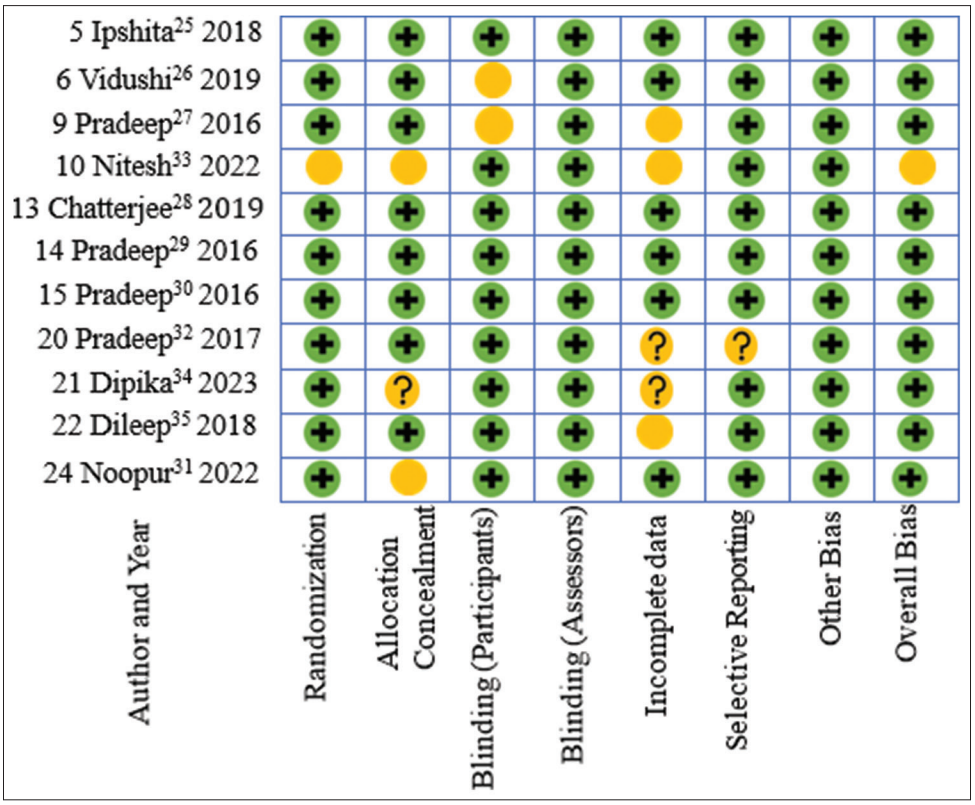

Figure 2: Risk of Bias Assessment in Studies on the Efficacy of Pharmacological Treatments for Bony Defects in Chronic Periodontitis.

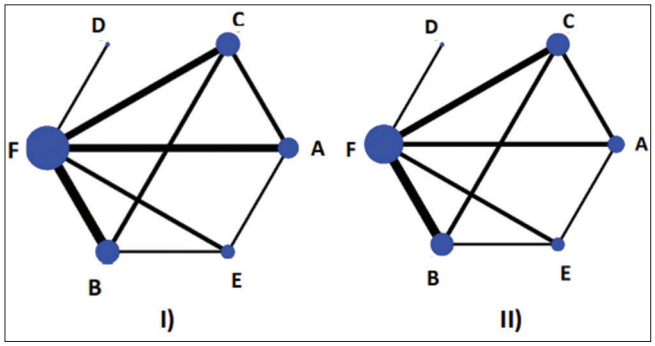

Figure 3: Network Plot for (i) clinical attachment level (II) bone fill The size of the six nodes, each representing a treatment, reflects the number of studies associated with that treatment, while the thickness of the lines connecting two nodes represents the volume of relevant data for those comparisons. (a) Alendronate; (b) Rosuvastatin; (c) Atorvastatin; (d) Melatonin; (e) Metformin; (f) Placebo.

effective treatment (SUCRA = 0.8), followed by RSV (SUCRA = 0.7).

Figure 5 (I) shows that among the top three treatments, again, MF appears to be the most effective treatment with the highest probability (84.7%) of being the best. RSV also follows closely (83.3%). Placebo is the least effective treatment consistently ranked worst.

Bone fill as an independent variable of regenerative procedure

Network plot

Figure 3 (II) illustrates the BF network as outlined previously.

Inconsistency in the network

Similar to CAL, loop inconsistency in BF was also explored by fitting side-splitting models. Supplementary Table 3 shows that most comparisons demonstrated consistency between direct and indirect evidence, with only the AE loop showing significant inconsistency ($P = 0.03$). All other comparisons had $P > 0.05$, indicating no statistically significant inconsistency across the network. A global test for inconsistency was also performed and yielded a nonsignificant result ($P > 0.05$), further supporting consistency across the network.

Results under consistency model

Under the frequentist consistency model, MF, ALN, RSV, and ATV yielded statistically significant

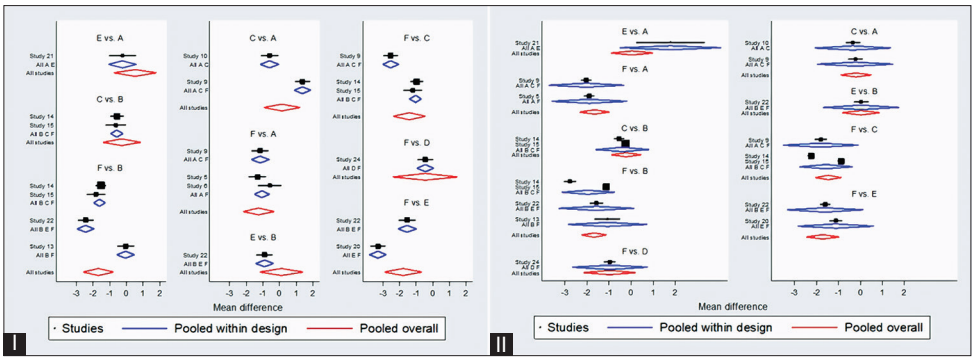

Figure 4: Network Forest Plot of Treatment Effects with Pooled Estimates for (i) clinical attachment level; (II) bone fill (a) Alendronate; (b) Rosuvastatin; (c) Atorvastatin; (d) Melatonin; (e) Metformin; (f) Placebo; Study 5: Sahu Ipshita 25; Study 6: Vidushi Sheokand26; Study 9: Avani R. Pradeep27; Study 10: Nitesh Kumar Sharma33; Study 13: Debopriya Chatterjee28; Study 14: A R Pradeep29; Study 15: A R Pradeep30; Study 20: A R Pradeep32; Study 21: Dipika Mitra34; Study 22: Dileep P35; Study 24: Noopur P. Go31.

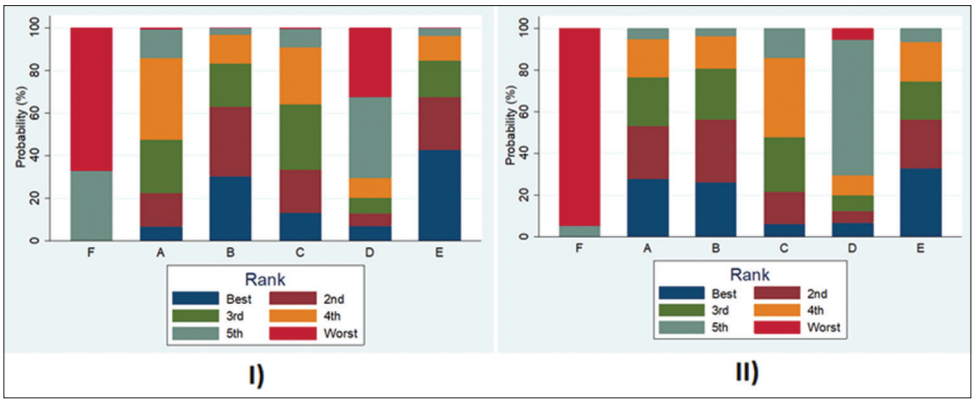

Figure 5: Cumulative rank probability of Treatments: (i) clinical attachment level, (II) bone fill.

improvements in BF, with *P* values between 0.009 and 0.034 [Supplementary Table 4]. MF had the highest effect size (Coef: 1.70, 95% CI: 0.95–2.45), followed by RSV (Coef: 1.67, 95% CI: 1.11–2.24).

Forest plot

Figure 4 (II) displays the point estimates and corresponding 95% CIs, emphasizing the superior efficacy of MF and RSV in the network.

Ranking of the treatments for bone fill

Table 2 (II) shows that based on SUCRA values MF, RSV and ALN demonstrated the highest probability of being the most effective (SUCRA = 0.7), followed by ATV (SUCRA = 0.5). The highest probability of ranking in the top was observed for MF, followed by ALN at 27.7%, and RSV closely following at 26.3%. Figure 5 (II) illustrates this ranking distribution.

Overall, MF emerges as the top choice, providing the most promising outcomes based on effect sizes and SUCRA values.

DISCUSSION

Summary of main results

SRP remains the gold-standard treatment for chronic periodontitis. However, when used as an adjunct, pharmacologic agents play a crucial role in enhancing CAL gain and BF, thereby improving the management of bony defects. In addition, there are no previous studies utilizing a NMA to evaluate the efficacy and comparative ranking of these agents in periodontal therapy, highlighting the need for further research in this area.

CAL and BF are the pivotal indicators of periodontal health and treatment success. CAL reflects the structural integrity of the periodontal attachment, while BF signifies the regeneration of the underlying bone. Both parameters are crucial for restoring functional capacity, minimizing disease progression, and improving long-term tooth retention. All the studies share the common conclusion that pharmacologic agents are effective in improving CAL and BF parameters

Table 2: Effect sizes and SUCRA values for treatments based on network meta-analysis for clinical attachment level; bone fill

[I] Ranking of the treatments for CAL						
Rank	**F**	**A**	**B**	**C**	**D**	**E**
Best	0.0	6.7	30.4	13.2	7.1	42.7
2nd	0.0	15.9	32.6	20.3	6.1	25.1
3rd	0.0	25.0	20.3	30.7	7.0	16.9
4th	0.3	38.3	13.6	26.9	9.4	11.6
5th	32.8	13.6	3.1	8.8	38.1	3.6
Worst	67.0	0.4	0.0	0.1	32.4	0.1
Mean rank	5.7	3.4	2.3	3.0	4.6	2.1
SUCRA	0.1	0.5	0.7	0.6	0.3	0.8
[II] Rankings of the treatment for BF						
Rank	**F**	**A**	**B**	**C**	**D**	**E**
Best	0.0	27.7	26.3	6.2	6.7	33.1
2nd	0.0	25.4	30.1	15.3	5.7	23.5
3rd	0.0	23.7	24.5	26.5	7.4	18.0
4th	0.0	17.9	15.6	38.0	9.5	19.0
5th	5.4	5.3	3.5	14.1	65.2	6.5
Worst	94.6	0.0	0.0	0.0	5.4	0.0
Mean rank	5.9	2.5	2.4	3.4	4.4	2.4
SUCRA	0.0	0.7	0.7	0.5	0.3	0.7

Assuming the maximum parameter is the best. Using 10,000 draws. Allowing for parameter uncertainty. CAL: Clinical attachment level; BF: Bone fill

compared to placebo, making them valuable adjuncts in the treatment of chronic periodontitis.

Our study employed a mixed-model NMA incorporating both direct and indirect comparisons. This approach enabled treatment ranking based on clinical and radiographic outcomes, with indirect comparisons enhancing the robustness of the findings. The review adhered to Cochrane Collaboration guidelines and the PRISMA-NMA framework, systematically identifying 11 RCTs published after 2016. Risk of bias was assessed using Cochrane guidelines to ensure study reliability.

The evaluation of soft (CAL) and hard tissue (BF) parameters confirmed MF was most effective for CAL gain and BF. These findings highlight the targeted regenerative potential of various pharmacological agents in periodontal therapy. We are further planning to conduct a research incorporating these pharmacologic agents alongside biologic agents such as PRF, aiming to provide a global ranking and perform both direct and indirect comparisons of their efficacy.

Limitations and potential biases in the review process

Most included studies had short follow-up periods, with only 6 months of data for most trials. Variations in study designs, such as differences in treatment methods (e.g., open flap debridement [OFD] vs. LDD), also contributed to inconsistencies. For example, study no. 21 on MF[29] used OFD, while other studies employed LDD, with both methods having a 6-month follow-up when comparing drugs to placebo or with each other.

Furthermore, the limited number of included RCTs, despite involving multiple interventions, may restrict the robustness of indirect comparisons within the NMA framework.

Small sample sizes and the lack of direct comparisons among treatment groups further reduced the statistical power and generalizability of the findings.

Agreements and disagreements with other studies or reviews

Direct evidence of the included studies in the review

A study by Avani R. Pradeep (2016)[27] *et al*. comparing ALN and ATV demonstrated that ALN resulted in a statistically greater defect depth reduction (DDR) than ATV. In contrast Sharma (2022) *et al*[33] conducted a study comparing ATV and ALN, which found both drugs to be equally effective in improving CAL and BF with no statistically significant difference between the groups.

Pradeep *et al*. (2016)[29,30] investigated the efficacy of RSV and ATV in both intrabony and interradicular defects. Their findings indicated that RSV was superior to ATV in improving both clinicoradiographic parameters, with a statistically significant difference favoring RSV.

Similarly, a study by Dipika *et al*. (2023)[34] comparing MF and ALN concluded that both agents were equally effective, with no statistically significant differences observed between the groups.

However, Dileep *et al*. (2018)[35] compared MF and RSV and found RSV to be more effective than MF, which contradicts the findings of our study.

Another studies

Alice *et al*. (2024)[36] conducted a SR and meta-analysis (MA) to evaluate the effectiveness of statins as adjunctive therapy for periodontal disease. The study compared ATV, Simvastatin (SMV), and RSV against each other and a placebo. The results indicated that SMV demonstrated a statistically significant reduction in probing pocket depth compared to ATV, while no significant differences were observed among the other drug comparisons for the remaining outcomes.

Another study by Wang *et al*. (2023)[37] on drug efficacy and safety of denosumab, teriparatide,

zoledronic acid, and ibandronic acid for the treatment of postmenopausal osteoporosis and concluded that denosumab or teriparatide might be a better choice for women with postmenopausal osteoporosis.

A study by Claudia Arena *et al*. (2022)[38] on effect of 1% ALN in bony defects: SR and MA aligns with the findings of our study, both demonstrating that ALN (1%) can positively impact periodontal parameters, including PD reduction, CAL gain, and bone DDR when used as an adjunct to periodontal therapy. Like their study, our results also show promising outcomes with the local application of ALN, further supporting its potential as an effective adjunct in periodontal treatment.

Another study by Ru-Yeu Liu *et al*.(2022)[39] on clinical efficacy of ML as adjunct therapy to nonsurgical treatment of periodontitis: SR and MA found that ML supplementation significantly improved periodontal status, suggesting its potential as a new adjuvant therapy when nonsurgical treatment alone does not achieve the desired results. Similarly, our study observed comparable positive effects of ML, reinforcing its potential as an effective adjunct in periodontal therapy.

A study by G. Cecoroet *et al*.(2021)[40] on "Efficacy of locally delivered statins as an adjunct to SRP in the treatment of periodontitis: SR and MA" concluded that locally delivered statins, such as SMV, ATV, and RSV, show promising potential as adjuncts to SRP in the treatment of periodontitis. They offer significant anti-inflammatory, antioxidant, and bone-regenerative effects, with fewer systemic side effects compared to oral statin administration.

A study by Z. Akram *et al*.(2018)[41] on "Locally delivered MF as adjunct to SRP in the treatment of periodontal defects: SR and MA" concluded that MF delivery significantly enhances CAL gain, bone defect fill, and PD reduction, findings align with our study.

The ability of these pharmacologic agents to enhance bone regeneration through their anti-inflammatory and osteogenic effects demonstrates their potential to improve CAL gain and BF. These findings contributed to the comparative analysis and ranking of these agents, providing a thorough understanding of their effectiveness in managing bony defects.

CONCLUSION

MF consistently emerged as the most effective treatment for both CAL and BF improvement, with the highest SUCRA values. RSV and ALN also demonstrated strong efficacy, ranking just below MF in both CAL and BF assessments. In addition, ML and ATV were found to enhance BF, although more studies are needed to compare its effectiveness with other LDD agents. In contrast, the placebo consistently ranked the lowest in treatment efficacy, confirming that adjunct drug therapies significantly enhance outcomes. These findings support the potential of MF, RSV, and ALN as effective adjuncts in the management of bony defects in chronic periodontitis, with MF being the preferred option based on efficacy and statistical significance.

Implications for future research

Further research is needed to validate these findings and refine treatment approaches for managing bony defects in chronic periodontitis. Future RCTs should include larger sample sizes and extended follow-up periods to assess the long-term efficacy of pharmacologic agents.

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Conflicts of interest

The authors of this manuscript declare that they have no conflicts of interest, real or perceived, financial or nonfinancial in this article.

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Supplementary Table 1: Inconsistency test assessing agreement between direct and indirect treatment comparisons for clinical attachment level

Side	Coefficient (direct)	SE (direct)	Coefficient (indirect)	SE (indirect)	Coefficient (difference)	SE (difference)	*P*
AF	−1.03	0.60	−1.72	0.89	0.69	1.07	0.52
AC	0.40	0.73	−0.25	0.92	0.65	1.18	0.58
AE	−0.23	1.05	1.02	0.84	−1.25	1.35	0.35
BF*	−1.46	0.46	−3.71	1.45	2.25	1.52	0.14
BC	−0.60	0.72	0.36	1.00	−0.95	1.24	0.44
BE	−0.90	0.93	0.97	0.85	−1.87	1.26	0.14
CF	−1.57	0.59	−0.90	1.01	−0.67	1.17	0.57
DF	-	-	-	-	-	-	-
EF	−2.43	0.64	−0.40	0.93	−2.02	1.13	0.07

*All the evidence about these contrasts comes from the studies which directly compare them. SE: Standard error

Supplementary Table 2: Results under multivariate meta-analysis for clinical attachment level

Factors	Coefficient (95% CI)	*P*
F	Reference	-
A	1.25 (0.31, 2.19)	0.009
B	1.67 (0.74, 2.59)	<0.001
C	1.40 (0.43, 2.37)	0.005
D	0.45 (−1.49, 2.39)	0.649
E	1.78 (0.65, 2.92)	0.002

CI: Confidence interval

Supplementary Table 3: Inconsistency test assessing agreement between direct and indirect treatment comparisons for bone fill

Side	Coefficient (direct)	SE (direct)	Coefficient (indirect)	SE (indirect)	Coefficient (difference)	SE (difference)	*P*
AF	−1.96	0.43	−1.05	0.62	−0.92	0.75	0.22
AC	−0.29	0.46	0.02	0.70	−0.30	0.84	0.72
AE	1.79	0.95	−0.47	0.48	2.26	1.06	0.03
BF*	−1.65	0.33	−1.88	1.04	0.23	1.09	0.83
BC	−0.38	0.43	0.14	0.65	−0.52	0.78	0.50
BE	0.03	0.65	0.07	0.66	−0.04	0.93	0.97
CF	−1.63	0.35	−0.78	0.67	−0.86	0.76	0.26
DF	-	-	-	-	-	-	-
EF	−1.37	0.40	−2.93	0.80	1.57	0.89	0.08

*All the evidence about these contrasts comes from the studies which directly compare them. SE: Standard error

Supplementary Table 4: Results under multivariate meta-analysis for bone fill

Factors	Coefficient (95% CI)	*P*
F	Reference	-
A	1.66 (0.97, 2.34)	<0.001
B	1.67 (1.11, 2.24)	<0.001
C	1.45 (0.86, 2.05)	<0.001
D	0.96 (−0.21, 2.13)	0.107
E	1.70 (0.95, 2.45)	<0.001

CI: Confidence interval