

Review

J Tissue Eng Regen Med . 2021 Aug 9. doi: 10.1002/term.3236. Online ahead of print.

Recombinant Human Derived Growth and Differentiating Factors in Treatment of Periodontal Intrabony Defects: Systematic Review and Network Meta-analysis

Sourav Panda 1 2, Shahnawaz Khijmatgar 2 3, Mohit Das 1, Heber Arbildo-Vega 4 5, Massimo Del Fabbro 2 6

Affiliations collapse

Affiliations

1 Department of Periodontics and Oral Implantology, Institute of Dental Sciences, Siksha O Anusandhan (Deemed to be) University, Bhubaneswar, Odisha, India, 751003.

2 Department of Biomedical, Surgical and Dental Sciences, University of Milan, Milan, Italy.

3 Nitte (Deemed to be University), AB Shetty Memorial Institute of Dental Sciences, Department of Oral Biology and Genomic Studies, Mangalore, India.

4 Department of General Dentistry, Dentistry School, Universidad San Martín de Porres, Chiclayo, 14012, Peru.

5 Department of General Dentistry, Dentistry School, Universidad Particular de Chiclayo, Chiclayo, 14012, Peru.

6 IRCCS Istituto Ortopedico Galeazzi, Milano, Italy.

PMID: 34370897 DOI: 10.1002/term.3236

Background: The introduction of recombinant human growth and differentiation factors (rhGFs) for intrabony defects regeneration has represented a considerable breakthrough in recent years. However, they have been used in different concentrations, doses and combined with various scaffolds, and there is no evidence on [which](#) the most effective formulation for periodontal regeneration is. Therefore, we aimed to evaluate and rank the various formulations of such bioactive agents through network meta-analysis of clinical studies. **Methods:** The protocol registration was done on PROSPERO with registration ID CRD42020213753. To report NMA, we followed PRISMA guidelines and searched PUBMED, Embase, Web of Science and Cochrane Central electronic databases. Studies were screened based on specific inclusion criteria. Primary outcomes extracted from included studies were the most common indexes for periodontal regeneration (PPD, CAL, %bone filling). The NMA analysis included network plots, contribution plots, inconsistency plots (if eligible to form the loop), predictive interval plots, SUCRA rankings and multidimensional scale ranking (MDS) plots. SUCRA would demonstrate the rankings of multiple competing bioactive agents based on their best performance. **Results:** Twelve clinical studies for qualitative and quantitative analysis were considered. Network meta-analysis found that rhFGF + hydroxyapatite was ranked highest in PPD and CAL outcome. rhPDGF-BB+ β -tricalcium phosphate was ranked highest in the percentage of bone filling. In addition, all bioactive agents performed better than control groups without rhGFs. **Conclusion:** Despite clear benefits deriving from rhGFs for periodontal regeneration, the present results should [be interpreted](#) with caution due to several confounding factors affecting the outcome. Nevertheless, further well designed randomized clinical trials will allow establishing guidelines for an appropriate indication of the use of rhGFs.

Keywords

bone regeneration | bioactive | biologics | intrabony defects | network meta-

analysis | NMA | periodontal regeneration | recombinant factors | rhGFs | scaffolds

Abbreviations NMA: Network Meta-analysis rh: Recombinant Human GF: Growth

Factor(s) rhGFs: recombinant human growth and differentiation factors PDGF: Platelet Derived Growth

Factor(s) rhPDGF: Recombinant Human Platelet Derived Growth Factor rh-FGF: Recombinant Human-

Fibroblast growth factor rh-BMP: Recombinant Human- Bone Morphogenetic Protein rhPDGF-

BB: Becaplermin DBBM: Deproteinized bovine bone matrix EMD: Enamel Derived

Matrix DFDBA: Demineralized freeze-dried bone allograft β -TCP: Beta-Tricalcium phosphate P-15 –

Pepgen

1 INTRODUCTION

Teeth encircled by structures like alveolar bone, cementum and the periodontal ligament that support them. In contrast, the inflammatory process of periodontitis destroys these supporting structures due to the microbial insult and the related host response. Bone destruction due to progressing periodontal disease is well recognized. It has been classified based on various factors, especially on the location of the pocket base relative to the crest of the alveolar bone. Bone loss is usually horizontal bone loss or an angular or vertical form called intrabony defect (Anderson and Pye, 2019; Karn et al., 1984). The intrabony defects have classified again based on remaining bone walls, as one, two and three wall defects (Newman et al., 2002).

Regeneration defined as the reconstitution of a lost part by restoring its form and function. The most crucial factor in the regeneration of periodontal tissues is the spatial relationship between the bony wall and the radicular surface of the tooth. The bone and root surface provides stability to the clot and the wound, facilitating periodontal regeneration (regeneration of bone, cementum and junctional epithelium) (Alpiste Illueca et al., 2006). Treatment of deep and angular bony defects with various procedures like conventional flaps, access flaps or respective techniques are used (Kaldahl et al., 1996; Polson and Heijl, 1978). Although these flap techniques have reduced probing depth and correcting bony defects, it has not resulted in ideal regeneration, i.e. resultant residual pockets or regeneration of bone, cementum and junctional epithelium (Kaldahl et al., 1996). In order to overcome these limitations, various regenerative biologics and biomaterials to obtain ideal regeneration did propose. Regenerative materials like enamel derived matrix (EMD), platelet isolates, bone grafts (DFDBA, β -TCP, Xenografts), Pegen (P-15), along with various barrier membranes for the treatment of periodontal intrabony defects are used (Del Fabbro et al., 2018; Lee et al., 2020; Panda et al., 2016, 2019; Polson and Heijl, 1978). The progress in molecular and cell biology allowed the identification of various bio-mediators that support enhanced wound healing and influence de-novo tissue formation if given in the right amounts. Growth factors (GF's) like PDGF, IGF-1, TGF- β , BMP-2 support periodontal wound healing and regeneration. GF's are readily available and required in a conducive amount and environment to accelerate and promote regeneration (Giannobile, 1996; Lee et al., 2020). Predictable regeneration of periodontium stimulates the proliferation of mesenchymal and PDL cells and prevent the migration of unrequired cells. Researchers came up with combining cell-stimulating proteins with other bioactive scaffolds (Nevins et al., 2003) and led the researchers to develop recombinant human growth factors like rhPDGF, rh-FGF, rh-BMP, which the clinicians are widely using (Cochran et al., 2016; Edmunds et al., 2014; Kitamura et al., 2011). A systematic review and consensus report (Reynolds et al., 2015) found consistent good-quality patient-oriented evidence in combination therapy (Cell-occlusive membrane, biomaterials, bone replacement graft, GTR and biologics).

Similarly, another systematic review (Tavelli et al., 2021) concluded that rhPDGF is safe and provides successful clinical outcomes when used in combination with bone grafts and bone scaffolds. However, there is little or no evidence regarding the combination of which rh growth factor combined with bone graft and scaffold is more effective in treating intrabony defects. Therefore, this network meta-analysis aimed to search for the clinical studies that portray the effectiveness of recombinant human growth factors and a bioactive scaffold to treat intrabony defects and carry out a network meta-analysis.

2 MATERIAL AND METHODS

According to the PRISMA (preferred reporting of items in systematic review and meta-analysis) guidelines (Liberati et al., 2009), this systematic review and meta-analysis were performed. The protocol for the systematic review was registered at PROSPERO with registration ID CRD42020213753.

2.1 Research question

What is the effect of Recombinant Human Derived Growth and Differentiating Factors and bioactive agents with/without scaffold biomaterial in the treatment of intra-bony defects?

P: The human subjects presenting with one or more intrabony defects.

I: Recombinant Human Derived Growth and Differentiating Factors bioactive agents with/without scaffold biomaterial used as test group in the treatment of intrabony defects.

C: In cases where bioactive agents are placed with/without scaffolds in the periodontal defect after open flap debridement, the control (OFD) with/without scaffold alone will be considered. Other comparisons include control (No material), Placebo, different biomaterial.

O: Primary outcomes assessed in terms of Full mouth plaque score (FMPS) will be recorded as the percentage of total surfaces (4 aspects per tooth); Bleeding on probing; Full mouth bleeding scores (FMBS); Probing pocket depths at the experimental and adjacent tooth; Probing pocket depth at the most profound interproximal site associated with the selected intrabony defect; Clinical Attachment Levels (CAL) or Relative attachment level (RAL); Amount of bone fill after surgery (Histology or Radiographic).

2.2 Search strategy

We conducted a digital search (using Medline, Scopus, Web of Science and Cochrane Central) using a series of keywords combined with boolean operators (Figure 1). The keywords used for the search were related to " (Intra-bony defects OR Intraosseous defects OR Intrabony defects OR Periodontal defects) AND (recombinant human-derived growth factors OR recombinant human platelet-derived growth factor OR rhPDGF OR rhPDGF-BB OR recombinant human fibroblast growth factor OR rhFGF OR recombinant human insulin derived growth factors OR recombinant human vascular endothelial growth factors OR recombinant human growth or differentiating factors OR recombinant human bone morphogenetic protein OR rhBMP2)". In addition, we searched for other relevant articles manually in peer-reviewed journals like *Journal of Clinical Periodontology*, *Journal of Periodontology*, *Journal of Periodontal Research*, *Journal of Dental Research*, *Journal of Periodontal and Implant Sciences*. The search was limited to publications in the English language until November 2020. A search for additional studies also conducted in the bibliography of previously published studies related to systematic reviews and other eligible studies.

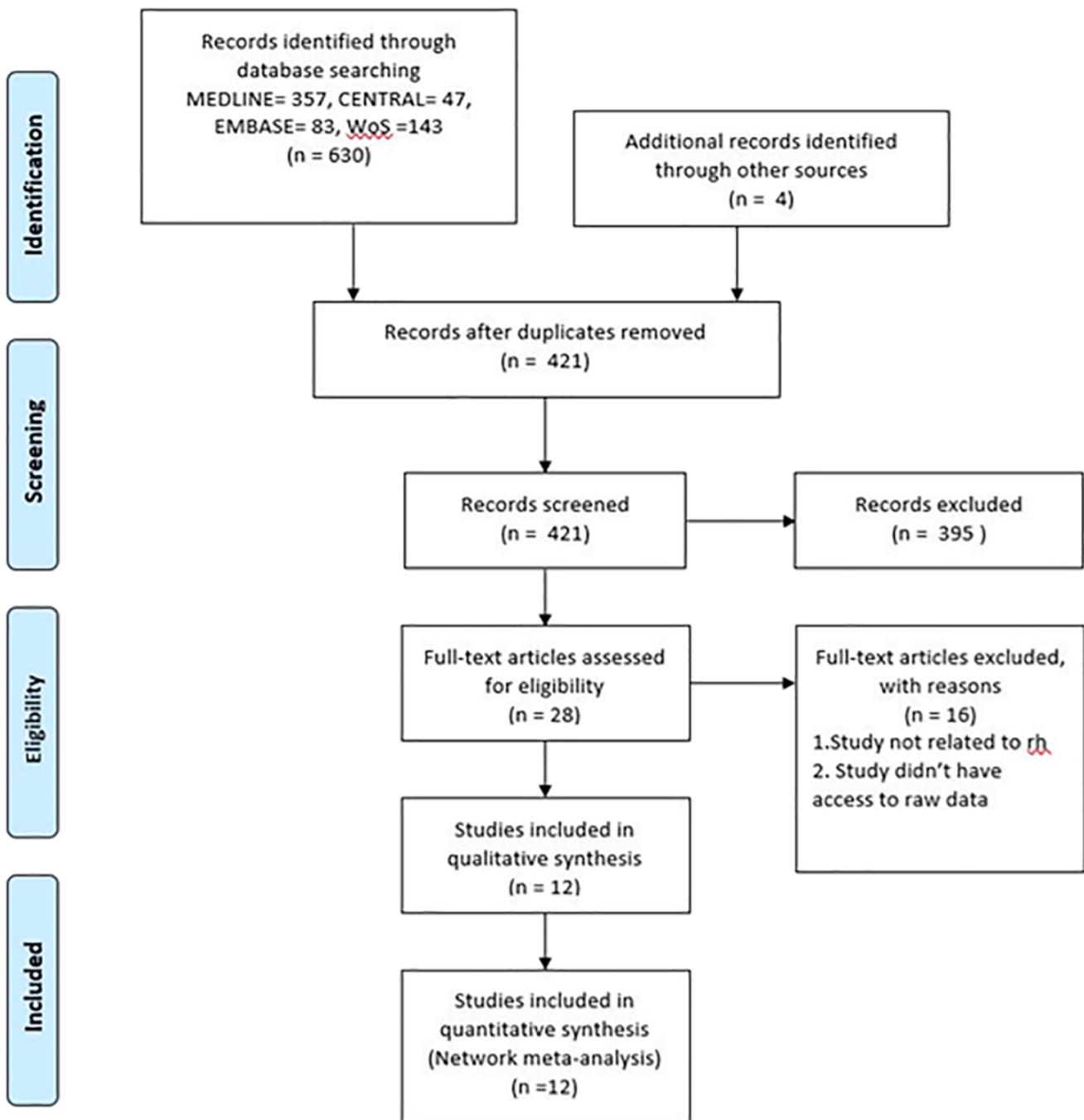


FIGURE 1 PRISMA flow chart

2.3 Selection criteria

The screening of the full texts of the retrieved studies was pre-determined based on inclusion and exclusion criteria. The inclusion criteria were as follows: Clinical trials or randomized controlled clinical trials, cross-over trials, cohort studies, cross-section studies which included $N = 10$ or more patients in each study and that evaluated the efficacy of recombinant human-derived growth and differentiating factors and bioactive agents with/without scaffold biomaterial. In addition, other studies that we excluded were; In-vitro, observational and retrospective studies, case series and case reports, in-vivo animal studies.

2.4 Data extraction

The relevant data from the included studies were extracted by two independent reviewers (MD, SP) using an Excel spreadsheet (Redmond, Microsoft, USA). The data extraction related to demographics like age, gender, location of the study conducted, interventional characteristics, the journal published, year of publication. Outcomes like Probing pocket depths (PPD) at the experimental and adjacent tooth; Probing

pocket depth at the most profound interproximal site associated with the selected intrabony defect; Clinical Attachment Levels (CAL) or Relative attachment level (RAL); Amount of bone fill after surgery (Histology or Radiographic) was extracted. In addition, the authors contacted over email for providing any missing or unclear information.

2.5 Data synthesis

Qualitative and quantitative data and the demographics tabulated from all the included studies. The quantitative data extracted for different outcomes were subjected to Network Meta-analysis (NMA). NMA analysis included network plot, contribution plot, predictive interval and confidence interval plot, inconsistency plot, SUCRA ranking and multidimensional scale ranking (MDS). Prediction Intervals (PrIs) were calculated to predict effects in a future clinical setting by incorporating heterogeneity. The results of all direct and mixed comparisons were presented in forest plots. The latter were augmented with contours of effect magnitude based on multiples of the mean, a standard deviation of the included outcome (10%): 0%–10% clinically irrelevant effect, 10%–20% moderate effect, 20%–30% significant effect, and >30% substantial effect. In order to rank treatments for an outcome, the surface under the cumulative ranking curves (SUCRA) was used. The (MDS) was for illustrating the dissimilarity between two materials. NMA was carried out using Stata version 16 (StataCorp, College Station, TX).

2.6 Risk of bias analysis

Two independent reviewers (H.A.V, S.K) assessed the risk of bias for all the included clinical trials, and the discrepancies were resolved by discussion and consultation with a third reviewer (M.D.F). The domains for risk assessment were graded as high, uncertain or low risk, based on: selection bias (random sequence generation and allocation concealment); performance bias (blinding); detection bias (assessor blinding); attrition bias (incomplete outcome data); reporting bias (selective reporting). Subsequently, the overall risk for individual studies was assessed as low, moderate and high risk based on the following criteria. The study was assessed to have a low overall risk only if all domains were found to have low risk and high overall risk if one or more of the six domains were found to be at high risk. A moderate risk assessment was provided to the studies when one or more domains were found to be uncertain and none at high risk.

3 RESULTS

Twelve studies (Abdal-Wahab et al., 2020; de Santana R. B. and de Santana C.M.M, 2015; Devi and Dixit, 2016; Dhote et al., 2015; Jayakumar et al., 2011; Joshi et al., 2019; Kavyamala et al., 2019; Kitamura et al., 2011; Maroo and Murthy, 2014; Mishra et al., 2013; Saito et al., 2019; Windisch et al., 2012) were included for qualitative and quantitative analysis (Figure 1). The control subjects assessed were $n = 217$, and the test subjects that were assessed were $n = 349$. The majority of studies were parallel RCTs except one (Maroo and Murthy, 2014), which was a split-mouth study. $N = 5$ were funded by societies and foundations and $N = 7$ were self-funded studies. The rh factors that were compared with controls in the studies were rhFGF-2, gingival fibroblasts, rhPDGF-BB, rhFGF-2 + DBBM, rhFGF + HA, beta-TCP + rh-PDGF-BB, rhPDGF + β -TCP, rhGDF-5 + b-TCP and rhPDGF-BB + β -TCP (Table 1). The mean, sd and n were extracted and illustrated in the research data file. PPD, CAL, and percentage of bone fill outcomes were reported from the studies shortlisted, and these were selected because the data was sufficiently available for network meta-analysis. The mean intra-bony defect size for control was 5.00 ± 2.22 mm and for the test was 4.97 ± 2.26 mm. There were $N = 113$ males and $N = 92$ females, and the mean age was 42.52 ± 7.89 years (min/max = 32.6-52.3 years). (Table 2)

TABLE 1 Characteristics of included study for quantitative analysis

TABLE 2 Characteristics of studies

3.1 PPD outcome

The network geometry plot, contribution plot, risk of bias between materials, publication bias and predictive and confidence interval plot illustrated in Supplemental Figure S1, S2 and S3 .

The (SUCRA) in PPD outcome expresses the percentage of effectiveness/safety each treatment has compared to an ‘ideal’ treatment consistently ranked first without uncertainty. (MDS) for PPD outcome illustrates the dissimilarity between the two treatments. rhFGF + HA was ranked higher in SUCRA ranking and is dissimilar to other interventions suggestive of (MDS) (Figure 2).

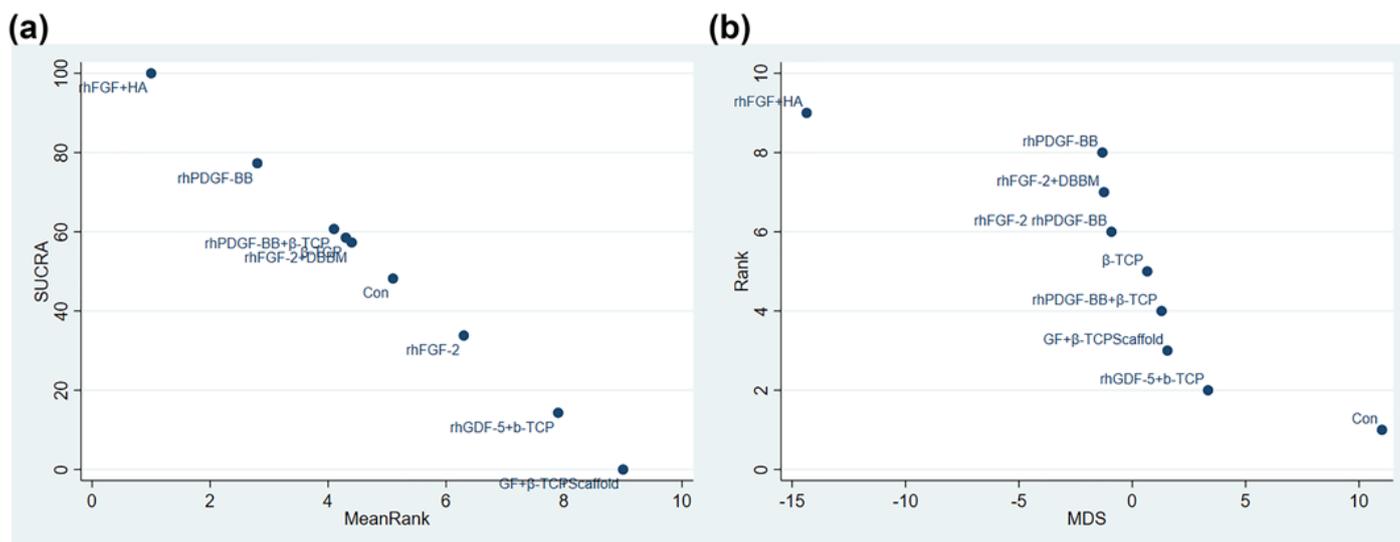


FIGURE 2(a) The SUCRA for PPD outcome in managing intrabony defects and (b) MDS for PPD outcome in managing intrabony defects, Abbreviation: MDS, Multidimensional Scale Ranking; PPD, Probing pocket depths; SUCRA, surface under the cumulative ranking curves

3.2 Clinical attachment level

NMA plots for clinical attachment levels outcome in Intrabony defects was illustrated in Supplemental Figure S4–S6.

The (SUCRA) in clinical attachment level (CAL) outcome expresses the percentage of effectiveness/safety each treatment has compared to an ‘ideal’ treatment consistently ranked first without uncertainty. MDS for clinical attachment level outcome illustrates the dissimilarity between the two treatments. rhFGF + HA was ranked higher in the SUCRA ranking (Figure 3).

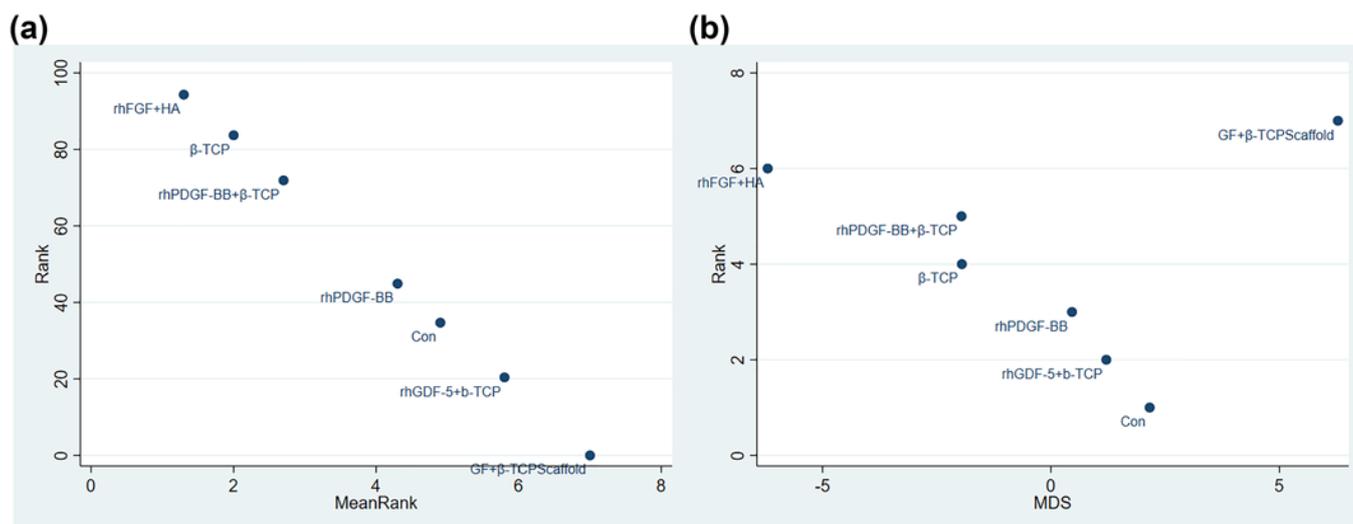


FIGURE 3A. The SUCRA for CAL outcome in managing intrabony defects and D. MDS for CAL outcome in managing intrabony defects, Abbreviation: CAL, clinical attachment levels; MDS, Multidimensional Scale Ranking; SUCRA, surface under the cumulative ranking curves

3.3 Percentage of bone fill

The network geometry plot, contribution plot, risk of bias between materials and predictive and confidence interval plot for % of bone outcomes was illustrated in Supplemental .Figure S7, S8.

The (SUCRA) for a percentage of bone fill outcome. It expresses the percentage of effectiveness/safety each treatment has compared to an ‘ideal’ treatment consistently ranked first without uncertainty. rhPDGF-BB+β-TCP was ranked higher in the amount of bone fill in MDS ranking (Figure 4).

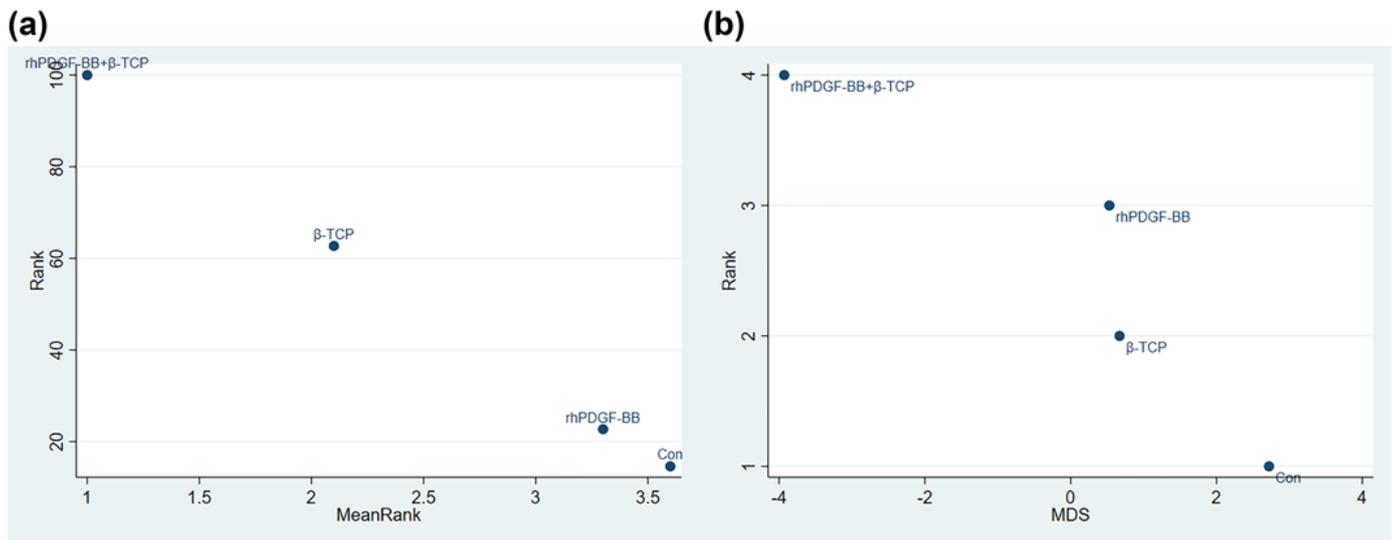


FIGURE 4(a) The SUCRA and (b) MDS for percentage of bone fill outcome in managing intrabony defects, Abbreviation: MDS, Multidimensional Scale Ranking; SUCRA, surface under the cumulative ranking curves.

The risk of bias from individual studies found that the majority of them have moderate risk, and three studies are high risk of bias (Dhote et al., 2015; Maroo and Murthy, 2014) (Figure 5).

	Publication Year	Author	Randomisation	Allocation Bias	Performance Bias	Blinding	Attrition Bias	Selective reporting bias	Overall Bias
1	2019	Abdal-Wahab et al	Yes	Low	Low	Yes	Low	Unclear	Moderate
2	2019	Joshi et al	Yes	Low	Low	Yes	Low	Low	Low
3	2019	Kavyamala et al	Yes	Low	Low	Yes	Low	Low	Low
4	2019	Saito et al	Yes	Low	Low	Yes	Low	Unclear	Moderate
5	2016	Devi et al	Yes	Low	Low	Yes	Low	Unclear	Moderate
6	2015	de Santana et al	Yes	Low	Unclear	Yes	low	Low	Moderate
7	2015	Dhote et al	Yes	Low	High	Yes	High	Unclear	High
8	2014	Maroo et al	Yes	Low	Low	Yes	High	Unclear	High
9	2012	Mishra et al	Yes	Low	Low	Yes	Low	Unclear	Moderate
10	2011	Windisch et al	Yes	Low	Unclear	Yes	High	Low	High
11	2010	Jayakumar et al	Yes	Low	Low	Yes	Low	Low	Low
12	2010	Kitamura et al	Yes	Low	Low	Yes	Low	Unclear	Moderate

FIGURE 5Risk of bias for individual studies

4DISCUSSION

The end goal of periodontal tissue regeneration is to prevent tooth loss by regenerating periodontal fibres, bone and cementum. Conservative treatment and supportive periodontal therapy play a vital role after any

non-surgical and surgical therapies. Periodontal regeneration using biologics, bioactive agents, and scaffolds are growing trends, and their biological effects create a well-defined microenvironment for the differentiation of specific cells that contain periodontal cells. Keratinocytes in periodontium and fibroblasts proliferate faster, and their replication is difficult to control after surgical therapy. The majority of the regenerative therapies are based on allowing epithelial cells and fibroblasts to overgrow and also at the same time maintain a space that can allow other cells to proliferate and differentiate (Horváth et al., 2013; Oztug et al., 2021).

Recombinant human (rh) growth factor (GF) like rhFGF, rhPDGF-BB and combinations with beta-tricalcium phosphate (β -TCP) and other bioactive materials, scaffolds (monophasic and multiphasic scaffolds) in clinical dentistry met with great enthusiasm due to its potential to render predictable clinical outcomes. The remodelling capacity by the rhGFs by recruiting cells is more as compared to typical growth factors (Hollinger et al., 2008). One of the essential GF is a platelet-derived growth factor (PDGF) (chemoattractant and a mitogen) that works by binding to the cell surface receptors of mesenchymal origin that enables bone regeneration (Elangovan, 2015; Hollinger et al., 2008; Kaigler et al., 2011).

A systematic review aimed to determine the beneficial effects of growth factors in human periodontal regeneration that can offer superior results compared with other accepted periodontal regeneration techniques (Elangovan, 2015). The results from five controlled trials confirmed moderate benefits in the regeneration of clinical attachment levels (CAL) with rhPDGF-BB, compared with β -TCP controls, after six months. The studies included in this systematic review were of small sample size and generally short duration of follow-up. Therefore, these factors should be considered before applying the results clinically.

In our review, we included 12 studies for qualitative and 12 studies for quantitative analysis. The data extracted from 10 parallel randomized clinical trials and one split-mouth trial. The majority of the projects were funded; the details are mentioned in the characteristic Table 1, and the follow-up period was between 3 to 12 months' duration. Although Kitamura et al. 2011 (Kitamura et al., 2011) were included in the review for further analysis, the data was not used for NMA and was an observational study (Table 1). Abdal-Wahab, et al., 2020; Devi and Dixit, 2016; Maroo and Murthy, 2014; Jayakumar et al., 2011 included beta-TCP as controls and other authors include PRF, rhFGF-2 as controls.

Our results have found that rhFGF + HA material was ranked higher in PPD and CAL outcome (Figures 2 and 3). rhPDGF-BB+ β -TCP was ranked higher in the percentage of bone fill outcome (Figure 4). The data included from different studies of network meta-analysis was demonstrated in Table 1 Santana R. B. and de Santana C.M.M., 2015 is the only study that compared rhFGF + HA along with the control group. The sample size and mean score was larger, and it is the possible reason rhFGF + HA was ranked higher. Jayakumar et al., 2011 and Dhote et al., 2015 included rhPDGF-BB+ β -TCP and compared it with β -TCP/control with a total sample size of $n = 78$. Beta-tricalcium phosphate (β -TCP), rhPDGF-BB+ β -TCP and control, rhFGF + HA comparisons are frequent in CAL outcome. In the PPD outcome, most comparisons were between β -TCP V rhPDGF-BB+ β -TCP and Control V rhFGF + HA (Figure 2A, 4A). The percentage of bone fill outcome was very few studies that diminish an opportunity to develop evidence through a standard gold method.

There was no direct, indirect or network evidence for most of the recombinant growth factors in the network. However, rhPDGF-BB V Con and rhPDGF-BB+ β -TCP V Control found insufficient evidence that they perform better in periodontal outcomes.

According to the SUCRA ranking, rhFGF + HA ranked higher for PPD and CAL outcome. Also, rhPDGF-BB+ β -TCP ranked higher in the percentage of bone fill. SUCRA ranks express the percentage of each treatment's effectiveness compared to an 'ideal' treatment always ranked first without uncertainty. However, there are five reasons why clinicians should not routinely choose a treatment with the higher SUCRA ranking. Firstly, the rankings are based on very low quality, and secondly, they have several relevant outcomes. A third reason is that issues with cost and a clinician's familiarity with the use of a particular treatment influence the better outcome from that particular material. Fourth, SUCRA does not consider the magnitude of differences in effects between treatments. Fifth is the ability to differentiate between the

treatments. Therefore, choosing the best material should be based on overall factors into consideration, like grade method of evidence and predictive intervals (Dobler et al., 2018).

The interaction of rh growth factors at the interface with bioactive materials and scaffolds are well established. Basically, GF's signal transmission mechanism initiates GF secretion by the producer cell and instructs cell behaviour by binding to transmembrane receptors on the target cells. Later, transduction by GF's involves complex events involving cytoskeleton protein phosphorylation, ion fluxes, changes in metabolism, gene expression, protein synthesis, and biological response. These stages of processes ultimately would lead to the initiation of specific cell response. The process by which the biomaterials interact with rh growth factors is mainly two ways; firstly, by chemical immobilization of GF in or onto the matrix and secondly, by physical encapsulation of GF. The chemical immobilization involves affinity interaction with GF containing polymer substrate, cell or tissue. Physical encapsulation is achieved by the pre-programmed release of GF into the surrounding tissue (Lee et al., 2011). These are the primary cell processed by which recombinant factors initiates bone regeneration. The bioactive materials used in combination and adjunct to the rh growth factors stimulate a biological response from the body by binding to bone and stimulate the bone on the surface of the bioactive material (osteoconductive). The mechanism of binding to the bone occurs by forming hydroxyapatite (HA) on the surface of materials (Kattimani et al., 2016).

During current times where the interventional approach is shifting towards personalized medicine, choosing the best treatment for better outcomes has become challenging for clinicians. This also has raised ethical issues for patients and clinicians where newer materials coming into the market at a rapid pace and left no time for evidence generation. Also, clinicians and end-users are left in the dark by the researchers and raise questions on where and how new treatments fit into clinical practice. In addition, biased pharmaceutical industry interests can again cause economic and health consequences.

The solution to the problem might be, after the introduction of new materials into the market, both industry and non-industry sponsors should support independent randomized trials that evaluate a products net clinical benefit as compared with current available effective treatments. In addition to that, research agencies, funders and government organizations should invest in developing collaborative research networks and data systems that help in meaningful translational biomaterial research.

Moreover, from the studies included, the mean intra-bony defect size for control was 5.00 ± 2.22 and for the test was 4.97 ± 2.26 . Other factors like age were 42.52 ± 7.89 years, and gender ratio had no significant difference in numbers (Table 2). Ageing would affect cementum, bone and periodontal ligament regeneration. Cementum deposition increases with age, and bone resorptions occur with ageing, but also ageing causes recession. Clinicians and researchers should consider these factors while evaluating periodontal regeneration.

The limitations of this study include a small number of studies that have heterogeneous data. Also, not all outcomes were considered due to the lack of data from the included studies. The most relevant outcomes should be considered while planning a clinical trial that evaluates any treatment of periodontal intrabony defects. No all rh preparation commercially available and need further approval for clinical applications.

4.1 Quality of evidence

The results of our study found that recombinant factors were effective in treating intrabony defects. Twelve RCTs were included and judged at moderate and high risk of bias. However, it was challenging to grade the evidence for effectiveness due to the diverse group of rhGFs formulations used in each study. Therefore, well-designed clinical trials are needed to develop a piece of evidence and provide clinical recommendations on the most effective rhGFs for periodontal intrabony defects regeneration.

5 CONCLUSION

Our network meta-analysis concluded that recombinant growth factors combined with alloplastic scaffolds provide the best outcomes for periodontal regeneration. NMA may help clinicians choose the most performant treatment option, but many variables should be considered to make the final decision, among which patient preferences, costs, and defect characteristics.

5.1 Recommendation

There was lack of evidence for interventions used within these clinical studies, because these studies used diverse rh groups. Therefore, to estimate the quality of evidence and draft a recommendation on most effective rh factor for the treatment of intrabony defects was challenging. In order to facilitate decision making for clinicians, through predictive interval plots, our review tried to explore materials that most likely to perform best in future clinical studies. This new direction of to choose materials in future clinical studies would build evidence.

CONFLICT OF INTEREST

None to declare.

SOURCE OF FUNDING

None

ACKNOWLEDGEMENTS

None

Open Research

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

AUTHOR CONTRIBUTION

Sourav Panda has contributed to conception, design, data acquisition and interpretation, drafted and critically revised the manuscript. Shahnawaz Khijmatgar has contributed to conception, design, data acquisition and interpretation, performed all statistical analyses, drafted and critically revised the manuscript and provided all the necessary material required for publication. Mohit Das has contributed to conception, design, and critically revised the manuscript. Herber Isaac Arbildo-Vega has contributed to conception, design, and critically revised the manuscript Massimo Del Fabbro has contributed to conception, design, data acquisition and interpretation, drafted and critically revised the manuscript. All authors discussed the results and contributed to the final manuscript and all of the authors gave their final approval and agree to be accountable for all aspects of the work.