M E T A - A N A L Y S I S

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Recombinant human platelet-derived growth factor-BB combined with grafting materials for the treatment of periodontal intrabony defects: a meta-analysis

Rekombinantni humani trombocitni faktor rasta BB u kombinaciji sa koštanim zamenicima za lečenje parodontalnih intrakoštanih defekata: meta-analiza

[1]Wensong Hao*, [1]Leilei Li†, Kun Huang‡, Xiaodong Sui‡, Yuanyuan Qi†

***Liaocheng University, School of Medicine, Liaocheng, Shandong, China; †Dongying People's Hospital, Dongying, Shandong, China; ‡Liaocheng Traditional Chinese Medicine Hospital, Liaocheng, Shandong, China**

[1] equal contribution of both authors

Abstract

Background/Aim. Periodontitis is a common dental disease affecting around 50% of adult patients globally. It can cause continuous deterioration of periodontal tissue inflammation, leading to irreversible periodontal bone resorption and even tooth loosening. Currently, suitable techniques for managing periodontal intrabony deformities include both allogeneic and autologous bone transplantation, but these methods have certain limitations. The aim of this study was to examine the effect of recombinant human platelet-derived growth factor-BB (rhPDGF-BB) in combination with grafting materials for the treatment of periodontal intraosseous defects using a meta-analysis. **Methods.** In March 2024, electronic databases (Cochrane Library, PubMed, Embase, Web of Science) were searched to gather data from studies on growth factors and grafting materials for the treatment of intrabony periodontal deficiencies. **Results.** A total of 11 articles were fully reviewed, of which nine were included in the meta-analysis. The 9 studies included 313 people, divided into two groups: experimental (n = 156) and control (n = 157). The results of the meta-analysis indicate significantly higher clinical attachment level (CAL) of the experimental group [$p < 0.01$, standardized mean difference (SMD): 0.80; 95% confidence interval (CI): 0.49, 1.10] compared to the control group. Changes in probing depth (PD) of the experimental group were greater ($p < 0.01$, SMD: 0.75; 95% CI: 0.39, 1.11) than in the control group. In addition, bone fill (BF) ($p < 0.01$, SMD: 22.33; 95% CI: 15.71, 28.95) and linear bone growth (LBG) ($p < 0.01$, SMD: 0.87; 95% CI: 0.43, 1.30) of the experimental group were greater. The gingival recession (GR) of the experimental group was lower ($p < 0.05$, SMD: -0.27; 95% CI: -0.51, -0.03) than in the control group. **Conclusion.** The results indicate that the rhPDGF-BB combined with the grafting material can improve CAL, PD, BF, LBG, and GR in periodontal intrabony defects.

Key words:
database; meta-analysis; periodontal diseases; platelet-derived growth factor.

Apstrakt

Uvod/Cilj. Parodontitis je uobičajena bolest zuba koja pogađa oko 50% odraslih pacijenata širom sveta. Može izazvati kontinuirano pogoršanje zapaljenja parodontalnog tkiva, što dovodi do nepovratne resorpcije parodontalne kosti, pa čak i pomeranja (klimanja) zuba. Trenutno, pogodne tehnike za rešavanja parodontalnih intrakoštanih deformiteta uključuju alogenu i autolognu transplantaciju kostiju, ali ove metode imaju određena ograničenja. Cilj rada bio je da se ispita efekat rekombinantnog humanog trombocitnog faktora rasta BB (*recombinant human platelet-derived growth factor*-BB – rhPDGF-BB) u kombinaciji sa koštanim zamenicima za lečenje parodontalnih intrakoštanih defekata primenom meta-analize. **Metode.** U martu 2024. godine izvršena je pretraga elektronskih baza (*Cochrane Library*, *PubMed*, *Embase*, *Web of Science*) kako bi se prikupili podaci iz studija o faktorima rasta i koštanim zamenicima za lečenje intrakoštanih parodontalnih nedostataka. **Rezultati.** Od 11 članaka koji su u potpunosti pregledani njih 9 je uključeno u meta-analizu. Ovih 9 studija je obuhvatilo 313 osoba podeljenih u dve grupe: eksperimentalnu (n = 156) i kontrolnu (n = 157). Rezultati meta-analize ukazuju na značajno viši nivo pripojnog epitela (*clinical attachment level* – CAL) eksperimentalne grupe [$p < 0,01$, *standardized mean difference* (SMD): 0,80; 95% interval poverenja (*confidence interval* – CI): 0,49, 1,10] u poređenju sa kontrolnom grupom.

Correspondence to: Yuanyuan Qi, Dongying People's Hospital, No. 317 Nanyi Road, Dongying District, Dongying 257 091, Shandong, China. E-mail: y44253056@gmail.com

Promene u dubini parodontalnog džepa (*probing depth* – PD) eksperimentalne grupe bile su veće ($p < 0,01$, SMD: 0,75; 95% CI: 0,39, 1,11) od kontrolne grupe. Takodje, koštani ispun (KI) ($p < 0,01$, SMD: 22,33; 95% CI: 15,71, 28,95) i linearni rast kosti (LRK) ($p < 0,01$, SMD: 0,87; 95% CI: 0,43, 1,30) eksperimentalne grupe bili su veći. Recesija gingive (RG) eksperimentalne grupe bila je niža ($p < 0,05$, SMD: -0,27; 95% CI: -0,51, -0,03) u odnosu na kontrolnu grupu. **Zaključak.** Rezultati ukazuju na to da rhPDGF-BB u kombinaciji sa koštanim zamenicima može poboljšati CAL, PD, KI, LRK i RG kod parodontalnih intrakoštanih defekata.

Ključne reči:
baze podataka; meta-analiza; periodontalne bolesti; faktor rasta, trombocitni.

Introduction

Periodontitis is a common dental disease that affects over half of all adults worldwide [1]. It may result in persistent inflammation of the periodontal tissues, irreversible loss of the periodontal bone, and loosening of the teeth [2]. Nowadays, frequent approaches for managing periodontal intrabony flaws consist of allogeneic and autologous bone transplantation, but these methods have certain limitations. For instance, the disadvantages of autologous bone transplantation are increased surgical trauma, longer operation time, limited graft availability, and high incidence rate of the donor site, while allograft bone transplantation may lead to disease transmission and immune rejection [3]. Periodontitis can cause periodontal bone resorption, which can be repaired using bone graft materials [4]. Periapical diseases, cysts, and injuries can all cause blemishes of bones in maxillofacial and oral sections, and bone graft materials are usually used for repair [5–7]. After tooth loss, absorption of the alveolar ridge is inevitable. Bone graft materials can be implanted into the extraction socket at the same time as tooth extraction to delay the absorption of the alveolar ridge. In response to these issues, bone tissue engineering based on biomaterials has great prospects in repairing bone defects [8]. In bone tissue engineering, scaffold materials are one of the three essential components that can act as templates for bone regeneration as well as a base for cell adhesion and proliferation [9]. A scaffold designed for bone tissue creation should be highly biocompatible. In addition, it should have high porosity, biodegradability, and good osteogenic induction activity. Therefore, its mechanical characteristics ought to coincide with the bone tissue of the host [10].

Natural bone tissue regeneration is a multi-stage cascade process, with specific biological factors playing a role at each stage. This inspires us to simulate the natural bone healing process to achieve bone regeneration [11, 12]. Based on the changes in demand for different biological signals during bone healing, precise coordination of drug release is required at each specific regeneration stage. However, this remains a confront in the bone tissue engineering field. The bone repair mechanism is complex, and the use of bioactive substances can enhance the tissue regeneration ability of cells. The growth factor (GF) is a protein secreted by activated bone cells, which can transmit signals to specific receptor target cells. The key role of GFs is to promote cell proliferation and differentiation, hasten the process of bone injuries and flaws healing, and therefore occupy a crucial position. For instance, the introduction of bioactive GFs like bone morphogenetic protein 2 (BMP-2) enhances the tissue renaissance ability of guided bone regeneration membranes. The addition of platelet-derived growth factor (PDGF) was found to have a similar effect [13]. It is known that BMP-2 has a dual effect on bone repair and induces bone formation at low concentrations, while high concentrations can lead to bone loss. So far, however, BMP-2 has been thought to be a potent bone healing activator even today, and its delivery strategy needs further optimization. Yet, surgical data indicate that more transplant materials may be required for posterior foot and ankle joint fusion surgery in some patient groups with various forms of arthritis, and platelet-derived growth factor-BB (PDGF-BB) was authorized as a class III combined medical device/drug in 2015. In terms of specific mechanisms, PDGF can recognize and activate PDGF receptors, recruit multiple cells, carry out signaling pathways transmission, and encourage the proliferation of cells [14]. PDGF has also been proven to induce new blood vessels in the target site through communication reactions with various cells, which is an important aspect of bone repair. Unfortunately, the use of bioactive GFs is restricted by their short half-life, erratic nature, and expensive nature of proteins.

The aim of this study was to examine the effect of recombinant human PDGF-BB (rhPDGF-BB) in combination with grafting materials for the treatment of periodontal intraosseous defects in humans since systematic research on such controlled trials are lacking.

Methods

Study type

This meta-analysis included controlled studies on using GFs in conjunction with grafting materials to repair intrabony periodontal problems.

Intervention types

Two types of subjects were examined – experimental and control. The experimental subjects were administered GF combined with grafting materials in periodontal intrabony defect management, whereas the control subjects were administered GF alone or grafting materials alone.

Outcome measure types

In order for a study to be included in our meta-analysis, at least one of the following outcome markers must be met:

clinical attachment level (CAL), changes in probing depth (PD), bone fill (BF), gingival recession (GR), and linear bone growth (LBG).

Literature retrieval strategy

The deadline for our English search was March 2024. We carried out computer searches of PubMed, Embase, Cochrane Library, and Web of Science electronic databases. The following are a few subject terms created for the English search: "growth factor", "grafting materials", and "periodontal intrabony defects".

Literature screening and data extraction

The screening process used for including or excluding literature is described in the text that follows. Two scholars independently examine the literature. If there are disagreements, they discuss and seek advice from a third party. The scholars read the abstracts and titles before choosing any literature to remove obviously irrelevant material. Afterward, they continue reading the complete book to decide whether or not to incorporate it into the analysis. The third party is engaged in discussions and negotiations to resolve any discrepancies that arise between the two researchers as they separately retrieve pertinent literature data using Microsoft Excel. Some details included in the literature extraction process were average age, gender ratio, sample size, first author, year of publication, intervention measures, and outcome indicators.

Statistical analysis

Stata software version 16 was utilized for the meta-analysis in this study. The odds ratio (OR) is used to show intergroup differences for binary variables, while the weighted mean difference (WMD) or standardized mean difference (SMD) is used to show intergroup differences for continuous variables. The study findings are represented by the 95% confidence interval (CI), and the I^2 index is used to determine the degree of heterogeneity. Depending on how heterogeneous each research is, either a fixed effects model (FEM) analysis or a random effects model (REM) analysis is employed. Additionally, the study's general publication bias is assessed using Egger's and Begg's tests. Sensitivity analysis is performed to identify the cause of any substantial clinical heterogeneity in the research.

Results

Results of the literature search

Two hundred and nineteen pertinent pieces of literature were ultimately searched, and 203 were obtained after screening out duplicate literature. Having perused the abstracts and titles, 11 publications were attained. Further exclusion due to lack of data resulted in the inclusion of 9 articles. In those 9 studies, there were 313 subjects, whom we divided into two groups: experimental (n = 156) and control (n = 157). The basic characteristics of the included studies and a PRISMA flowchart are detailed in Table 1 [15–23] and Figure 1, respectively.

Clinical attachment level

There were a total of 9 literature reports on the CAL of rhPDGF-BB combined with grafting materials in periodontal intrabony defect management. The findings demonstrated that there was a statistically significant difference ($p < 0.01$,

Table 1

Basic characteristics of the included studies

Studies	Cases (n = 313) experimental/ control	Gender (male/ female)	Age (years)	Experimental group	Control group	Outcomes measures
Jayakumar et al. [15]	27/27	25/29	32.6 ± 7.3 / 30.9 ± 5.1	rhPDGF+β-TCP	β-TCP	CAL, PD, BF, LBG
Deshpande et al. [16]	9/9	NA	35.76 ± 7.38	rhPDGF+β-TCP	HA+β-TCP	CAL, PD, BF, GR, LBG
Maroo and. Murthy [17]	15/15	NA	38.4 ± 7.6	rhPDGF+β-TCP	β-TCP	CAL, PD, BF, GR
Qiao et al. [18]	15/16	NA	47.7 ± 13.9	CGF+BPBM	BPBM	CAL, PD, GR
Xu et al. [19]	30/30	NA	55.2 ± 8.3	CGF+Bio-Oss	Bio-Oss	CAL, PD
Saito et al. [20]	16/16	13/19	52.3 ± 10.1 / 50.0 ± 10.9	rhFGF-2+DBBM	rhFGF-2	CAL, PD, GR
Bahammam et al. [21]	15/15	16/14	37.4 ± 4.4 / 40.2 ± 5.9	PRF+HA	HA	CAL, PD
Seshima et al. [22]	16/16	NA	NA	rhFGF-2+DBBM	rhFGF-2	CAL
Priyanka et al. [23]	13/13	NA	33.08 ± 7.70 / 35.23 ± 6.47	rhPDGF-BB+DFDBA	rhPDGF-BB	CAL, PD, LBG

NA – no answer; rhPDGF – recombinant human platelet-derived growth factor; β-TCP – beta-tricalcium phosphate; CAL – clinical attachment level; PD – probing depth; BF – bone fill; GR – gingival recession; LBG – linear bone growth; CGF – concentrated growth factor; BPBM – bovine porous bone mineral; DBBM – deproteinized bovine bone mineral; rhFGF – recombinant human fibroblast growth factor; PRF – platelet-rich fibrin; HA – hydroxyapatite; DFDBA – demineralized freeze-dried bone allograft.
All values are given as mean ± standard deviation or numbers.

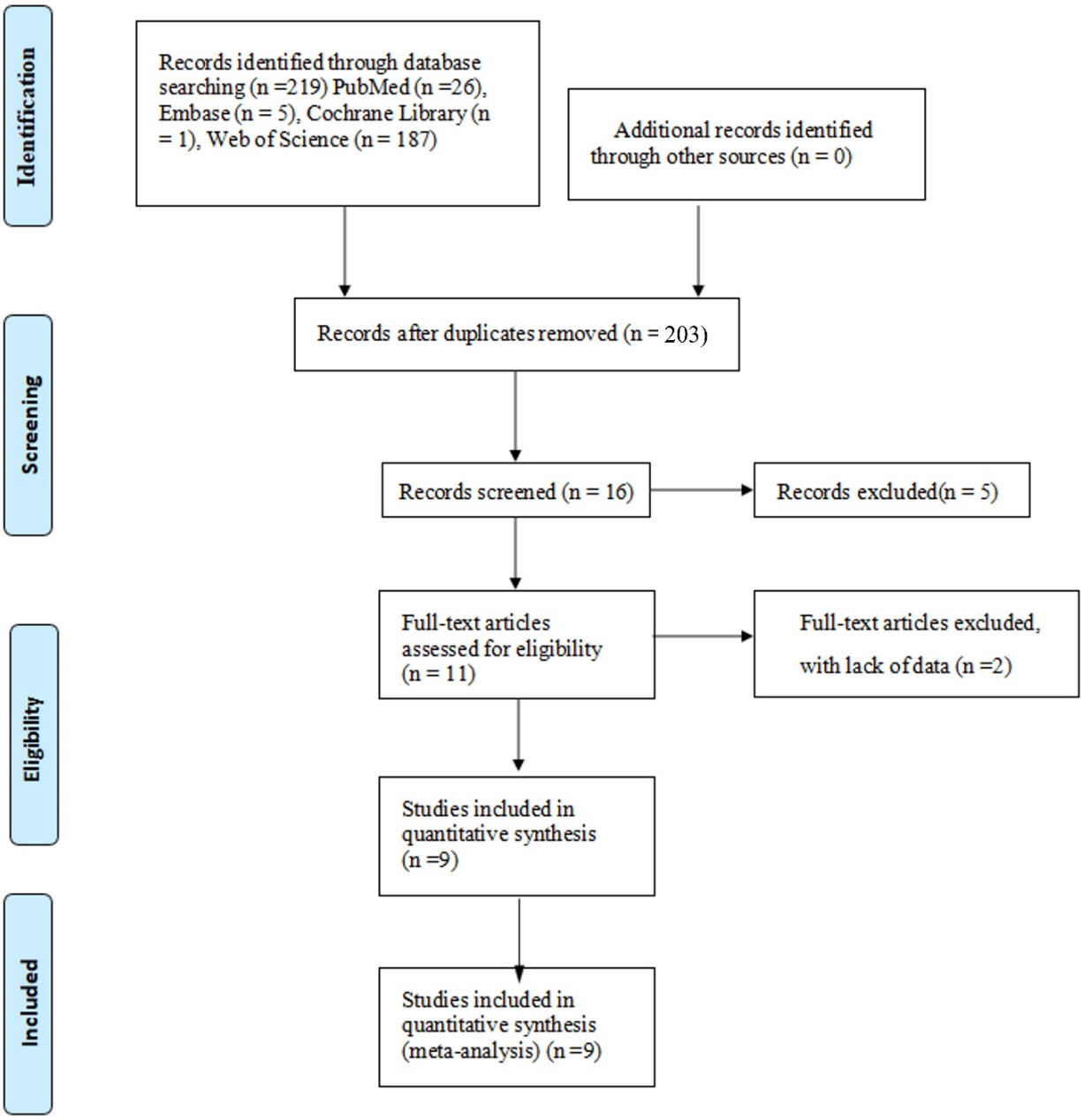

Fig. 1 – Flow chart of growth factor combined and grafting materials in the treatment of periodontal intrabony defects.

SMD: 0.80; 95% CI: 0.49, 1.10) (Figure 2) [15–23]. A funnel plot for the outcome indicators was drawn, and the results show that the funnel plot is symmetrically distributed (Figure 3). I^2 index was 23.6%, with low heterogeneity. This study conducted Egger's and Begg's tests on outcome indicators to govern bias in publications. Begg's and Egger's tests showed $p = 0.118$ and $p = 0.191$, respectively, representing no bias in publication. This indicated that the CAL of patients receiving rhPDGF-BB, pooled with the materials of grafting, was greater than in the control group.

Changes in probing depth

There were a total of seven literature reports on the PD of rhPDGF-BB combined with grafting materials in periodontal intrabony defect management. According to the findings, there was a statistically significant difference ($p < 0.01$, SMD: 0.75; 95% CI: 0.39, 1.11) (Figure 4) [15–21]. This showed that individuals receiving rhPDGF-BB in addition to grafting materials had greater PD than those in the control group.

Bone fill

There were a total of four literature reports on the BF of rhPDGF-BB combined with grafting materials in periodontal intrabony defect management. The outcomes revealed a statistically significant difference ($p < 0.01$, SMD: 22.33; 95% CI: 15.71, 28.95) (Figure 5) [15–17, 23]. This indicated that the BF of patients receiving rhPDGF-BB, pooled with grafting materials, was greater compared to the control group.

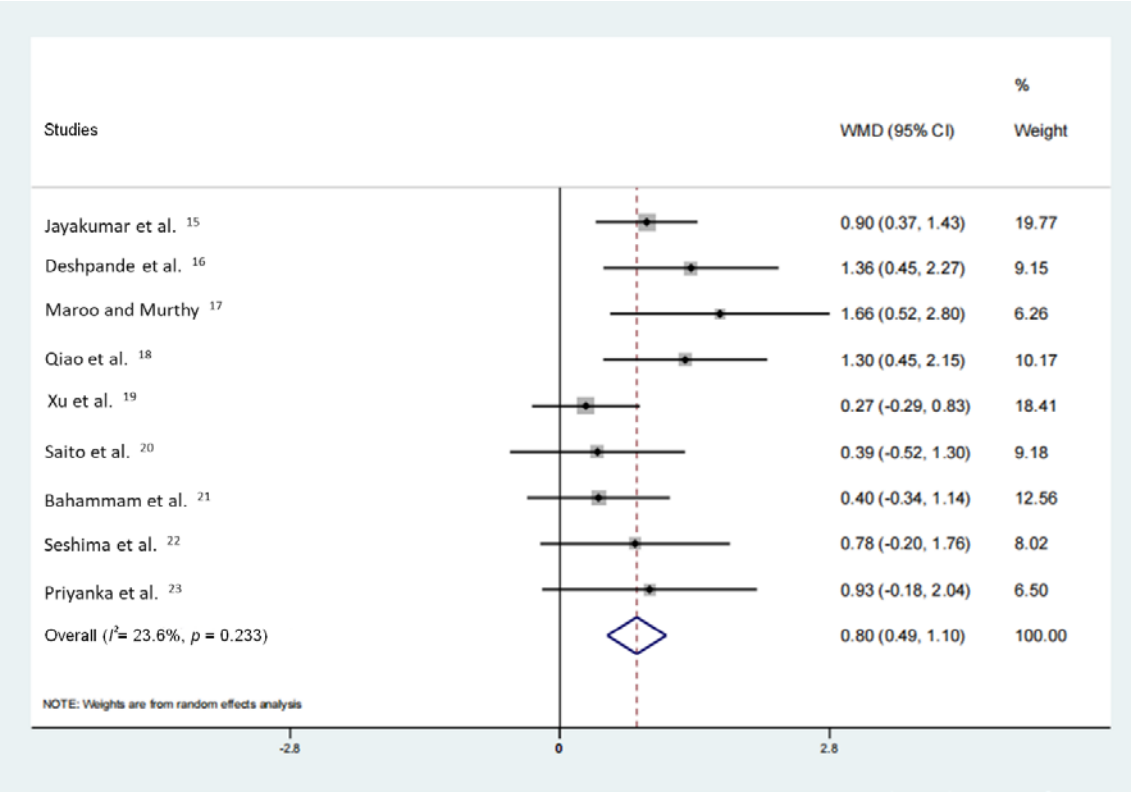

Fig. 2 – Forest plot of clinical attachment level of growth factor combined and grafting materials in the treatment of periodontal intrabony defects. WMD – weighted mean difference.

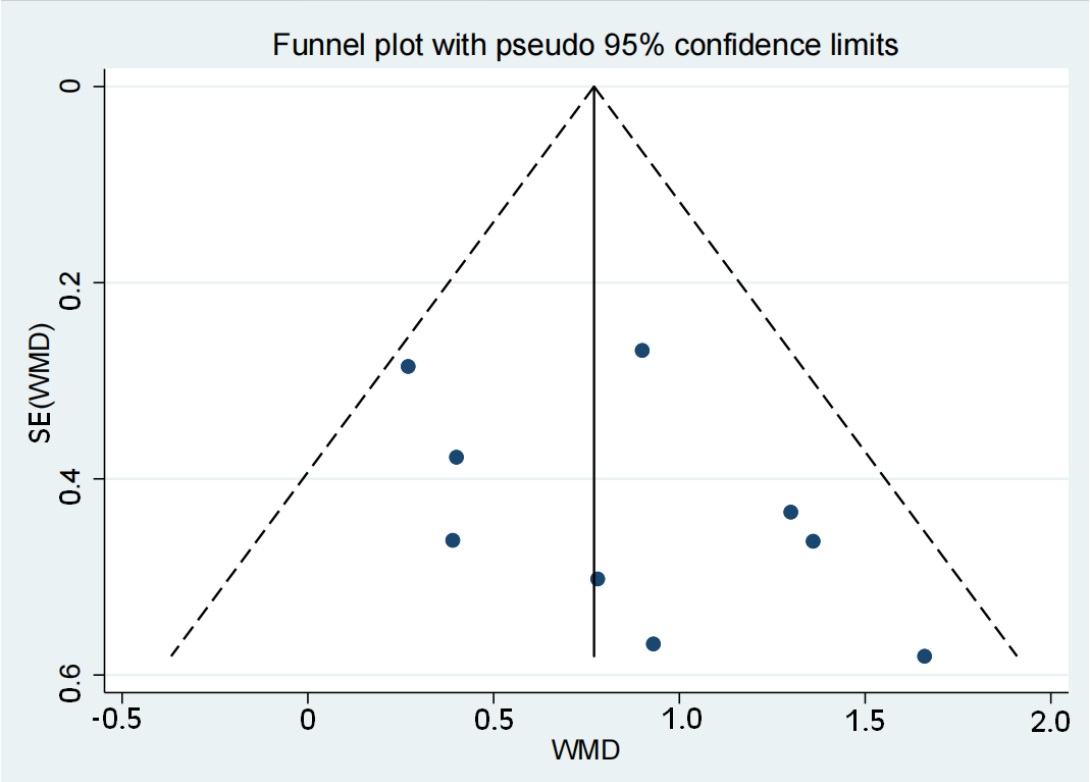

Fig. 3 – Published bias funnel plot of clinical attachment level of growth factor combined and grafting materials in the treatment of periodontal intrabony defects. SE – standard error; WMD – weighted mean difference.

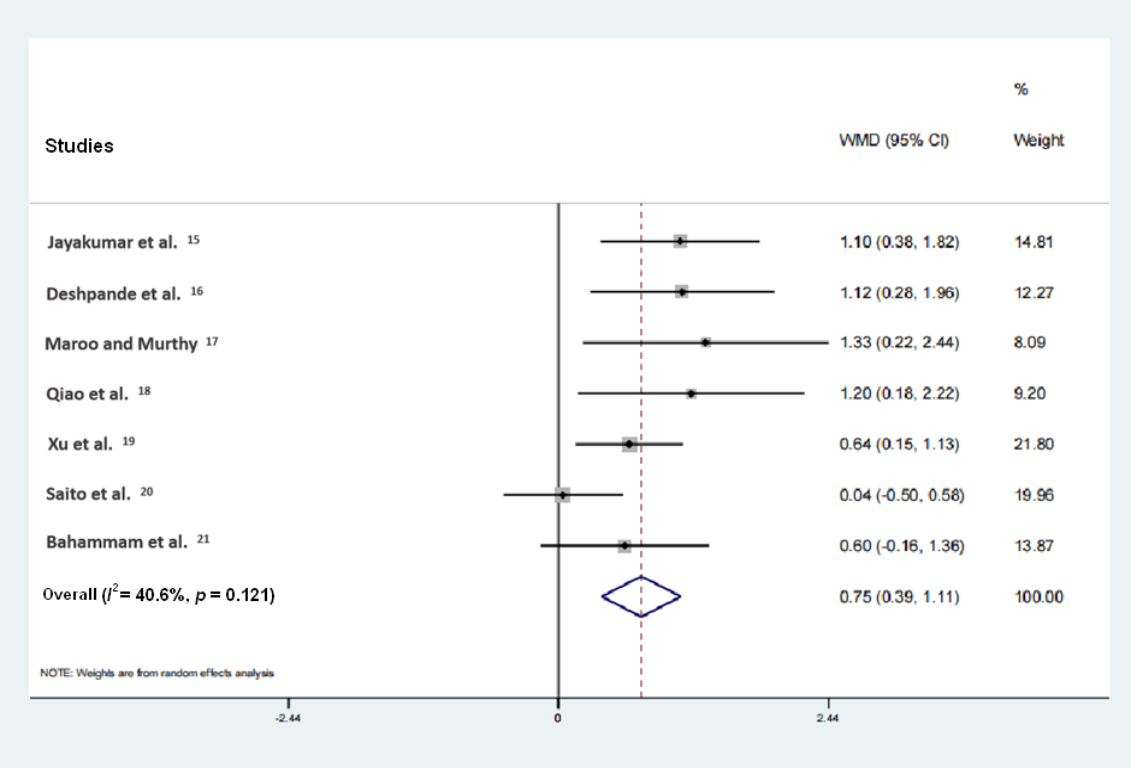

Fig. 4 – Forest plot of changes in probing depth of growth factor combined and grafting materials in the treatment of periodontal intrabony defects. WMD – weighted mean difference.

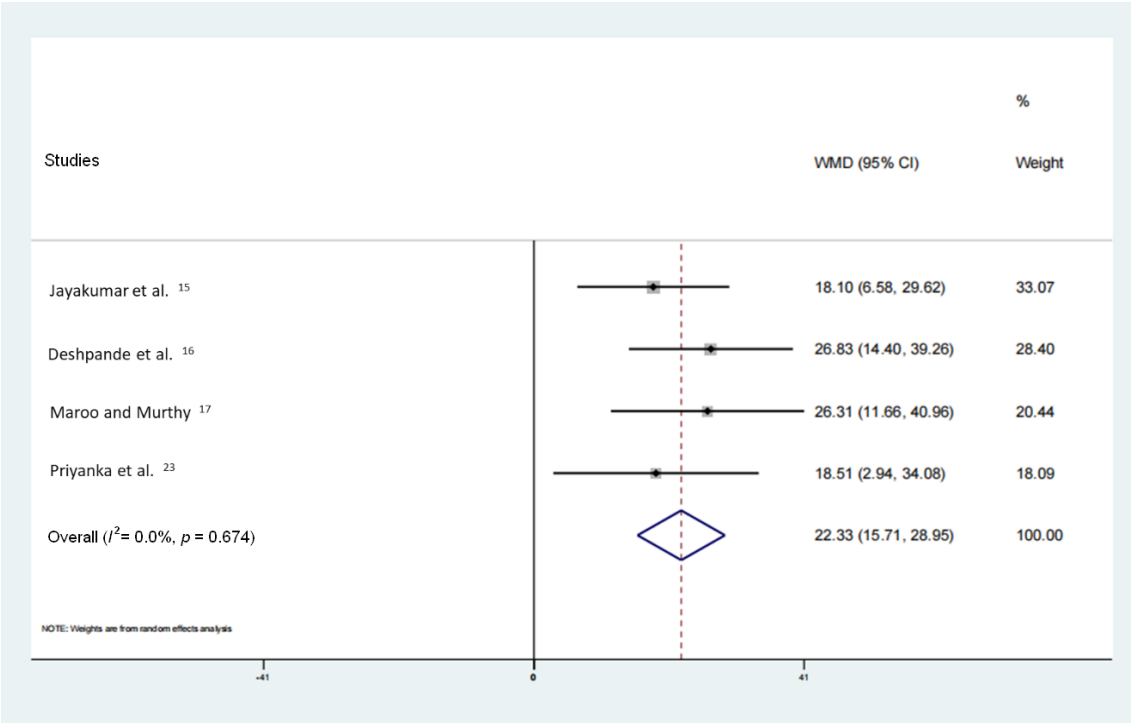

Fig. 5 – Forest plot of bone fill of growth factor combined and grafting materials in the treatment of periodontal intrabony defects. WMD – weighted mean difference.

Gingival recession

There are a total of four literature reports on the GR of rhPDGF-BB added to the grafting materials in periodontal intrabony defect management. The outcomes revealed a statistically significant difference ($p < 0.05$, SMD: -0.27; 95% CI: -0.51, -0.03) (Figure 6 [16–18, 20]). This indicated that the GR of patients receiving rhPDGF-BB added to grafting materials was lower compared to the control group.

Linear bone growth

There were a total of three literature reports on LBG of rhPDGF-BB added to the grafting materials in periodontal intrabony defect management. The outcomes revealed a statistically significant difference ($p < 0.01$, SMD: 0.87; 95% CI: 0.43, 1.30) (Figure 7) [15, 16, 23]. This indicated that the LBG of patients receiving rhPDGF-BB, pooled with grafting materials, was greater compared to the control group.

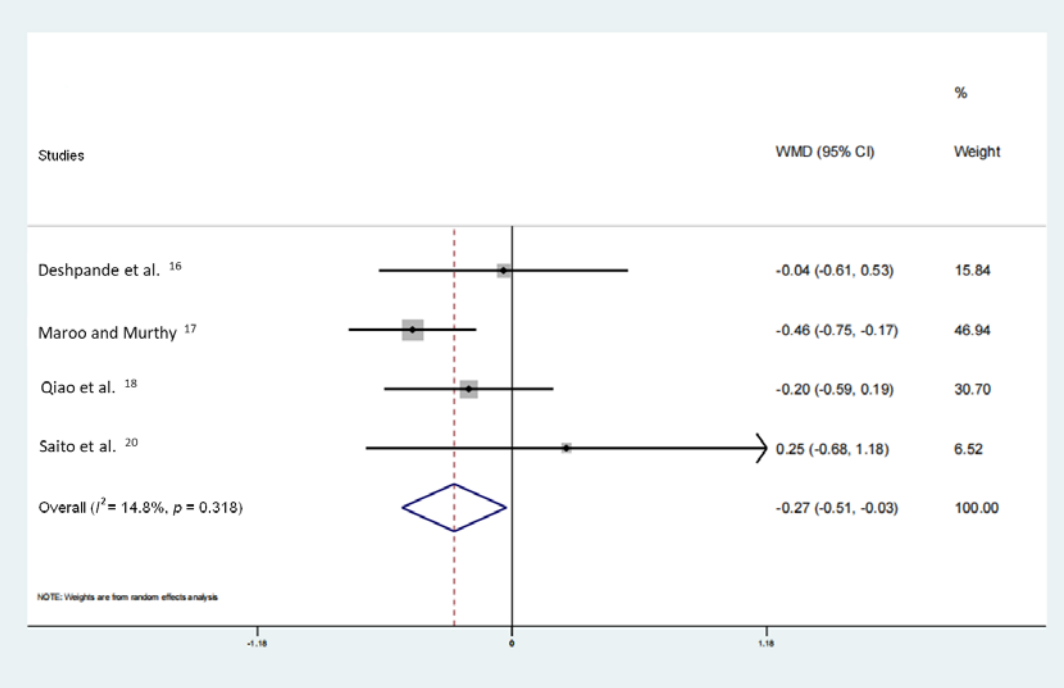

Fig. 6 – Forest plot of gingival recession of growth factor combined and grafting materials in the treatment of periodontal intrabony defects. WMD – weighted mean difference.

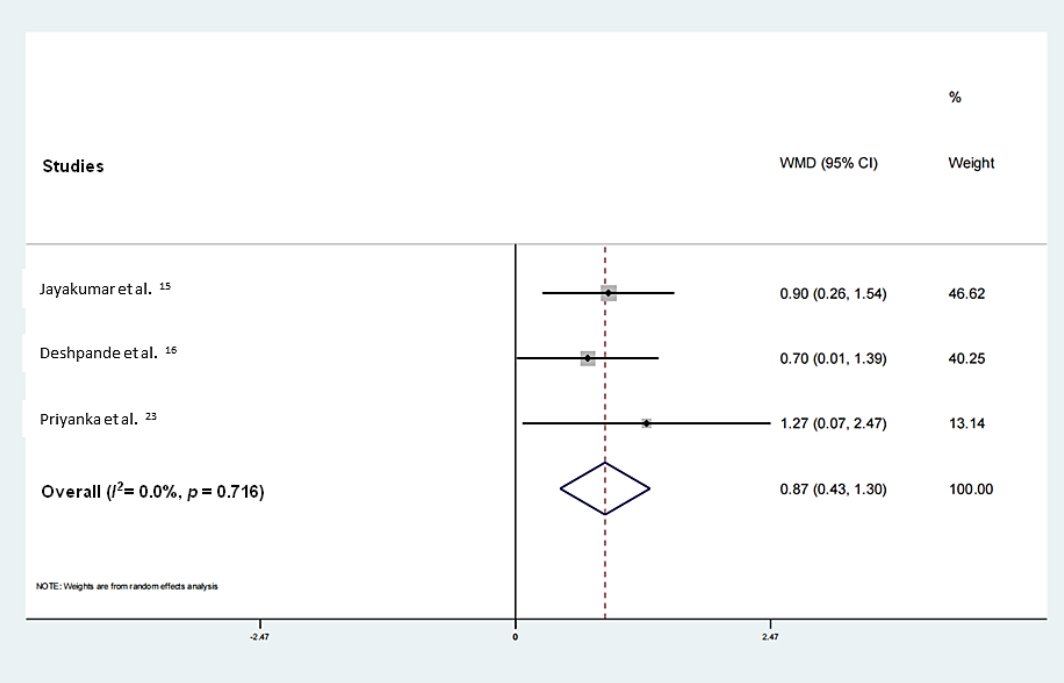

Fig. 7 – Forest plot of linear bone growth of growth factor combined and grafting materials in the treatment of periodontal intrabony defects. WMD – weighted mean difference.

Discussion

After screening, 9 studies were examined. There were 9 literature reports [15–23] on the CAL of patients with periodontal intrabony defects, and the integration outcomes presented substantial heterogeneity. The difference was statistically significant ($p < 0.01$, SMD: 0.80; 95% CI: 0.49, 1.10). This result indicates that the combination of rhPDGF-BB and grafting materials effectively enhances tissue integration and periodontal regeneration. The low heterogeneity ($I^2 = 23.6\%$) suggests consistency across the studies. This is particularly noteworthy as improved CAL is a cornerstone of successful periodontal defect management, reflecting the biological integration of new tissue with the existing periodontal structure. There were seven literature reports [15–21] on the PD of patients with periodontal intrabony defects. The difference was statistically significant ($p < 0.01$, SMD: 0.75; 95% CI: 0.39, 1.11). This indicates that the changes in PD of periodontal intrabony defects after a combination therapy of rhPDGF-BB and grafting materials were more prominent in the experimental than in the control group. Meanwhile, this parameter highlights the restoration of periodontal health, with reduced PD indicative of pocket resolution and reduced inflammation. The positive outcomes can be attributed to the bioactive properties of rhPDGF-BB, which promote cellular proliferation and migration critical for tissue repair. There were four literature reports [15–17, 23] on the BF of patients with periodontal intrabony defects. The transformation was statistically significant ($p < 0.01$, SMD: 22.33; 95% CI: 15.71, 28.95), which indicates that the BF of patients with periodontal intrabony defects after rhPDGF-BB therapy combined with grafting materials was higher than that of the control group. This substantial improvement also underscores the osteogenic potential of rhPDGF-BB, which facilitates mineralized matrix deposition. BF is a direct measure of defect resolution, representing the structural regeneration of periodontal architecture. There were four literature reports [16–18, 20] on the GR of patients with periodontal intrabony defects. The transformation was statistically significant ($p < 0.05$, SMD: -0.27; 95% CI: -0.51, -0.03), which indicates that the GR of patients with periodontal intrabony defects after rhPDGF-BB treatment combined with grafting materials was lower than in the control group. This finding is critical as excessive GR can compromise aesthetics and sensitivity, despite other successful regenerative outcomes. The combination therapy not only promotes bone and tissue regeneration but also mitigates soft tissue recession, contributing to overall periodontal stability. There were three literature reports [15, 16, 23] on the LBG of patients with periodontal intrabony defects. The difference was statistically significant ($p < 0.01$, SMD: 0.87; 95% CI: 0.43, 1.30), indicating that LBG of patients with periodontal intrabony defects after rhPDGF-BB, along with grafting materials, was greater than in the control group. This metric reflects the vertical regeneration of alveolar bone, essential for restoring periodontal support. The bioactivity of rhPDGF-BB in stimulating angiogenesis and osteoblast activity appears to play a pivotal role in this enhancement.

When dental bone transplant materials were first studied in the 1960s, researchers discovered that demineralized dentin matrix has osteoinductive properties and can induce ectopic osteogenesis [24]. The use of demineralized dentin matrix as a material for bone grafting has been validated by further research. Scholars have also studied methods such as boiling and calcination to prepare dentin matrix, which also has osteogenic ability [24–27]. The autologous dental bone powder is developed based on research on dentin matrix and is a bone graft content prepared from a patient's self-unusable teeth [25–27]. The first instance of autologous dental bone powder successfully used for maxillary sinus elevation surgery in a clinical setting was documented by researchers in 2003 [25]. A teeth grinder was created in 2007 by Japanese researchers, which simplified the process of making autologous tooth bone powder [26]. In 2009, the Korea Tooth Bank was founded to gather, preserve, and prepare teeth for use as bone transplant materials. The research on autologous tooth bone powder has developed rapidly in recent years, confirming its safety and effectiveness. However, there is relatively little comparative research with other bone transplant materials. The Bio-Oss bone powder is a deproteinized bovine bone matrix proven to be a safe and effective bone transplant material, having several different clinical uses [27].

Commonly used GFs comprise platelet-rich plasma (PRP), platelet-rich fibrin (PRF), basic fibroblast growth factor (bFGF), BMP-2, rhPDGF-BB, etc. After a growth factor is recognized, it is attached to a receptor on the cell membrane, which thereby triggers intracellular signaling pathways that govern cell growth and several cellular functions [28]. Among them, rhPDGF-BB has the strongest osteogenic activity, achieved by upregulating angiogenesis. However, due to the extremely low content of rhPDGF-BB in human bones, it is difficult to meet the needs of various complex bone defect repairs, and the high cost of separation and purification seriously limits its application.

Such GFs can be used alone with many biomaterials or in combination. Özveri Koyuncu et al. [29] applied concentrated GF to the alveolar fossa of impacted mandibular third molars, and the results showed that rhPDGF-BB can effectively alleviate postoperative pain in patients and have a positive effect in eliminating swelling. A prior meta-analysis indicated that rhPDGF-BB when used in conjunction with grafting materials for the treatment of periodontal intrabony defects, had superior efficacy compared to the application of grafting materials alone [30]. The use of rhPDGF-BB for growth in conjunction with bone replacement materials in the bone defect repair field has gradually gained the favor of clinical physicians.

Conclusion

According to the findings, the combination of growth factor and grafting materials has the potential to enhance the clinical attachment ratio, changes in probing depth, gingival recession, bone fill, and linear bone growth in periodontal intrabony defects.

Conflict of interest

The authors declare no conflict of interest.

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