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Outcomes of regenerative treatment with rhPDGF-BB and rhFGF-2 for periodontal intra-bony defects: a systematic review and meta-analysis

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Abstract

Background: The aim was to evaluate the effects of recombinant human platelet-derived growth factor-BB (rhPDGF-BB) and recombinant human fibroblast growth factor-2 (rhFGF-2) on treating periodontal intra-bony defects, compared to the control (carrier alone).

Methods: Electronic and hand searches were performed to identify eligible studies. The weighed mean differences of linear defect fill (LDF), probing depth (PD) reduction, clinical attachment level (CAL) gain and gingival recession (GR) were calculated using random effect meta-analysis.

Results: The searches yielded 1018 articles, of which seven studies were included. Only one included study was considered at low risk of bias. The outcomes that reached statistical significance in comparison to carriers alone included: LDF (0.95 mm, 95% CI: 0.62–1.28 mm or 20.17%, 95% CI: 11.81–28.54%) and CAL gain (0.34 mm, 95% CI: 0.03–0.65 mm) for PDGF, and LDF (21.22%, 95% CI: 5.82–36.61%) for FGF-2.

Conclusions: Within the limits of this review, rhPDGF-BB demonstrated significantly more LDF and CAL gain; rhFGF-2 resulted in significantly higher percentage of LDF.

Key words: bioengineering; oral reconstruction and wound healing; regenerative medicine; repair; tissue engineering

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Conflict of interest and source of funding statement

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Regeneration of periodontal structures, characterized by formation of cementum, alveolar bone and periodontal ligament (PDL), has been a challenge and a major goal for clinicians. Common procedures attempting to achieve periodontal regeneration include the use of cell occlusive barrier membranes (Gottlow et al. 1986), bone substitutes with (Bowers et al. 1989b, Mellonig 2000) or without membranes (Froum et al. 1975, Trombelli & Farina 2008), enamel matrix derivatives (Heijl et al. 1997) and root conditioning with chemical agents (Mariotti 2003). Although yielding satisfactory results (Karring et al. 1980, 1984, Gottlow et al. 1986, Bowers et al. 1989a, Zetterstrom et al. 1997), there is a high degree of

variability in clinical outcomes following these regenerative procedures (Aichelmann-Reidy & Reynolds 2008). The application of growth factors, shown to be able to promote periodontal regeneration (Lynch et al. 1989, Giannobile et al. 1994, 1996, Camelo et al. 2003, Nevins et al. 2003, Ridgway et al. 2008), might be another promising approach.

Dimeric platelet-derived growth factor (PDGF), including four isoforms, is primarily secreted from platelet α-granules. As a potent agent for wound healing, rhPDGF-BB has been extensively used for treating neuropathic diabetic ulcers (Smiell et al. 1999). The rhPDGF-BB is also an FDA approved biological agent for periodontal regeneration (Nevins et al. 2005). Mitogenic and chemotactic effects of rhPDGF-BB on periodontal ligament and bone precursor cells have been demonstrated (Lynch et al. 1989, Camelo et al. 2003). Several human histological studies have provided proof-of-principle evidence that rhPDGF-BB results in periodontal regeneration in both periodontal intra-bony (Nevins et al. 2003, Ridgway et al. 2008) and furcation defects (Camelo et al. 2003, Nevins et al. 2003, Mellonig et al. 2009). Clinical studies have shown improvement in probing depth reduction, rate of clinical attachment level gain and bone fill (Giannobile & Somerman 2003, Nevins et al. 2005, McGuire et al. 2006, Jayakumar et al. 2011).

Fibroblast growth factors (FGFs) belong to a large polypeptide family with more than 20 member of similar structures (Ornitz & Itoh 2001). FGF-2 promotes endothelial cell proliferation and physical organization of endothelial cells; thus, it enhances angiogenesis and the growth of new blood vasculature (Cao et al. 2003). In addition, FGF-2 exhibits powerful angiogenic activity and mitogenic ability on mesenchymal cells (Kao et al. 2009). Recently, rhFGF-2 has shown the ability to regenerate periodontal tissues in periodontal intrabony defects (Kitamura et al. 2011) and in surgically created defects in pre-clinical studies (Murakami et al. 1999, 2003, Takayama et al. 2001, Nakahara et al. 2003).

With the encouraging evidence of using rhPDGF-BB and FGF-2 for treating periodontal defects in clinical trials, a systematic review and meta-analysis were therefore conducted to summarize the clinical efficacy of these growth factors for regenerating periodontal intra-bony defects.

Materials and Methods

Focused question

Does applying rhPDGF-BB or rhFGF-2 for treating periodontal intra-bony defects offer better clinical and/or radiographic benefits in comparison to the carriers alone?

Selection criteria

Human comparative trials attempting regenerative treatments with the application of rhPDGF-BB or rhFGF-2 for at least eight intra-osseous defects with a minimum follow-up period of 6 months were included. Animal studies and human trials with insufficient information or lack of data and a proper control arm were excluded. Potential articles were reviewed in full-text and confirmed for their eligibility.

Search strategy

A search of five electronic databases, including PubMed, Ovid (MEDLINE), EMBASE, Web of Science and Cochrane Center for relevant studies published was conducted from 1990 up to June 2013 in accordance with PRISMA guidelines (Moher et al. 2009). A combination of MeSH terms and keywords was designed to identify all pertinent articles using growth factors for periodontal regeneration. For this review, we only considered PDGF-BB and FGF-2 because they are the only two clinically tested recombinant human growth factors in the US for which more than one randomized controlled clinical trial has been published.

The key terms used in the search included "growth factor", "regeneration", "periodontal defect", "periodontitis regenerative treatment", "guided tissue regeneration", "biological agent", "bone graft", "platelet-derived growth factor" and "fibroblast growth factor". Boolean operators, "OR" and "AND", were used to combine the literature searches. Furthermore, a search in the references of included papers was conducted for publications that were not electronically identified. Two reviewers (VK and JM) evaluated potential relevant articles. Disagreement between the reviewers was resolved with discussion. The level of agreement between the reviewers regarding study inclusion was expressed with the kappa value. In addition, funnel plots were also used to assess the presence of publication biases.

Data extraction

Two reviewers extracted the data (VK and JM). Any disagreement was resolved between the reviewers following a discussion. The parameters recorded for each study included authors' names, year of publication, study design, sample size, linear defect fill (LDF), percentage of defect fill, probing depth (PD) reduction, clinical attachment level (CAL) gain, gingival recession (GR) and follow-up period. If indicated, authors of the potentially qualified papers were contacted for more detailed data.

Risk of bias assessment

The following criteria modified from the randomized clinical trial checklist of the Cochrane Center and the CONSORT statement (Schulz et al. 2010) were used: representative of general population, defined inclusions/exclusions, randomization methods, allocation concealment method, masking of the examiner, intervention different only, participants drop-out and analysis accounts for patient losses. The degree of bias were categorized as: low risk if all the criteria were met, unclear risk when only one criterion was missing and high risk if two or more criteria were missing. One reviewer (JM) assessed all the included articles and another examiner (VK) confirmed the results.

Data analysis

The primary outcome was linear defect fill (LDF) in mm and %, and the secondary outcome was CAL gain (mm). PD reduction (mm) and GR (mm) were the 3rd outcomes. For the included comparative studies, the pooled weighted mean differences (WMD) and the 95% confidence interval (CI) of each

variable were calculated using random effect meta-analysis by a computer program (Review Manager, RevMan, version 5.0., Copenhagen; The Nordic Cochrane Centre, The Cochrane Collaboration, 2008). Forest plots were produced to graphically represent WMD and 95% CI for the outcomes of all included studies using "defect site" as the analysis unit. In addition, heterogeneity among studies was assessed with the chi-square test, and a p value <0.05 represents significant heterogeneity. The reporting of these meta-analyses adhered to the PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analyses) statement (Liberati et al. 2009).

Results

The screening process is illustrated in Fig. S1. Electronic and hand searches yielded 1018 articles, of which 11 articles were selected for full-text evaluation after screening their titles and abstracts. After full-text evaluation and cross-referencing, four articles were excluded. Reasons for exclusion included redundant cohorts (Nevins et al. 2013), different radiographic analysis and insufficient data reported (Nevins et al. 2003) and lack of proper control arms (Ridgway et al. 2008, Rosen et al.2011). Seven randomized controlled trials (RCT) (Howell et al. 1997, Nevins et al. 2005, Kitamura et al. 2008, 2011, Jayakumar et al. 2011, Thakare & Deo 2012, Mishra et al. 2013) were included in the review. The kappa value for the inter-reviewer agreement of the included publications was 0.96. The main features and conclusions of the included studies were summarized in Table 1. The outcomes of various parameters for each included study were presented in Table 2.

Features of the included studies

Study design and participant features

In one study (Howell et al. 1997), a combination of PDGF and IGF-1 (Insulin like growth factor-I) was used, in four studies (Nevins et al. 2005, Jayakumar et al. 2011, Thakare & Deo 2012, Mishra et al. 2013) PDGF-BB was evaluated, and in two studies (Kitamura et al. 2008, 2011) FGF-2 was applied. Patients

Table 1. Summary of the features of the included studies

Author	Study design	Arms	F/U period (months)	*N*	Patients age	Smokers (%)	*N* defects & type	Defect depth (mm)	GF	Dose	Carrier
#1 Howell et al.(1997)	RCT	4	9	19	46.1	0	76 i.b & f	≥3(Rx)	PDGF-BB/ IGF- I	50/50 $\mu g/\mu l$ 150/150 $\mu g/\mu l$	Methylcellulose gel
				19							
				19							
				19							
#2 Nevins et al. (2005)	RCT	3	6	60	49.4 ± 1.3	20	60 i.b	6.0 ± 0.2	PDGF-BB	0.3 mg/ml	ß-TCP
				61	50.4 ± 1.7	31.1	61i.b	5.7 ± 0.2		1.0 mg/ml	
				59	52.8 ± 1.2	20.3	59i.b	5.7 ± 0.2		0	
#3 Kitamura et al. (2008)	RCT	4	9	20	49.2 ± 8.9	75	20 i.b	4.7 ± 1.5	FGF-2	0	3% HPC
				19	46.2 ± 11.1	89.5	19 i.b	4.8 ± 2.4		0.03%	
				20	46.8 ± 10.3	80	20 i.b	4.6 ± 1.7		0.10%	
				20	47.7 ± 10.5	70	20 i.b	5.7 ± 2.6		0.30%	
#4 Jayakumar et al. (2011)	RCT	2	6	27	30.9 ± 5.1	11.1	27i.b	6.7 ± 1.9(Rx)	None	None	ß-TCP
				27	32.6 ± 7.3	11.1	27i.b	6.3 ± 1.9(Rx)	PDGF	0.3 mg/ml	
#5 Kitamura et al. (2011)	RCT	4	18	61	52.2 ± 11.2	13.1	63 i.b	5.0 ± 1.8(Rx)	FGF-2	Vehicle alone	3% HPC
				68	53.2 ± 11.8	26.5	68 i.b	4.8 ± 1.6(Rx)		0.20%	
				57	52.8 ± 11.5	21.1	58 i.b	4.8 ± 1.7(Rx)		0.30%	
				63	52.5 ± 10.7	28.6	64 i.b	4.7 ± 1.6(Rx)		0.40%	
#6 Thakare & Deo (2012)	RCT	2	12	9	35.76 ± 7.38	0	18 i.b	>3	PDGF-BB	0.3 mg/ml	ß-TCP
				9					None	None	
#7 Mishra et al. (2013)	RCT	2	6	12	25–50	0	15 i.b	5.19 ± 1.60	PDGF-BB	0.3 mg/ml	1% sodium hyaluronate gel
				12			16 i.b	5.08 ± 1.50	None	None	

Key: ND, Not determined or reported; CS, Case series; RCT, Randomized controlled trial; F/U, Follow-up; PDGF, platelet-derived growth factor; FGF, Fibroblast growth factor; All, Allograft; i.b, Intra-bony; f, furcation; HPC, Hydroxypropylcellulose.

Table 2. Summary of the regenerative outcomes investigated of selected studies

No	Author	Group	Carrier	GF	Dose	N defect (BL)	N defect (FE)	Clinical		Rx		Other parameters				
								Initial bone defect (mm)	Final bone defect (mm)	Bone growth (mm)	Bone fill%	Initial PD (mm)	PD reduction (mm)	Initial CAL (mm)	CAL gain (mm)	Gingival Recession (mm)
#1	Howell et al.(1997)	T	4% methylcellulose gel	PDGF-BB IGF- I	50 μg/μl	8	8	4.63 ± 0.84	ND	ND	ND	5.13 ± 0.35	0.69 ± 1.21	6.77 ± 0.49	1.77 ± 0.62	ND
		C	4% methylcellulose gel	ND		8	8	4.69 ± 1.12	ND	ND	ND	6.25 ± 0.53	2.38 ± 0.71	6.38 ± 0.31	1.22 ± 0.56	ND
		T	4% methylcellulose gel	PDGF-BB IGF- I	150 μg/μl	11	11	4.25 ± 0.38	ND	2.08 ± 0.40	42.3 ± 9	5.67 ± 0.88	2.00 ± 1.14	6.63 ± 0.50	1.52 ± 0.62	ND
		C	4% methylcellulose gel	ND		11	11	4.18 ± 0.36	ND	0.75 ± 0.28	18.5 ± 7	6.17 ± 2.17	1.30 ± 1.40	6.41 ± 0.47	1.98 ± 0.49	ND
#2	Nevins et al. (2005)	T	ß-TCP	PDGF-BB	0.3 mg/ml	60	60	6.0 ± 0.2	ND	2.6 ± 0.2	57.0 ± 6	8.6 ± 0.2	ND	9.1 ± 0.2	3.8 ± 0.2	0.5 ± 0.2
					1.0 mg/ml	61	58	5.7 ± 0.2	ND	1.5 ± 0.2	34.0 ± 4	8.2 ± 0.2	ND	8.8 ± 0.2	ND	ND
		C	ß-TCP	ND		59	56	5.7 ± 0.2	ND	0.9 ± 0.1	18.0 ± 6	8.3 ± 0.2	ND	8.8 ± 0.2	3.5 ± 0.2	ND
#3	Kitamura et al. (2008)	T	3% HPC	FGF-2	0.03%	19	19	4.8 ± 2.4	ND	0.54 ± 1.26	20.19 ± 38.09	5.4 ± 1.6	ND	8.4 ± 2.7	2.00 ± 2.08	ND
					0.1%	20	19	4.6 ± 1.7	ND	1.06 ± 1.16	29.39 ± 37.71	5.1 ± 2.0	ND	8.4 ± 2.8	2.02 ± 2.08	ND
					0.3%	20	17	5.7 ± 2.6	ND	1.85 ± 1.75	58.62 ± 46.74	5.8 ± 1.7	ND	8.3 ± 3.0	2.18 ± 1.33	ND
		C	3% HPC	ND		20	19	4.7 ± 1.5	ND	0.95 ± 1.26	23.92 ± 27.52	5.7 ± 1.2	ND	9.3 ± 2.2	2.63 ± 1.54	ND
#4	Jayakumar et al. (2011)	T	ß-TCP	PDGF-BB	0.3 mg/ml	27	25	6.3 ± 1.9	ND	3.7 ± 1.1	65.6 ± 21.7	8.7 ± 1.9	4.3 ± 0.9	8.4 ± 2.5	3.7 ± 1.0	ND
		C	ß-TCP	NA		27	25	6.7 ± 1.9	ND	2.8 ± 1.2	47.5 ± 19.8	7.7 ± 1.9	3.2 ± 1.6	7.8 ± 1.2	2.8 ± 0.9	ND
#5	Kitamura et al. (2011)	T	3% HPC	FGF-2	0.2%	68	61 (bone fill); 63 (CAL)	4.8 ± 1.6	ND	ND	39.11 ± 37.32	5.7 ± 1.5	ND	ND	2.48 ± 1.79	ND
					0.3%	58	54 (bone fill); 55(CAL)	4.8 ± 1.7	ND	ND	52.15 ± 38.12	5.6 ± 1.4	ND	ND	2.35 ± 1.78	ND
					0.4%	64	52 (bone fill); 56(CAL)	4.7 ± 1.6	ND	ND	48.85 ± 34.14	5.7 ± 1.4	ND	ND	2.46 ± 1.91	ND
		C	3% HPC	NA		63	56 (bone fill); 57 (CAL)	5.0 ± 1.8	ND	ND	15.86 ± 22.14	5.8 ± 1.6	ND	ND	2.12 ± 1.72	ND
#6	Thakare & Deo (2012)	T	ß-TCP	PDGF-BB	0.3 mg/ml	9	9	3.00 ± 0.81	ND	3.00 ± 0.81	80.99 ± 14.03	7.16 ± 1.14	3.82 ± 1.07	7.50 ± 1.71	3.42 ± 1.24	0.42 ± 0.40
		C	ß-TCP + HA	NA		9	9	2.30 ± 0.67	ND	2.30 ± 0.67	54.16 ± 12.84	6.36 ± 0.69	2.70 ± 0.70	6.88 ± 0.56	2.06 ± 0.63	0.30 ± 0.38
#7	Mishra et al. (2013)	T	1% sodium hyaluronate gel	PDGF-BB	0.3 mg/ml	15	14	5.19 ± 1.60	1.72 ± 0.96	1.89 ± 0.60	36.20 ± 17.74	7.73 ± 1.19	4.18 ± 0.60	7.36 ± 1.28	3.00 ± 0.89	0.82 ± 0.60
		C	1% sodium hyaluronate gel	NA		16	14	5.08 ± 1.50	1.83 ± 1.18	1.85 ± 1.18	35.02 ± 10.99	7.64 ± 0.67	3.82 ± 0.87	6.91 ± 0.70	2.64 ± 0.67	0.55 ± 0.52

Key: ND, Not determined or reported; GF, Growth factor; CAL, Clinical attachment level; PD, Probing depth; CS, Case series; RCT, Randomized controlled trial; Rx, Radiographic; F/U, Follow-up; FE, Final examination; T, Test; C, Control; PDGF, platelet-derived growth factor; FGF, Fibroblast growth factor; All, Allograft; i.b, Intra-bony; f, furcation; HPC, Hydroxy-propylcellulose.

between the ages 36–68 were treated and followed between 6 and 18 months. In one study (Howell et al. 1997) smokers were not included in the trial. In one study (Howell et al. 1997), both furcation and intra-bony defects were treated; however, only the results of the intra-bony defects were used and analysed for this review.

Defect features

Four studies (Howell et al. 1997, Kitamura et al. 2008, 2011, Thakare & Deo 2012) measured defects depth radiographically, whereas in two studies (Nevins et al. 2005, Jayakumar et al. 2011) the depth of the defects was measured directly during the surgery and in another (Mishra et al. 2013) bone sounding was used. In four studies (Nevins et al. 2005, Kitamura et al. 2008, Jayakumar et al. 2011, Mishra et al. 2013) detailed baseline defect configuration data were available.

Results of the meta-analysis

Results of the primary outcome

The WMD of LDF were 0.95 mm (95% CI = 0.62–1.28 mm, $p < 0.00001$) and 0.17 mm (95% CI = −0.52–0.86 mm, $p = 0.63$), respectively, favouring PDGF but not FGF, (Fig. 1). A significant heterogeneity among selected studies using PDGF ($p = 0.009$) was noticed. The WMD of LDF (%) were 20.17% (95% CI = 11.81–28.54%, $p < 0.00001$) and 21.22% (95% CI = 5.82–36.61%, $p = 0.007$) for PDGF and FGF groups, respectively, favouring the growth factor groups (Fig. 2). Significant heterogeneity among the studies using PDGF was also found ($p = 0.0002$).

Results of the secondary outcome

The WMD of CAL gain for the PDGF group was 0.34 mm (95% CI = 0.03–0.65 mm), favouring the PDGF group ($p = 0.03$) (Fig. 3). For the FGF-2 group, the WMD of CAL gain was −0.06 mm (95% CI = −0.92 to 0.79 mm, $p = 0.88$). There was no significant heterogeneity among the selected studies using PDGF-BB ($p = 0.08$) as well as FGF-2 ($p = 0.08$).

Results of the 3rd outcomes

The WMD of PD reduction in the PDGF group was 0.57 mm (95% CI = −0.04 to 1.18 mm, $p = 0.07$) (Fig. 4) with significant heterogeneity among selected studies ($p = 0.03$). The WMD of GR was 0.18 mm (95% CI = −0.09 to 0.46 mm) ($p = 0.18$) (Supplemental Figure S2) with no significant heterogeneity among selected studies ($p = 0.59$). No data were available for assessing the 3rd outcomes in the FGF group.

Risk of bias assessment

Two of the included RCT studies (Thakare & Deo 2012) (Mishra et al. 2013) were identified with a high risk of bias, one study identified with a low risk of bias (Jayakumar et al. 2011) and the rest were identified with an unclear risk of bias (Supplementary table 1). Funnel plots evaluating the publication bias of each parameter were prepared (Figs S3–S7).

Discussion

PDGF-BB for promoting periodontal regeneration

Summary of the main findings

Topical delivery of PDGF resulted in statistically significantly higher LDF (0.95 mm or 20.17%) than the carriers alone, supporting that PDGF is beneficial in promoting periodontal defect fill. The amount of defect fill with PDGF, ranging from 36.2% to 81%, is comparable with other regenerative procedures. Previous studies have reported 34% bone fill after 6 months (Kilic et al. 1997) and 31% bone fill after 3 years (Zetterstrom et al. 1997) following GTR and the use of enamel matrix derivatives respectively. The difference in the amount of CAL gain was 0.34 mm, favouring the PDGF group. A systematic review (Esposito et al. 2009) showed a mean 1.1 mm more CAL gain in periodontal defects treated with enamel matrix derivatives (EMD) than open flap debridement alone. However, no head-to-head comparison study was

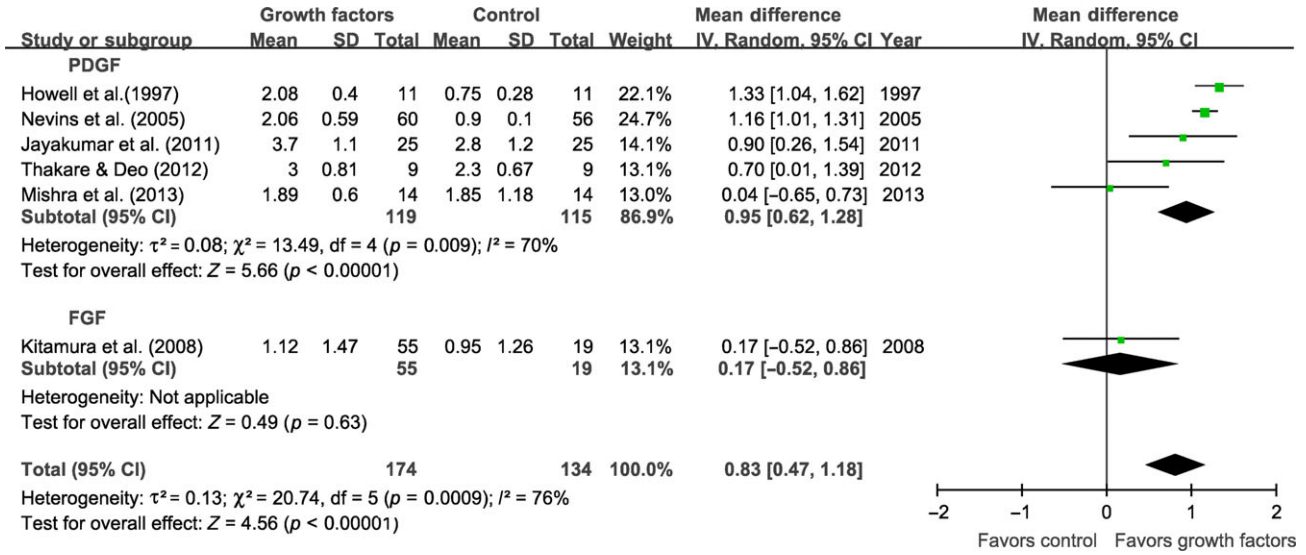

Fig. 1. Meta-analysis for comparison of linear defect fill among selected studies. The overall weighted mean difference (WMD) is 0.83 mm (95% CI = 0.47–1.18 mm) in between growth factor group and control group ($p < 0.00001$).

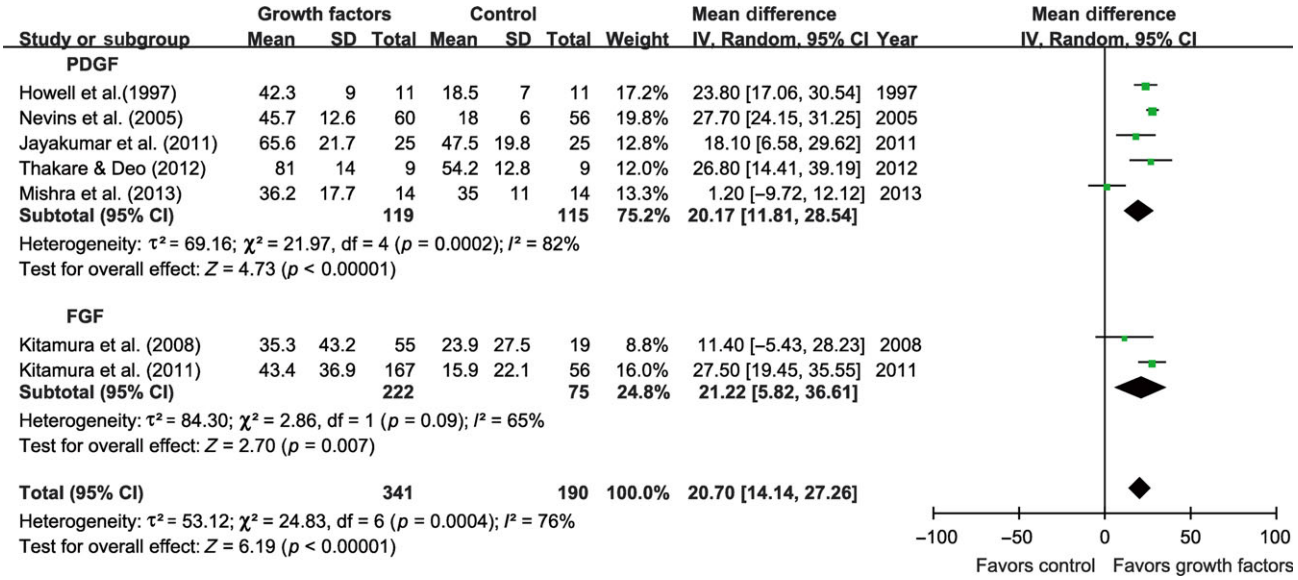

Fig. 2. Meta-analysis for comparison of percentage of defect fill among selected studies. The overall weighted mean difference (WMD) is 20.70% (95% CI = 14.14–27.26%) in between growth factor group and control group ($p < 0.00001$).

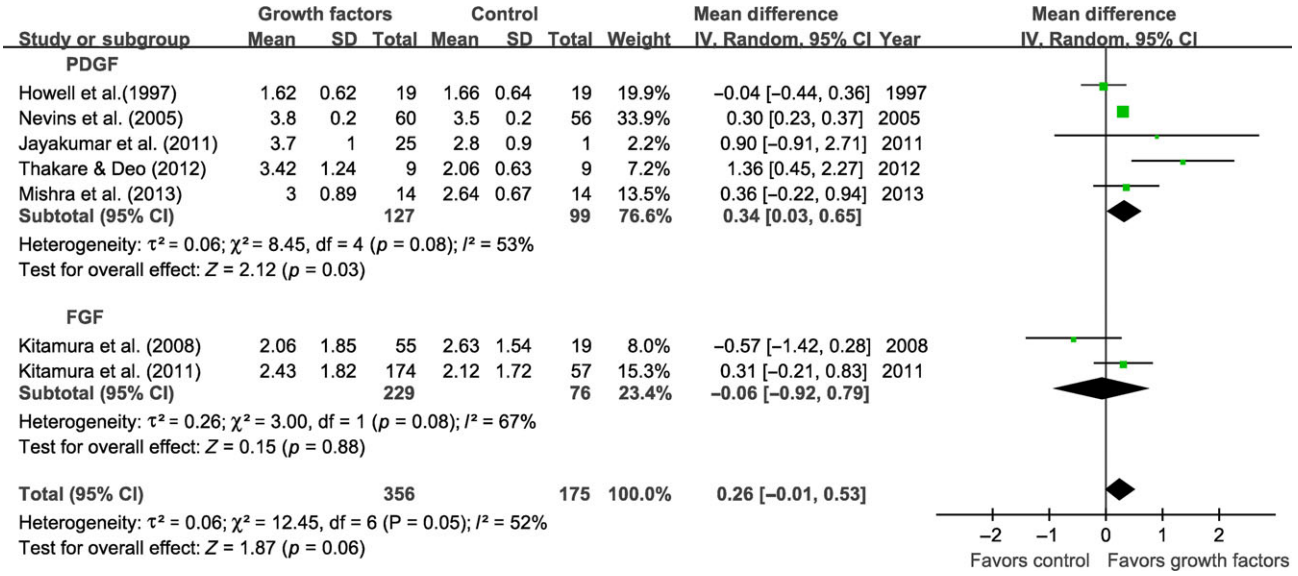

Fig. 3. Meta-analysis for comparison of CAL gain among selected studies. The overall weighted mean difference (WMD) is 0.26 mm (95% CI = –0.01 to 0.53 mm) in between growth factor group and control group ($p = 0.06$).

available to support if PDGF or EMD is superior. The modest CAL gain from PDGF over the control might be due to the profound effect of the bone fillers on CAL gain.

The addition of PDGF may result in more favourable tissue attachment than vehicle alone or ß-TCP carrier. Conventional periodontal therapy that reflects the vehicle alone groups healing pattern most likely will result in repair by long junctional epithelium (Caton & Zander 1976, Bowers et al. 1982, Wikesjo et al. 1992). This epithelial attachment does not require new bone formation or cementum on the root surface but provides resistance to probing force. Histological studies (Stahl & Froum 1986, Stavropoulos et al. 2010) have shown that β-TCP does not result in periodontal regeneration whereas proof-of-principle has been provided by histological studies (Camelo et al. 2003, Nevins et al. 2003, Ridgway et al. 2008) that PDGF-BB results in periodontal regeneration in human periodontal osseous defects.

In one study (Mishra et al. 2013), the use of PDGF in a methylcellulose gel without an osteoconductive scaffold did not provide an additional benefit to the vehicle alone that underscore the significant role of delivery method; hence, for optimizing bioavailability of growth factors, a proper method of delivery is important. One study (Rosen et al.

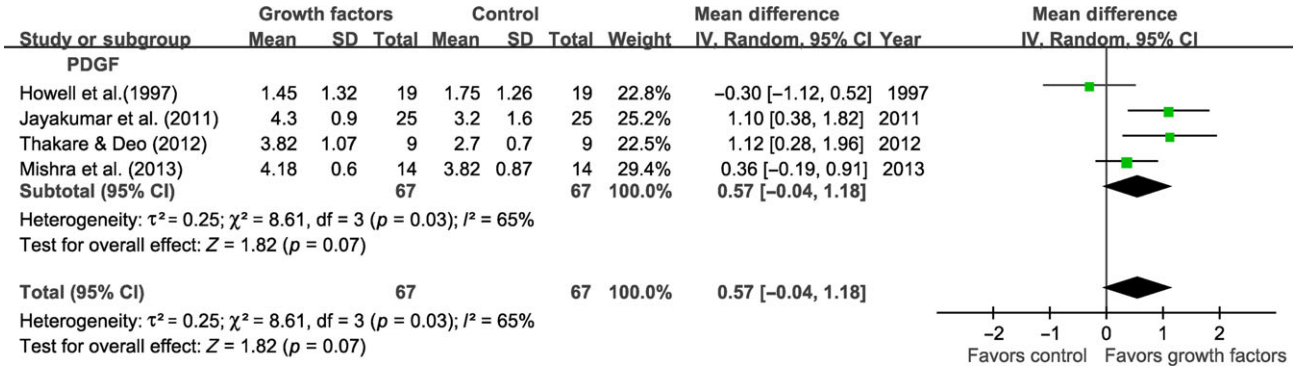

Fig. 4. Meta-analysis for comparison of PD reduction among selected studies. The overall weighted mean difference (WMD) is 0.57 mm (95% CI = −0.04 to 1.18 mm) in between growth factor group and control group ($p = 0.07$).

2011) by utilizing FDBA and β-TCP as carriers for PDGF yielded a mean of 4.1 mm CAL gain in treating 50 intra-bony defects. Although it is arguable that case series studies do not provide the same level of evidence as RCTs, the favourable outcome suggested the use of an osteoconductive carrier with a lower degradation rate might be beneficial.

Optimal dosage is required for growth factors to exert the greatest effect. The 0.3 mg/ml of rhPDGF-BB resulted in a mean 2.6 mm bone gain, compared to 1.5 mm with the 1.0 mg/ml dose in a multicentre study (Nevins et al. 2005). The results suggested that higher dose of PDGF might have a reduced effect on tissue healing due to likely feedback inhibition with such high local doses in a bolus release.

Previous studies (Polson & Heijl 1978, Cortellini et al. 1998) have shown that there is an increased potential for better treatment outcomes in well-contained defects, for example 3–wall deep and narrow periodontal defects, following regenerative procedures. In two included RCTs using PDGF (Nevins et al. 2005, Jayakumar et al. 2011) although the majority of the defects were 1 or 2 walls, significant more LBG and bone formation were observed in the test groups. Moreover, subgroup analysis revealed a significant increase in bone fill in all defect types in comparison to β-TCP group (Nevins et al. 2005). The results suggest the potential of using PDGF in challenging clinical scenarios.

FGF-2 for promoting periodontal regeneration

Somewhat less information is available for the use of FGF-2 in periodontal regeneration. Although there was significantly more bone fill (21.2%, 95% CI: 5.82–36.61%) with the use of FGF-2 in comparison to vehicle alone groups, the WMD of CAL gain was not significant ($p = 0.88$). Histological observation on the effect of FGF-2 in promoting periodontal regeneration in humans has not been studied; however, preclinical studies revealed that FGF-2 induced significant periodontal regeneration comprised of new cementum with Sharpey's fibres, new functionally oriented periodontal ligament fibres and new alveolar bone (Takayama et al. 2001, Murakami et al. 2003).

In spite of the absence of an osteoconductive carrier, the percentage of bone fill was 39%, 52% and 49% for 0.2%, 0.3% and 0.4%, respectively, for FGF-2 after 9 months, whereas this value was 15.86 ± 22.14% for the vehicle control group. Although better results with addition of an osteoconductive bone substitute may be expected, to date, no human clinical trial is available to validate this consideration. The choice of osteoconductive material in combination with growth factors may have an important impact on the outcomes.

Limitations and potential biases

The limitations of this systematic review include: (1) a fairly low number of randomized controlled trials are currently available; (2) risk of bias was high or unclear in most of the included studies (3) inconsistencies in methodologies and treatment modalities among studies and (4) relatively short observational period. In addition, the sensitivity and standardization of assessing bone gain from radiographs might not be optimal. Radiography often underestimates actual bone fill; in addition, the inherent measurement variability in the radiographs should be considered. In most of the included studies, standardized radiographs were not employed. Finally, only studies written in English were included, which could introduce a selection bias.

Most of the included studies had an unclear risk of publication bias and only one study was recognized with low risk of bias suggesting that the results have to be interpreted with great caution. A common risk of bias of the included papers is subject dropout. Nevertheless, all the studies with subject attrition had described methods to account for subject losses. Other biases include a small subject number that might not be representative of generation population, no description about the allocation concealment method, and calibration of examiners.

Research implications

It is recognized that the delivery systems for growth factors are continuously evolving (Ramseier et al. 2012). Given the fact that growth factors dilute fast in periodontal environment, the half-lives of them are significantly impacted (Anusaksathien & Giannobile 2002, Ramseier et al. 2012); therefore, future research is warranted for enhancement of delivery strategies to improve substantiality of growth factors in periodontal defects.

Clinical implications

The use of PFGF is well supported by clinical trials. If the cost and benefit

are justifiable, PDGF can be an option to maximize the healing potential in periodontal defects, especially for teeth of strategic importance and challenging periodontal defects. FGF might be another biological agent with a great potential for augmenting periodontal healing but more clinical trials are needed.

Conclusions

For treating intra-bony defects, applying PDGF-BB demonstrated significantly more defect fill and CAL gain than carriers alone. Controlled clinical trials on FGF-2 are limited; the available evidence suggested that FGF-2 resulted in significantly more defect fill (%) but not in CAL gain. Therefore, PDGF may be used to maximize the regenerative outcomes, provided that the cost/benefit is justified. Future research can be focused on engineering more suitable carriers that can deliver biological agents more effectively.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:&FigureS1.doc"/>

Table S1. Risk assessment of publication bias for the included RCTs.
Figure S1. Flow chart illustrating study selection for the systematic review.
Figure S2. Meta-analysis for comparison of the amount of gingival recession among selected studies. The overall weighted mean difference (WMD) is 0.18 mm (95% CI = −0.09 to 0.46 mm) in between growth factor group and control group ($p = 0.18$).
Figure S3. Funnel plot illustrating publication bias for linear bone growth.
Figure S4. Funnel plot illustrating publication bias for the percentage of bone fill.
Figure S5. Funnel plot illustrating publication bias for the clinical attachment level gain.
Figure S6. Funnel plot illustrating publication bias for probing depth reduction.
Figure S7. Funnel plot illustrating publication bias for gingival recession.

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Clinical Relevance

Scientific rationale for the study: Applying biological factors such as growth factors for periodontal regenerative procedures is an emerging technology for clinical application.

Principal findings: rhPDGF-BB and rhFGF-2 result in greater linear defect fill and bone fill (%) than standard of care therapies for treatment of intra-bony periodontal defects.

Practical implications: Local administration of rhPDGF-BB or rhFGF-2 to periodontal osseous defects provides promising clinical benefits to repair lost periodontal tissues.