

Synergistic Effects of Growth Factor, Bone Graft, and Resorbable Barrier Membrane in Management of Dehiscence and Fenestration of Dental Implants

¹Rachita Arora, ²Umesh P Verma, ³Jaya Dixit, ⁴Nand Lal

ABSTRACT

Aim: The present study was primarily designed to evaluate the outcome of guided bone graft regeneration in peri-implant defects by combining recombinant human platelet-derived growth factor-BB (rhPDGF-BB) and granules of beta-tricalcium phosphate (β -TCP) mounted by resorbable biomesh membrane. Secondary objective was to determine the value of resorbable barrier membrane to improve the efficacy of the growth factor-mediated regeneration.

Materials and methods: A randomized controlled study comprised 14 participants (8 males and 6 females, mean age 37 years, range 19–55 years), in which a total of 15 implants (10 in maxilla and 5 in the mandible) were placed. Fifteen implant sites were randomly divided by picking a code into three groups: Test group I (n = 5) β -TCP + rhPDGF (0.3 mg/mL) + biomesh, test group II (n = 5) β -TCP + rhPDGF, and control (n = 5) β -TCP + biomesh. The experimental site was examined clinically for the gingival status and radiographically for the bone status.

Results: Statistically significant difference in preoperative and postoperative measurements was observed for test groups I and II in all the parameters except width; in contrast, there was no significant difference observed for the control group from baseline to 5 months postoperatively. On intergroup comparison, statistically significant difference was observed between test group I vs control group and test group II vs control group, but it was not significant between test groups I and II, which was further confirmed using global performance scale score.

Conclusion: It concluded that rhPDGF-BB and β -TCP mounted by resorbable biomesh membrane played a synergistic role in the management of peri-implant defects.

Clinical significance: Bone regenerated using β -TCP with rhPDGF-BB in the reversal of peri-implant defects.

Keywords: β -Tricalcium phosphate, Dehiscence, Dental implant, Fenestration, Recombinant human platelet-derived growth factor-BB, Regeneration.

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INTRODUCTION

Deficient alveolar ridges predispose clinician to various challenges at the time of implant placement which is in prosthetically driven and esthetically pleasing position. With changing trends, it is not always necessary to augment the ridges in a staged approach. Peri-implant defects restored simultaneously at the time of implant placement show promising results.

In such compromised ridges, dehiscence is the most common type of bone defect; clinicians encounter at the time of implant placement. This type of defect does not heal without treatment and possess a biomechanical risk at implant loading.¹ To overcome such limitations, guided bone graft augmentation (GBGA) for the critical size defects offers the combined use of graft and membrane where the graft acts as a scaffold and barrier membrane application helps to preserve and maintain the bone graft itself and is thus distinguished from guided bone regeneration (GBR) where graft material is not used.

Today, regenerative or rejuvenating therapy has become one centerpiece of biomedical research. The use of several growth factors in peri-implant healing has yielded improvements in bone-implant contact as well as in the rate of bone formation.^{2,3} Platelet-derived growth factor is a proven mitogen and chemotactic factor for cells of mesenchymal origin, including periodontal ligament cells and osteoblasts.⁴ Immunohistochemical staining for angiogenesis using recombinant human platelet-derived growth factor-BB (rhPDGF-BB) at 3 weeks exhibited the formation of vascular structures arising from open marrow spaces of the adjacent alveolar bone as PDGF upregulates vascular endothelial growth factor, increasing blood supply to the defect area. Sarment et al⁵ and Schwarz et al⁶ observed increased levels of bone turnover markers and suggested that active turnover occurs following local delivery of rhPDGF-BB. Its use in implant dentistry began two decades back where it has shown synergistic effects with insulin-like growth factor and has stimulated bone formation with increased density,^{2,3} but still role and use of individual growth factors remain area of study.

This study was primarily designed to evaluate the outcome of guided bone graft regeneration in peri-implant

¹⁻⁴Department of Periodontology, Faculty of Dental Sciences King George's Medical University, Lucknow, Uttar Pradesh, India

Corresponding Author: Umesh P Verma, Department of Periodontology, Faculty of Dental Sciences, King George's Medical University, Lucknow, Uttar Pradesh, India, Phone: +919450195422, e-mail: umeshpratapverma@kgmcindia.edu

defects by combining rhPDGF-BB and granules of beta-tricalcium phosphate (β -TCP) mounted by a resorbable biomesh membrane. Secondary objective was to determine the value of resorbable barrier membrane to improve the efficacy of the growth factor-mediated regeneration.

MATERIALS AND METHODS

A randomized controlled study approved by the Institutional Ethical Committee comprised 14 participants (8 males and 6 females, mean age 37 years, range 19–55 years), in which a total of 15 implants (10 in maxilla and 5 in the mandible) were placed.

Selection Criteria

Inclusion criteria

Participants with good systemic and periodontal health, missing anterior tooth/teeth in maxillary or mandibular arch, with soft tissue concavity at facial aspect, and where exposure of the fixture could be anticipated were enrolled. Written consent was obtained from all the participants.

Exclusion criteria

Participants with thin gingiva at the site of implant placement, severe bruxism, or clenching habits, defective occlusal contacts in the anterior region of the maxillary and mandibular arch, smokers, tobacco chewers, and alcoholics were excluded from the study.

Randomization

Fifteen implant sites were randomly divided by picking a code into the following three groups: Test group I, test group II, and control:

- Test group I (n = 5): β -TCP (RTR-septodont) + rhPDGF (0.3 mg/mL) + biomesh (biodegradable membrane; Shark Health Care Pvt. Ltd.)
- Test group II (n = 5): β -TCP + rhPDGF
- Control (n = 5): β -TCP + biomesh

Preoperative Examination

The experimental site was examined clinically for the gingival status and radiographically for the bone status. Bone status was determined in terms of bone height (BH), bone width, and interdental space using intraoral periapical radiograph and computed tomography scan (DentaScan). Initial periodontal therapy consisted of full-mouth scaling and root planing utilizing both hand and ultrasonic instruments. Oral hygiene instructions were specified at each visit and were reinforced throughout the study period of 5 months. Occlusal adjustments were performed by selective grinding when required.

Surgical Procedure

All instruments to be used in surgery were sterilized, and the facial skin around oral cavity was scrubbed with povidone solution and participants were asked to rinse with 0.2% chlorhexidine for 60 seconds before surgery. Full-thickness flap was reflected using a mid-crestal and vertical incisions,⁷ and care was taken to avoid unnecessary trauma to the gingiva of the adjacent teeth. The site was prepared using successive drills; the socket was flushed with sterile normal saline, following which the implant was screwed into the bone with the hex ratchet using insertion torque of 30 to 35 N/cm² until the implant was seen flushed with the alveolar bone. Implants once placed in desired position were thoroughly irrigated and cover screws were secured. Site/sites were checked for any dehiscence or fenestration defect.

A number of exposed threads were recorded; the height and width of the defects were measured with a periodontal probe (PCP-UNC15, Hu-Friedy, Chicago). The shoulder of the implant was used as a reference point for height measurement. The bony edge of the defects mesiodistally was measured at two distinct levels; one at the widest point and other at the narrowest. The mean of the two was the width. Thereafter, the defects were augmented according to the assigned treatment.

Defect Augmentation

Beta-tricalcium phosphate was used in all cases to fill the defect. For the control sites, β -TCP graft was packed over the defect to maintain the space underneath the barrier and was secured using the synthetic bioabsorbable barrier membrane (biomesh) which was trimmed and adapted to cover the defect and extended 2 to 3 mm sideways. For test groups I and II, graft was mixed with reconstituted 0.3 mg/mL rhPDGF-BB in dappen dish and was then placed over the defect. Test group I was tented with resorbable barrier membrane in a similar fashion as it was done for the control sites whereas no membrane was used in test group II. After the completion of GBR procedure, tension-free primary closure was achieved with 4 to 0 non-resorbable black silk suture. An intraoral periapical radiograph was taken after the final insertion to see parallelism with the adjacent roots and to serve as the baseline for future comparison.

Postoperative Instructions

Participants were then advised with the postoperative instructions including ice packs to the area intermittently for 20 minutes (on and off) over the first 24 to 48 hours and soft diet for the first few days. Drugs prescribed were amoxicillin 500 mg + clavulanic acid 125 mg thrice daily, ibuprofen 600 mg every 8 hours, and B-complex once

daily for 7 days. Participants were also given adequate oral hygiene instructions including mouth rinses with chlorhexidine gluconate (0.2%) twice daily for the first 2 weeks. Participants were recalled the following day and then after 2 weeks for the suture removal. Thereafter, postoperative recalls were scheduled at 1, 3, and 5 months for evaluation of any untoward consequences.

Reentry

Surgical reentry was performed 5 months after implant placement, using crestal and vertical incisions as mentioned before. Flap was reflected, and the amount of regenerated bone was measured using the same periodontal probe, and the measurements were compared with the initial values. Healing cap was secured after removing the cover screw. Flap was repositioned and sutured. Participants were recalled after 2 weeks for suture removal. Subsequently, abutment was placed and prosthesis was delivered thereafter.

Statistical Analysis

Statistical analysis was done using Statistical Package for the Social Sciences version 15.0 statistical analysis software. The values are represented in numbers (%) and mean \pm standard deviation.

RESULTS

The postoperative healing was uneventful for all the cases. No signs of infection or wound dehiscence were

encountered during the entire study period. Role of growth factor and importance of membrane for bone augmentation in dehiscence defects were evaluated by assessing preoperative and postoperative measurements and calculated dimensions in terms of a number of exposed threads, defect height, defect width, and surface area. Data for all the groups are summarized in Tables 1 and 2.

In Table 1, statistically significant difference in preoperative and postoperative measurements has been seen for test groups I and II in all the parameters except width; in contrast, there was no significant difference was observed for the control group from baseline to 5 months postoperatively.

On intergroup comparison, statistically significant difference was seen between test group I vs control group and test group II vs control group, but it was not significant between test groups I and II (Graph 1), which was further confirmed using global performance scale (GPS) score.

DISCUSSION

The demand for replacing missing teeth with dental implants has increased dramatically. However, ridge defects noted during implant placement remain a challenge in implant dentistry. With the advancement of GBR, this type of defect can be easily corrected. The concept of GBR evolved from guided tissue regeneration and is used to compartmentalize bone neogenesis using barrier membranes by protecting the blood clot, creating space, and excluding soft tissue cell proliferation.⁸⁻¹⁰

Table 1: Overall comparison between control group, test group I, and test group II at pre- and postprocedure intervals

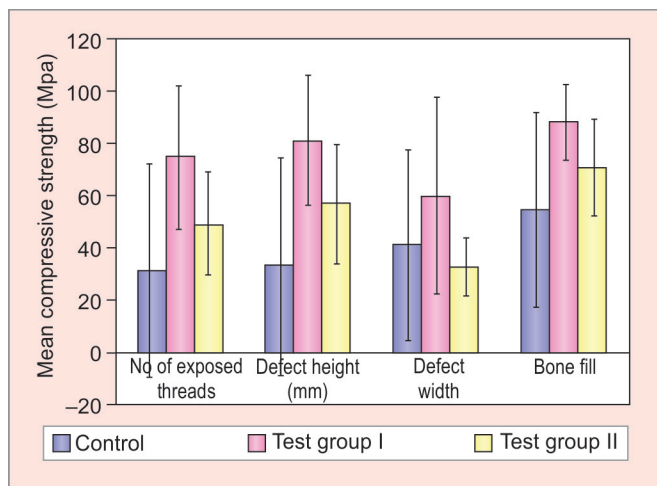
Parameters	Control (n = 5) ^a		Test group I (n = 5) ^b		Test group II (n = 5) ^c	
	Pre	Post	Pre	Post	Pre	Post
No. of exposed threads	6.4 \pm 1.52	4.8 \pm 2.95	7.0 \pm 1.41	1.6 \pm 1.67*	7.2 \pm 1.10	3.6 \pm 1.14*
Defect height (mm)	5.6 \pm 1.14	4.0 \pm 2.55	5.8 \pm 1.10	1.0 \pm 1.22*	6.2 \pm 1.10	2.6 \pm 1.14*
Max defect width (mm)	2.6 \pm 0.55	1.4 \pm 1.14	3.2 \pm 0.45	1.2 \pm 1.10*	3.2 \pm 0.45	2.0 \pm 0.00
Min defect width (mm)	1.6 \pm 0.55	1.0 \pm 0.71	1.4 \pm 0.55	0.8 \pm 0.84	1.4 \pm 0.55	1.0 \pm 0.00*
Defect width (mm)	2.1 \pm 0.55	1.2 \pm 0.91	2.3 \pm 0.27	1.0 \pm 0.94*	2.3 \pm 0.45	1.5 \pm 0.00*
Surface area of exposed implant (mm ²)	9.11 \pm 2.82	4.87 \pm 5.39	10.44 \pm 2.16	1.26 \pm 1.45*	11.38 \pm 3.77	3.06 \pm 1.34*
Global performance score	3.40 \pm 3.36		8.80 \pm 3.03 ^a		6.20 \pm 3.27	

Intergroup differences significant (Mann–Whitney U test): ^acompared with control group, ^bcompared with test group I, ^ccompared with test group II; *Significant intragroup differences (Wilcoxon signed rank test). No superscript mark denotes no significant intragroup or intergroup difference

Table 2: Comparison of proportional change in different parameters among three groups from baseline to 5 months reentry (values in %)

Parameter	Control (n = 5)	Test group I (n = 5)	Test group II (n = 5)	Significance of difference (Kruskal–Wallis test)	
	Mean \pm SD	Mean \pm SD	Mean \pm SD	χ^2	p-value
No. of exposed threads	31.43 \pm 40.91	75.00 \pm 27.64	49.17 \pm 19.63	4.814	0.090
Defect height (mm)	33.33 \pm 40.82	81.14 \pm 24.63	57.14 \pm 22.95	4.485	0.106
Defect width	41.33 \pm 36.33	60.00 \pm 37.42	33.00 \pm 11.51	1.340	0.512
Bone fill	54.64 \pm 37.23	88.11 \pm 14.69	70.85 \pm 18.46	3.814	0.149

SD: Standard deviation



Graph 1: Postoperative proportional change for different parameters in the peri-implant defect. For all the parameters, maximum change was observed for test group I, and minimum for control group, yet the difference was not significant statistically

The present study was primarily designed to evaluate the efficacy of purified rhPDGF-BB in combination with β -TCP, an alloplastic bone substitute in GBGA for peri-implant dehiscence and fenestration defects. A secondary aim was to appraise the need for a resorbable biomesh barrier membrane using growth factor-mediated regeneration.

The incorporation of growth factors, such as rhPDGF-BB with bone grafting materials, has been the focus in recent tissue engineering. When produced recombinant for clinical application, PDGF is known to stimulate migration and proliferation of mesenchymal cells including osteogenic lineage. In our present study, 0.3 mg/mL concentration of rhPDGF-BB was used with β -TCP for defect augmentation which was in agreement with the previous work of Nevins et al,¹¹ Sarment et al,⁵ and McGuire et al.¹²

In this study, one-stage approach was used for the reconstruction of dehiscence or fenestrated implants where the initial defect size was larger than 2 mm in vertical dimension as stated by Zitzmann et al.^{13,14} The one-stage approach has the advantage of reducing the total treatment time over the staged approach which requires the time lapse of several months between the GBR procedures and implant placement and involves a second surgical intervention as suggested by Hämmerle and Jung.¹⁵ Bone regeneration utilizing one-stage procedure around submerged implants has been successful both in humans^{13,14,16-19} and animals.²⁰⁻²³

Reconstruction of bony defects in alveolar ridge is one of the major challenges that continued to perplex the periodontist. Restoration of these defects becomes all the more important when we desire to place the implants in prosthetically determined and esthetically pleasing position. For achieving long-term success, these defects

can be restored either before the implant placement (staged approach) or can be augmented simultaneously at the time of implant placement. In this study, one-stage approach was used for the reconstruction of dehiscence or fenestrated implants where the initial defect size was larger than 2 mm in vertical dimension as stated by Zitzmann et al.^{13,14} The one-stage approach has the advantage of reducing the total treatment time over the staged approach which requires the time lapse of several months between the GBR procedures and implant placement and involves a second surgical intervention as suggested by Hämmerle and Jung 2003.¹⁵

Guided bone graft augmentation for peri-implant dehiscence and fenestration defects was performed in conjunction with the placement of implants in the present study. In our study, reentry for the evaluation of defect coverage was done at 5 months to appraise the effects of rhPDGF-BB as Becker et al² discerned the clinical gain in bone levels at 18 weeks with the use of rhPDGF-BB. Similar time period of 5 months was also chosen by Palmer et al.¹⁷ Bone regrowth and osseointegration have also been evidenced at 3 and 4 months by Carmagnola et al.²² However, it has been observed that in majority of the studies, 6 months or more opted for the reentry.^{11,12,24}

In test group I, percentage reduction in a number of exposed threads after 5 months was $75.00 \pm 27.64\%$ with a mean change of 5.40 ± 2.61 . Out of five cases, in two cases, complete coverage was seen. Results were comparable with the study of Becker et al² who observed highest mean change of 5.60 ± 1.70 in a number of exposed threads around implant. For test group II, mean change and percentage reduction in a number of exposed threads at 5 months were $3.60 \pm 1.52\%$ and $49.17 \pm 19.63\%$. Unlike our results, Dahlin et al⁹ obtained 66.4% coverage of threads but without membrane and graft. In the control group, mean change in a number of exposed threads at the end of the study period was 1.60 ± 1.67 and percentage reduction was 31%, whereas Becker et al² obtained the coverage of 3.5 ± 3.12 for the sites with graft and membrane but without growth factor. Dahlin et al⁹ observed 95.6 to 100% coverage of threads but with the use of polytetrafluoroethylene membrane. The reason for the differences in augmented bone could be due to the type of membrane used.

In the test groups I and II, percentage diminution in defect height was 81 and 57% respectively. In contrast, Byun and Wang²⁵ in their case study and Weng et al²⁶ in their histologic study observed complete healing. Oh et al,²⁷ in their study using no membrane observed 44.28% linear fill which on comparison was lower than what we observed for test group II and the possible reason for enhanced bone formation could be the use of rhPDGF-BB. In our study the mean change in BH for the control group was 1.60 ± 1.67 which was much less compared with the

results obtained in the study of Moses et al., 3.90 ± 0.86 mm ($75.11 \pm 18.99\%$) gain and 5.63 ± 1.84 mm) Park et al.⁷ noticed 4.82 ± 2.16 mm and after 6 months compared with 5 months scheduled for our study and different osseous graft used could be the reasons for observed difference. Oh et al.²⁷ observed nearly 58% and Weng et al.²⁶ 75.4% reduction in defect height.

Mean defect width reduction for all the three groups was nonsignificant and similar to the previous study of Park et al.⁷

After 5 months, mean reduction in defect area for test group I was 9.18 ± 2.38 mm² and percentage bone fill of $88.11 \pm 14.69\%$. Comparable results were obtained in various other studies.^{5,16} Without the use of membrane reduction in mean defect area was 8.32 ± 3.91 and percentage bone fill of $70.85 \pm 18.46\%$, and the results of our study were comparable with study of Schwarz et al.⁶ As this reduction was comparatively less than the reduction achieved with the use of membrane, he concluded that application of barrier membrane did not seem to interfere with factor activity but ensured the stabilization of the graft particles. This is in support to our findings observed in test group I. For the control group, percentage bone fill was only $54.64 \pm 37.23\%$; on the contrary, dissimilar results were also noticed without the use of growth factor.^{7,28}

Overall significant reduction was observed in test groups from baseline to 5 months but was nonsignificant for the control group. This emphasizes the fact that external application of PDGF-BB did stimulate bone regeneration and this has been witnessed as early as 7 days following implant placement in histologic studies of Lynch et al.³ Along with that, it has a crucial role in healing²⁹ and attracting fibroblasts into the clot.³⁰ Even though maximum coverage had been achieved for test group I, it was only two of the five dehisced implants which by 5 months had 100% coverage remaining three had 64.02, 87.97, and 88.57% bone fill. Possibly, these defects would have been resolved completely if the reentry period was extended to 6 months or more. To further support, Diès et al.³¹ in their study stated that bone regeneration seems to take more time when grafting material is used.

Furthermore, to be noted as the defects were randomly allocated to the particular group, the only fenestration defect that was encountered fell into the control group, and in contrast to other defect sites in control group, complete regeneration was seen for the fenestration defect at 5 months. Possible explanation for it can be the healing pattern of fenestration defect which is completely encased by bony margins and membrane restricting the different cell types to separate tissue compartments which lead to the bone ingrowth. Therefore, this single case was acting as a confounder, and despite showing a postoperative reduction in four threads, it showed a 100% reduction,

whereas some cases showing coverage of six threads had shown 85.7% reduction only.

Thereby a GPS was developed which with its dimensions provided a better assessment of group behaviors on different dimensions. As compared with absolute changes and percentage changes which often provide a wrong impression owing to the difference in baseline values, the GPS was based on an objective criterion after studying the magnitude and nature of changes for different parameters. It not only provided the opportunity to give an absolute picture of procedure's performance by a single score GPS but also evaluated the individual parameters more efficiently.

In this study, postprocedural changes in test groups I and II were significant statistically, whereas same was not true for the control group. This was highlighted with GPS system showing the maximum regeneration for the test group I with a score of 8.80 followed by the test group II (6.20) and was least for the control group (3.40). As in the present study, sample size was small and no histological evaluation was performed; further interventions are required to provide evidence-based conclusions.

CONCLUSION

Within the limits of the present study, the following conclusions can be drawn:

- The present study provides evidence that β -TCP is a suitable delivery system for rhPDGF-BB.
- Copolymer of polyglycolide, polylactide, and d, l-lactide/glycolide resorbable membrane can be safely used in peri-implant defect coverage as no untoward complications were encountered with its use.
- As significant reduction was observed in test groups for all the parameters except the defect width from baseline to 5 months, reentry, and insignificant reduction attained for the control group; on intergroup comparison, significant difference was noticed between test group I and control group, which emphasized the role of rhPDGF in enhanced bone formation at the site of peri-implant defects (Graph 1).
- It was also concluded that membrane plays an important role in GBR of peri-implant defects and does not interfere with the factor activity.

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