Efficacy and Safety of Concentrated Growth Factors and Platelet-Rich Fibrin on Stability and Bone Regeneration in Patients with Immediate Dental Implants: A Randomized Controlled Trial

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Purpose: Immediate dental implants revolutionized the field of implant dentistry with significant advantages over conventional implants. The lack of adequate bone in the extraction socket raises the question of the appropriate timing of implant loading. Platelet concentrates have been used widely to accelerate bone regeneration in the maxillofacial region. This study evaluates the effect of platelet concentrates on bone healing and implant stability in the maxillary and mandibular molar regions. Bone regeneration is regulated by several growth factors, particularly vascular endothelial growth factor (VEGF) and transforming growth factor-β1 (TGF-β1); therefore, quantification of these factors in platelet concentrates and its correlation with bone healing has been assessed in this study. ***Materials and Methods:*** The primary aim of this randomized clinical trial was to compare the stability of immediate dental implants in the maxillary and mandibular molar regions treated with platelet-rich fibrin (PRF) versus concentrated growth factors (CGF) using resonance frequency analysis (RFA). The secondary objectives were to evaluate the bone regenerate around implants with the use of PRF and CGF and to quantify growth factors VEGF and TGF-β1 in the prepared CGF and PRF and their correlation with bone healing, if any. A total of 36 patients were randomized into three groups (12 each): control, PRF, and CGF. In all patients, immediate implants were placed either with or without platelet concentrate (PRF or CGF). Implant stability was measured using RFA immediately postoperatively and at 4, 8, and 12 or 16 weeks (12 weeks for mandible and 16 weeks for maxilla) postoperatively. Radiodensity and the bone gap (horizontal/vertical) were measured on intraoral periapical radiographs immediately postoperatively and at 8 weeks and 12 or 16 weeks postoperatively. ***Results:*** On comparing the implant stability quotient (ISQ), radiodensity/grayscale (GS), and horizontal and vertical bone gap (HG and VG), there was no significant difference noted between the three groups at any point in time. On ISQ analysis at 8 weeks, the control group showed a significant improvement ($P = .04$), whereas at 12 or 16 weeks, significant improvement was seen in PRF ($P = .03$) and CGF groups ($P = .02$). In GS assessment, only the control group showed significant improvement at 12 or 16 weeks ($P = .009$). In horizontal and vertical bone gap analysis all three groups showed significant improvement at 8 weeks (control [$P < .001$], PRF [$P = .001$], CGF [$P = .01$]) as well as 12 or 16 weeks (control [$P < .001$], PRF [$P < .001$], CGF [$P = .006$]). The enzyme-linked immunosorbent assay (ELISA) quantification of VEGF and TGF-β1 showed significant concentration of VEGF in PRF as compared to the plasma, while concentration of TGF-β1 was found to be comparable in both groups. ***Conclusion:*** The application of platelet concentrates seems to enhance stability of implants, but intergroup results were nonsignificant at all time points. There was no statistically significant difference between the three groups when comparing quality (radiodensity/grayscale) and quantity (horizontal and vertical gap reduction) of bone regenerate. Studies with larger sample sizes are required to make conclusive assertions regarding efficacy of platelet concentrates in dental implants. *Int J Oral Maxillofac Implants 2022;37:784–792. doi: 10.11607/jomi.8924*

Keywords: concentrated growth factors, dental implant, immediate implant, implant stability quotient, osseointegration, platelet-rich fibrin

Dental implants are currently indispensable in the field of oral rehabilitation. On the basis of timing of placement, implants have been classified by Esposito et al[1] into immediate, immediate-delayed, and delayed implants. They termed implant placement in fresh extraction sockets as *immediate*; if implant placement was done within 8 weeks after extraction but not at the time of extraction, then the procedure was called *immediate-delayed*; all implants placed after 8 weeks of extraction were termed as *delayed* implant placement.

In immediate implant cases, significant space is present between the residual bone and the implant surface. Successful integration of the implant requires the deposition of bone in these gap areas for proper implant support. A good quality and quantity of bone formation in this gap area is thus warranted for loading of implants at the earliest time point possible.

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Healing and repair processes can be accelerated[2–4] by certain bioactive molecules called *growth factors*, which modulate the process of cell differentiation and accelerate the process of osseointegration. Platelets in autologous blood are a rich source of numerous growth factors in high quantities, such as bone morphogenetic protein (BMP), transforming growth factor-β1 (TGF-β1), platelet-derived growth factor (PDGF), insulin-like growth factor (IGF), and vascular endothelial growth factor (VEGF).[5] Various techniques have been developed to obtain platelet-derived concentrates such as platelet-rich plasma (PRP) and platelet-rich fibrin (PRF) by Choukroun et al[6] in 2000 and concentrated growth factors (CGF) by Sacco[7] in 2006.

In the maxillofacial region, for the reconstruction of bone defects, platelet concentrates are used widely with good success rates. However, the efficacy of PRF and CGF in accelerating the osseointegration of immediate posterior implants needs to be evaluated.

Resonance frequency analysis (RFA) is one of the most reliable and predictable indicators of adequate osseointegration and stability of an implant. The objective of our study was to prospectively compare the implant stability and quality of bone regenerate formed around the immediate implant with the use of CGF and PRF to immediate implants placed without any platelet concentrates using RFA and radiologic methods. The platelet concentrates formed (PRF and CGF) were also evaluated quantitatively for concentration of growth factors (VEGF and TGF-β1).

MATERIALS AND METHODS

Trial Design

This study was a single-center, prospective, parallel-group, randomized controlled trial conducted in accordance with the CONSORT guidelines.

Setting and Location

All the patients presenting to the dental outpatient department (OPD) of a tertiary care hospital requiring immediate implant placement in the maxillary or mandibular molar regions were screened for eligibility criteria. After obtaining written consent, the cases were enrolled as per the inclusion and exclusion criteria. The study was conducted in accordance with the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use Good Clinical Practice (ICH-GCP) and Indian Council of Medical Research (ICMR) guidelines, and ethical approval was obtained from the Institutional Ethics Committee. The trial was prospectively registered with the Clinical Trial Registry of India: CTRI/2018/10/015965.

Study Duration

The trial started with the placement of an immediate dental implant, followed by subsequent follow-up visits at 4, 8, and 12 or 16 weeks (12 weeks for mandible and 16 weeks for maxilla). The final prosthesis was provided at 12 or 16 weeks. The recruitment started in October 2018, and the observation period ended in May 2019.

Sample Selection Criteria

Patients between ages 18 and 65 years requiring immediate implant placement in the maxillary or mandibular molar regions were recruited. Patients with inadequate bone available, local or systemic infection, or abnormal platelet count and patients taking antiplatelet drugs or drugs affecting bone metabolism were excluded (Fig 1).

Randomization and Allocation

A total of 36 patients undergoing immediate dental implant placement were randomly allocated into three groups (control, PRF, and CGF), ie, 12 in each group, using a block randomization scheme. The randomization sequence was created using random allocation statistical software and was stratified with a 1:1:1 allocation using random block sizes of six and nine by a co-investigator unrelated to surgical procedure and assessment.

The allocation sequence was placed in sequentially numbered, opaque, sealed, and stapled envelopes and concealed from the researcher enrolling and assessing participants.

Intervention

Immediate implants were placed using a standard drilling protocol just below the crest of the socket immediately after extraction. Titanium implants with a sandblasted, large-grit, acid-etched surface and a double-threaded tapered body design with a flat cutting end were placed. The implants had a platform-switched design with an internal conical connection. An undersized osteotomy was done, ie, 0.5 mm shorter than the implant diameter. For use in molar sites, most implants used were of regular diameter (5 to 6 mm) and 12 to 14 mm in length, were placed just below the crest, and were evaluated at the same time points. After placing the implant, a cover screw was placed, and primary closure was achieved. Platelet concentrates were placed in the vicinity of the implant in the extraction socket during the procedure in the PRF and CGF groups.

For PRF preparation, vacutainer tubes containing blood without anticoagulant were placed in a centrifugal machine and were centrifuged at a speed of 3000 revolutions per minute (rpm) for 10 minutes. For CGF preparation, vacutainer tubes were immediately centrifuged at different speeds: 2,700 rpm for 4 minutes,

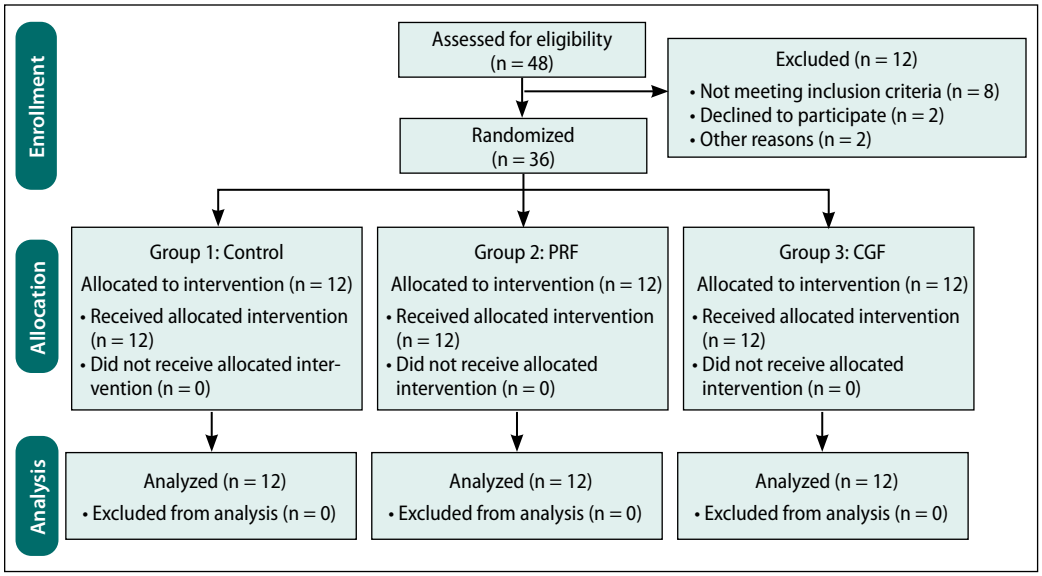

Fig 1 CONSORT flow diagram.

2,400 rpm for 4 minutes, 2,700 rpm for 4 minutes, and 3,000 rpm for 3 minutes.

All the cases were evaluated for implant stability quotient (ISQ), mean grayscale/radiodensity (GS), horizontal bone gap (HG), and vertical bone gap (VG). All the patients completed a follow-up period of 6 months with no failures or infection reported. Change from baseline was calculated for week 4, week 8, and week 12 or 16 and was used for statistical analysis.

Assessment

Resonance frequency analysis. ISQ was measured at two locations (buccal and palatal/lingual) on the implant using an RFA device in all three groups immediately postoperatively (day 0) and at 4, 8, and 12 or 16 weeks. The mean of the buccal and palatal/lingual reading at each time point was used for statistical analysis.

Radiographic Assessment

Radiographic assessment of quality of bone was done by comparing intraoral periapical radiographs (IOPA) taken immediately postoperatively (day 0) and at 8 weeks and 12 or 16 weeks postoperatively for all three groups. On day 0, a customized occlusal putty bite was fabricated for each patient after placing an intraoral sensor with a standardized intraoral sensor holder. The same index bite was used on subsequent follow-up visits for obtaining IOPAs.

A radiovisiography system (Vatech) with digital imaging software was used to compare the density of bone as well as the HG and VG in the peri-implant region (Figs 2 and 3). The measurement of bone levels was adjusted according to the magnification factor.

$$\text{Magnification factor } (M) = \frac{\text{Actual implant length}}{\text{Radiographic implant length}}$$

$$\text{Actual horizontal bone gap} = M \times \text{radiographic HG}$$

$$\text{Actual vertical bone gap} = M \times \text{radiographic VG}$$

All horizontal and vertical markings on IOPAs in the radiovisiography software were taken from the collar of implant, which is an easily identifiable landmark.

Quantification of Growth Factors

The level of growth factors TGF-β1 and VEGF in platelet concentrates was measured using antibody sandwich enzyme-linked immunosorbent assay (ELISA; Immunotag, G-Biosciences), which is a semiquantitative method of estimation.

Outcomes

The primary outcome was the stability of the immediately placed dental implants in maxillary and mandibular molar regions with PRF and CGF using RFA. The secondary outcomes were: *(1)* bone regenerate around implant with the use of PRF and CGF; and *(2)* quantification of growth factors VEGF and TGF β1 in prepared PRF and CGF and its correlation with bone healing, if any.

Statistical Analysis

Analysis was done using SPSS version 23 (IBM). Intragroup analysis was done by paired *t* test, while intergroup analysis was done by one-way ANOVA analysis. A *P* value less than .05 was considered to be significant.

RESULTS

The 12 patients were randomly allocated into a control or one of two intervention groups (PRF and CGF). Baseline demographic characteristics of the three groups

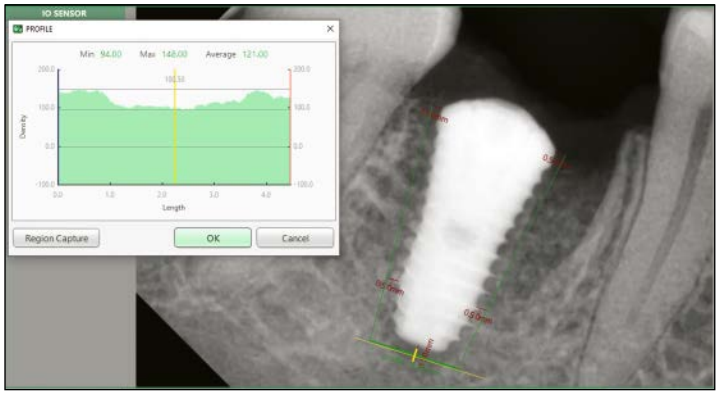

Fig 2 Grayscale/radiodensity measurement at apical surface of implant. The graph of variance on each radiograph gives minimum, maximum, and an average values. Average values obtained at the mesial, distal, and apical surfaces were used to calculate mean GS at day 0, week 8, and week 12 or 16.

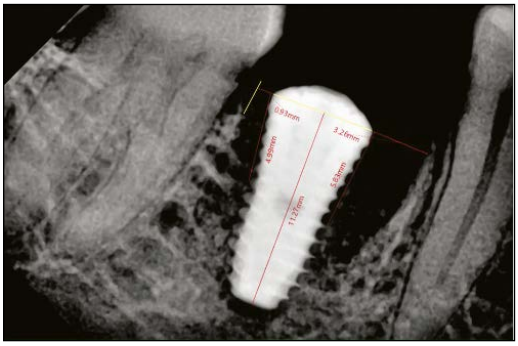

Fig 3 HG and VG measurements at the mesial and distal aspects at day 0.

Table 1 Baseline Demographic Characteristics of Control and Treatment Groups

Variables		Control (Group 1)	PRF (Group 2)	CGF (Group 3)	*P* value[a]
Age (y, mean ± SD)		37.8 ± 14	41.1 ± 15	43.2 ± 13	.86[b]/.71[c]/.96[d]
Sex (n)	Male	5	5	3	.61
	Female	7	7	9	
Arch distribution (n)	Maxilla	2	3	4	.64
	Mandible	10	9	8	

[a]*P* value ≤ .05 was considered statistically significant.
[b]Control vs PRF.
[c]Control vs CGF.
[d]PRF vs CGF.

Table 2 Comparison of Baseline Measurements in Three Treatment Groups at Implant Placement (Day 0)

Parameters	Group 1 (Control; mean ± SD)	Group 2 (PRF; mean ± SD)	Group 3 (CGF; mean ± SD)	ANOVA with post-hoc Scheffe *P* value[a]
ISQ-0	70.2 ± 17	66.8 ± 12.6	66.5 ± 14.2	.85[b]/.83[c]/.99[d]
GS-0	102.9 ± 17	113.9 ± 16.4	120.2 ± 17.7	.30[b]/.06[c]/.66[d]
HG-0 (in mm)	2.0 ± 0.5	1.6 ± 0.9	1.7 ± 1.09	.61[b]/.72[c]/.98[d]
VG-0 (in mm)	3.7 ± 2.7	3.1 ± 2.6	2.5 ± 2.1	.84[b]/.48[c]/.81[d]

ISQ-0 = mean ISQ at day 0; GS-0 = mean GS at day 0; HG-0 = mean HG at day 0; VG-0 = mean VG at day 0.
[a]*P* value ≤ .05 was considered statistically significant.
[b]Control vs PRF.
[c]Control vs CGF.
[d]PRF vs CGF.

were compared using one-way ANOVA, and no significant difference was observed between the groups ($P > .05$). All three groups had comparable demographics (Table 1).

Baseline clinical and radiographic measurements (ISQ-0, GS-0, HG-0, and VG-0) were also similar in all three groups, with nonsignificant *P* values (Table 2).

The mean ISQ increased progressively in all treatment groups at all time points, except in the control group, where a minor decrease was noted at week 12/16. Although there was an increase in ISQ at week 4 (ISQ 4-0) in all three treatment groups, the increase was not significant. At week 8, implants in the control group showed significant improvement in ISQ (ISQ 8-0: 7.6 ± 11.6, $P = .04$). In the PRF and CGF groups, there was no significant improvement in ISQ 8-0. At week 12/16, there was no significant improvement in ISQ 12/16-0 in the control group. However, in the PRF (9.5 ± 13.9) and CGF (11.3 ± 14) groups, a significant improvement in ISQ 12/16-0 was noted ($P = .04$ and $P = .02$, respectively). The intergroup comparison of ISQ 4-0, ISQ 8-0, and ISQ 12/16-0, performed using one-way ANOVA, showed that there was no significant difference between ISQ 4-0, ISQ 8-0, and ISQ 12/16-0 in all three treatment groups (Table 3).

The baseline grayscale value (GS-0) was greater in the PRF and CGF groups than in the control group, although the difference was statistically nonsignificant.

Table 3 Intragroup and Intergroup Comparison of Change in Mean ISQ, GS, HG, and VG

	Control				PRF				CGF				
	Change in mean (mean ± SD)	*P* value[a]	95% CI of the difference		Change in mean (mean ± SD)	*P* value[a]	95% CI of the difference		Change in mean (mean ± SD)	*P* value[a]	95% CI of the difference		ANOVA with post–hoc Scheffe *P* value[a]
			Lower	Upper			Lower	Upper			Lower	Upper	
ISQ 4-0	0.6 ± 4.3	.61	−2.12	3.45	5.5 ± 11.9	.13	−2.07	13.07	2.3 ± 16.5	.63	−8.16	12.91	.62[b]/.94[c]/81[d]
ISQ 8-0	7.6 ± 11.6	.04	0.24	15.01	7.7 ± 13.2	.06	−0.71	16.12	8.6 ± 14.2	.06	−0.44	17.69	> .99[b]/.98[c]/.98[d]
GS 8-0	9.1 ± 16.1	.07	−1.13	19.33	−5.9 ± 13.7	.161	−14.64	2.76	2.7 ± 16.5	.58	−7.82	13.26	.07[b]/.60[c]/.40[d]
HG 8-0 (mm)	1.48 ± 0.69	< .001	−1.92	−1.04	1.11 ± 0.84	.001	−1.65	−0.578	0.98 ± 1.09	.01	−1.67	−0.29	.60[b]/.40[c]/.93[d]
VG 8-0 (mm)	3.35 ± 2.6	.001	−5.04	−1.66	2.35 ± 2.13	.003	−3.71	0.99	1.53 ± 1.19	.001	−2.29	−0.77	.51[b]/.12[c]/.63[d]
VG 12/16-0 (mm)	3.52 ± 2.59	.001	−5.17	−1.88	2.84 ± 2.32	.001	−4.32	−1.36	1.57 ± 1.29	.002	−2.39	−0.74	.74[b]/.09[c]/.36[d]

[a]*P* value ≤ .05 was considered statistically significant.
[b]Control vs PRF.
[c]Control vs CGF.
[d]PRF vs CGF.

Table 4 Comparison of Amount of Growth Factors (pg/mL) in PRF and CGF

		Plasma	Concentrate	*P* value
PRF	VEGF	869.75	914.1	.03
	TGF-β1	595.25	630.25	.15
CGF	VEGF	802.25	836.45	.27
	TGF-β1	617.83	643.25	.18

The mean grayscale value increased progressively in all treatment groups, except in the PRF group, in which a decline was noted in GS 8-0. There was no significant difference in GS 8-0 in the control (9.1 ± 16.1), PRF (–5.9 ± 13.7), and CGF groups (2.7 ± 16.5) (*P* = .07, .16, and .58, respectively). At week 12/16, there was a significant difference in GS 12/16-0 (9.2 ± 10.1) in the control group (*P* = .009). The GS 12/16-0 values in the PRF (6.2 ± 11.6) and CGF groups (2.9 ± 20.0) were nonsignificant (*P* = .09 and *P* = .62, respectively). The intergroup comparison of the three groups, using one-way ANOVA, showed that there was no significant difference between changes in mean GS measurements in the control, PRF, and CGF groups at any point in time (see Table 3).

The mean horizontal and vertical bone gap progressively decreased in all three groups. In all three groups, HG 8-0 and HG 12/16-0 was found to be significant. The one-way ANOVA showed no significant results in intergroup comparison for either the horizontal or vertical bone gap analysis (see Table 3).

The results showed that a significant amount of VEGF (44.3 ± 62.9 pg/mL, *P* = .03) was obtained in prepared PRF as compared to plasma, but the amount of VEGF obtained in CGF (34.2 ± 103.3 pg/mL, *P* = .27) was found to be nonsignificant. The amount of TGF-β1 concentrated in both PRF (35 ± 78.6 pg/mL, *P* = .15) and CGF (25.42 ± 62.2 pg/mL, *P* = .18) was not significant (Table 4).

DISCUSSION

Immediate dental implants have revolutionized the field of implant dentistry. There are several biologic as well as psychologic advantages of immediate implants, ie, decreased total treatment duration, fewer surgical interventions, and preservation of bone and gingival tissue. The success rate of immediate dental implants as reported in various studies is 87.5% to 96%.[8–10] In this study, immediate implants were placed in the mandibular or maxillary molar regions, which are known to have type 3 or type 4 bone, respectively. The success rates of implants have been reported to be lower in type 4 bone.[11–14]

Implant stability assessment is a clinical parameter measured in terms of implant stability quotient (ISQ) using RFA, which validates osseointegration. Implants having an ISQ greater than 70 are considered to be highly stable. ISQ between 60 to 69 denotes medium stability. Implants having an ISQ lower than 60 are considered to be less stable.

At week 4, the mean ISQ increased in all three groups, but again the change was nonsignificant. At week 4, a greater number of implants in both experimental groups (PRF and CGF) showed an increase in ISQ. Decline in stability in the initial few weeks is a known phenomenon as osteoclastic activity dominates osteoblastic activity, followed by reversal to bone deposition. The maximum change in mean ISQ was noted in the PRF group, followed by the CGF and control groups.

In terms of individual implants, also at week 4, a maximum gain of +41 in mean ISQ was seen in an implant in the CGF group, followed by + 29 in an implant in the PRF group. In the control group, the maximum gain in mean ISQ was +9, which is much lower than the PRF and CGF groups. Greater increase was noted in both platelet concentrate groups. Thus, these platelet concentrates can be used as adjuncts in cases where early loading is required.

According to the literature, and as noted above, osteoclastic activity predominates in the early healing period (usually up to 2 to 4 weeks), and some reduction in implant stability can be expected during this osteoclastic activity.[15–17] This activity is said to be maximum at 3 weeks. In our study, implant stability using ISQ is the only parameter that could be studied at week 4 during this early healing phase because radiographic changes usually take 6 to 8 weeks to be appreciated quantitatively, especially on conventional radiographs. Ideally, implant stability also should have been measured at least weekly for the first month, which would have provided a better picture. However, for measuring ISQ, the cover screw had to be removed each time, and a Smartpeg (Osstell) screwed inside the implant. This would have led to micromotion, which could have been detrimental to implant success, especially in the first 3 weeks, when osteoclastic activity is at its maximum. A method that is as reliable as RFA but less invasive needs to be developed. Though not significant, PRF and CGF groups showed a greater increase in ISQ in the early healing period (week 4) than the control group, leading us to propose that these platelet concentrates can help in accelerating osteoblastic activity while counteracting osteoclastic activity and eventually may help in early healing.

It is known that changes in ISQ and bone density are inversely proportional. Implants placed in soft bone with low initial primary stability show a greater increase in stability in contrast to implants placed in dense bone, which show higher primary stability. Healing and remodeling in delicate trabecular bone increases the bone stiffness in the peri-implant region in soft bone. In dense bone, a slight decrease in stability is likely due to marginal bone remodeling of the cortical bone, which contributes to high initial ISQ readings. Also, if the initial stability is high in dense bone cases, subtle changes may not be evident.[18]

In all three groups in the present study, there was a decrease in ISQ value in cases that had an initially high ISQ value (> 70). The number of implants with baseline ISQ > 70 was highest in the control group, followed by the CGF group, and was lowest in the PRF group. For this reason, change in ISQ at 4 weeks is least in control and maximum in PRF. Similar findings were noted in other studies as well.

In our study, cases that had low ISQ-0 (< 65) showed maximum improvement at week 4 in all the groups. But this effect was most prominent in the PRF and CGF groups. Thus, according to our data, platelet concentrates may have an important role in improving osseointegration in implants with low primary stability by inducing new bone formation in the peri-implant region. These findings are in accordance with various other studies.[19,20]

At week 8, a greater number of implants in the control group showed improvement. The change in mean ISQ was also significant in the control group ($P = .04$), with a maximum gain of +39.5 seen in any implant, followed by the CGF group with a maximum gain of +38. Thus, we may say that the control group could catch up with osseointegration by week 8. This could be a representation of the regular bone remodeling process, or it may question the effect of platelet concentrates on bone healing in the long term.

Despite significant results in the PRF and CGF groups, intergroup comparison of change in mean ISQ found that the final outcome at week 12/16 was similar in all three groups. Though there was no significant difference noted at any point in time, PRF and CGF both performed better than control at all time points. But lack of statistically significant intergroup results raises concerns about the efficacy of platelet concentrates in enhancing osseointegration and implant stability at final outcome. Similar results are shared by some other studies in the literature.[21–23]

The minor changes in quantity and quality of bone formation in the healing phase are difficult to interpret radiographically. Computed tomography (CT) is the preferred imaging method to interpret qualitative and quantitative changes in bone volume. However, considering radiation hazards and financial burden, conventional radiography was used for evaluation of bone formation around implants.

Grayscale measurement on the radiovisiography software was used to quantify the radiodensity objectively. The difference in mean radiodensity in the three groups at baseline (GS-0) was found to be nonsignificant. However, the mean radiodensity value measured as baseline immediately postoperatively (day 0) was found to be highest in CGF and PRF as compared to the control group. The higher radiodensity values in the CGF and PRF groups could have been due to the filling effect of the platelet plug, which altered the bone density values in the peri-implant region on radiographs, giving a false high reading of density in the baseline radiograph. In contrast, the control group had absolute radiolucency in the peri-implant region at baseline.

The mean change in each at different time points (GS 8-0 and GS 12/16-0) seems a better predictor than actual value (GS-0, GS-8, and GS-12/16), but mean change

is also unreliable if any of the readings are falsely high or low. Although the highest GS-8 was noted in the CGF group, on comparison of the change in mean grayscale value at week 8, the control group showed the highest increase among the three groups. This could be because, in the control group, the baseline value of radiodensity (GS-0) was much lower than in CGF and PRF. Therefore, a larger change in mean could be appreciated in the control group at week 8, after adequate bone had formed. This could be marked as a limitation of assessment in conventional radiographs.

At week 12/16, the mean grayscale value was again highest in the CGF group, followed by the PRF and control groups. This corroborates the maximum ISQ value also seen in the CGF group at week 12/16. Though in terms of change from baseline, the control group again showed a significant increase in mean radiodensity at week 12/16. If we accept that both platelet concentrates had falsely high baseline readings, then the mean change in PRF and CGF should have been greater than in the control and also significant in both experimental groups. This would then have corroborated the stability result (ISQ), which was found to be significantly better in both platelet concentrates. This hypothesis can be proved only with a definitive radiologic evaluation technique, like a CT scan, which gives exact readings in Hounsfield units. With the conventional radiographs used in our study, the control group showed a significant increase in density at final outcome. However, on intergroup comparison, as with ISQ, there was no significant difference in mean radiodensity at any point in time.

Though there was no significant difference in the baseline mean horizontal bone gap of the three groups, the control group had the highest mean horizontal gap, followed by the PRF group, then the CGF group. This minor difference could be because of the empty socket in the control group versus the filled socket in the experimental groups (PRF and CGF).

The mean reduction in horizontal bone gap was significant in all three groups. The remaining mean horizontal defect size was lowest in the PRF group, followed by the control group, then the CGF group. But there was no significant difference noted among the three groups at any point in time.

Comparison of the bone gap results in all three treatment groups showed significant reduction in horizontal as well as vertical bone gaps, both at week 8 and week 12/16. At both time points, the maximum reduction in vertical bone gap was again noted in the control group, followed by the PRF group, then the CGF group.

The lowest rate of bone formation and least reduction in horizontal and vertical bone gap being found in the CGF group is contradictory with the findings of Sohn et al,[24] who reported a faster rate of bone formation with use of CGF as the sole material in sinus floor augmentation.

The nonsignificant results obtained upon comparison of the three groups are in agreement with many other studies. A meta-analysis conducted by Liu et al,[20] which included randomized controlled clinical trials assessing histologic and clinical results to reveal the additional effects of PRF in sinus floor augmentation, concluded that there were no statistical differences in survival rate and new bone formation between the non-PRF and PRF groups.

No significant interaction was found between age, sex, or location of the implant and ISQ or horizontal or vertical bone gap over 12 or 16 weeks.

Platelets act as a reservoir of numerous growth factors. CGF is also similar to PRF as it is in solid form. It is prepared with variable centrifugation speeds, which is claimed to isolate much larger, denser concentrates that are richer in growth factors.[5,23] However, there are other studies that mention other factors that could affect the architecture of platelet concentrates. Dohan et al[24] discussed the effect of centrifuge-related factors, such as weight of the machine, vibrations, and temperature rise during the process, which could affect the structure of platelet concentrates. Therefore, centrifugation speed is not the only factor affecting platelet concentrates.

VEGF has an important role in initiating an angiogenic response in the inflammation stage. According to Hicklin et al,[28] VEGF is required for the angiogenesis-osteogenesis coupling process in bone healing. It also helps in regulating osteoclasts in the remodeling stage. They also proposed that local administration of VEGF may be useful in the treatment of impaired bone healing/regeneration. Similar effects also have been reported by other authors.[29,30]

TGF-β1 is released due to degranulation of platelets and several other cells participating in tissue healing. It has an effect on osteoblast activity. Its ability to improve bone regeneration has been studied widely. Noda and Camilliere[31] reported that TGF-β stimulates bone formation and has an anabolic effect on local bone metabolism.

Thus, VEGF and TGF-β1 were chosen for their direct role in angiogenesis and osteogenesis as both are crucial for early healing. We compared PRF and CGF for the presence of these two growth factors using double-antibody ELISA. The concentration of these growth factors was compared both in the plasma and concentrate that was formed and placed in the vicinity of implants.

According to our results, a significantly higher amount of VEGF was found in PRF as compared to its plasma. This is in contrast to a study done by Dohan et al,[26] in which only VEGF was found to be in significantly higher serologic concentrations than the rates in exudates, supernatants, or plasma. The amount of VEGF

and TGF-β1 found in CGF was found to be nonsignificantly different than that found in its plasma.

In the present study, no adverse effects were noted after using autologous platelet concentrates (PRF/CGF) in both the experimental groups. Hence, platelet concentrates have been found to be safe.

The concentration of growth factors is also related to preparation techniques, as reported in the literature. According to Oh et al,[32] the double-spin method generally led to a higher concentration of platelets relative to the single-spin method. However, the cytokine content was not necessarily proportional to the cellular composition of the PRPs, as the greater content could be different between the single-spin vsdouble-spin method, depending on the type of cytokine.

The concentration of both the growth factors was found to be higher in PRF as compared to CGF. This could have been the reason for the faster and better bone fill that led to greater reduction of the horizontal and vertical bone gaps in the PRF group compared with the other two groups. This is in contradiction to the study done by Rodella et al,[5] which reported CGF to have a matrix that is denser and richer in growth factors. Lee et al[33] compared PRF and CGF for tensile strength, growth factor content, and ability to promote periodontal cell proliferation. The authors concluded that tensile strength of CGF was significantly higher. Concentrations and amounts of PDGF and EGF were significantly higher in CGF than in PRF.

The effectiveness of platelet concentrates is still controversial in both the medical and dental fields. The less-effective clinical and radiologic results could have various reasons. According to several authors, the effect of growth factors depends on cell population and culture conditions. Moreover, many growth factors have an antagonistic effect. Sprugel et al[34] noted that fibroblast growth factor (FGF), TGF-β, and PDGF can increase DNA synthesis but decrease alkaline phosphatase (ALP) synthesis. Giannobile et al[35] compared combinations of IGF-1, PDGF, TGF-β1, and FGF on bone remodeling and differentiation and found that combining IGF-1 and other growth factors increases mitogenic activity and protein synthesis of osteoblasts, while decreasing ALP synthesis. ALP increases the bone mineralization process; therefore, a decrease in ALP may have resulted in the nonsignificant results.

Overall, the literature presents a mixed representation of the effects of platelet concentrates in terms of improved bone healing. Diana et al[19] compared immediate anterior dental implants placed with and without using PRF. They reported a significant increase in stability in both the groups after 3 months, which is in accordance with the present study. They also reported that there was no significant difference between groups in terms of stability. Knapen et al[36] also concluded that L-PRF did not improve the kinetics, quality, or quantity of bone in guided bone regeneration, which also is in accordance with the results of our study. Though there are a few systematic reviews and meta-analyses, the ones available could not provide conclusions due to the paucity of randomized controlled trials.

CONCLUSIONS

In terms of the stability of implants measured using RFA, the PRF and CGF groups showed a statistically significant increase in ISQ at the final outcome (week 12/16). Though statistically not significant, the change in the mean ISQ at week 4 was also better in the PRF and CGF groups, suggesting the positive role of platelet concentrates in cases requiring early loading. The application of platelet concentrate seems to enhance stability, but the intergroup results were not significant. The radiodensity/grayscale measurements showed a statistically significant increase in the control group at week 12/16. Upon comparing the three groups, no statistically significant difference was found in the quality (radiodensity/grayscale) and quantity (horizontal and vertical gap reduction) of bone regenerate formed. The concentration of VEGF was found to be significantly higher in PRF as compared to CGF. The concentration of TGF-β1 was nonsignificant and comparable in both the PRF and CGF. Thus, we could infer that platelet concentrates may help in the early healing phases by accelerating osteogenesis, but in the long term, control and experimental groups were comparable in terms of ISQ as well as bone density. Further studies with larger sample sizes are required to establish a conclusive correlation of growth factors in platelet concentrates with clinical and radiographic parameters.

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