



To evaluate and compare the synergetic effect of Cranberry extract with PRF versus the use of PRF alone in the treatment of Chronic Periodontitis: A Clinical and a Radiological study

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ABSTRACT

Background: Among the several types of periodontitis, chronic periodontitis is the utmost common form of periodontal disease which can progress with a slow rate but may have a sudden rapid rate of progression along with a remarkable bone loss. In terms of adequacy in sufficient periodontal regeneration, periodontal flap surgeries lack the potential and takes often a back seat. Several other regenerative methods have been promoted among which platelet rich fibrin (PRF) is seen to be most extensively used. It is an old and successful trend to either add PRF or to infuse it along with other drugs at the wound site to enhance periodontal regeneration. Several herbal products were used as an infusion with PRF in the past for the antimicrobial effect but no herbal products were used in the form of a synergetic agent with PRF for enhancing periodontal regeneration. Cranberry fruit, its origin is from North America has been much popular because of its essential ingredients for a good health. It has got a significant therapeutic potential as an antimicrobial agent and as an antioxidant agent, but been never used for enhancing periodontal regeneration. Hence, the current study's goal is to assess and compare the synergetic effect of Cranberry extract with PRF versus the use of PRF alone in the treatment of chronic periodontitis.

Materials and Method: A double blinded randomized clinical trial (RCT) was done with twenty subjects which included patients based on the selection criteria in the age group of 35 to 55 years having periodontal intrabony defects. The Control Group A received PRF alone and the Test Group B received PRF+CRN at the site of intrabony defects.

Subjects in each group were assessed for their clinical parameters such as probing pocket depth (PPD), relative attachment level (RAL), gingival index (GI), plaque index (PI) and radiographical parameters such as defect depth (DD), defect area (DA) and defect fill % (DF %) at baseline. The follow up period was decided according to the the previous studies at three, six and nine months respectively.

Results: There was a statistically significant enhancement in the clinical and radiographic parameters from baseline to three, six and nine months in each group. However, the treated group showed statistically significant than the control group. **Conclusion:** Within the limitations of the given study, use of PRF+CRN was efficacious in comparison to the use of PRF alone in the treatment of intrabony defect.

Keywords: *Cranberry extract, Platelet rich fibrin, Intrabony defect, Chronic Periodontitis*

INTRODUCTION

Chronic periodontitis is defined as an inflammatory state which results because of the interaction of the periodontal pathogens and immune responses from host resulting into the devastation condition of the periodontium. (1). The anaerobic microflora in matured plaque comprises of virulent periodontal pathogens from the red complex, and thus these virulence factors has been proven to play a substantial part in periodontal ailment. (2).

To start with the treatment part of chronic periodontitis, scaling and root planing (SRP) is the first line of treatment. Though, a few systematic reviews have shown an improvement in the periodontal status followed by SRP, however, it is also true that the nonsurgical periodontal therapy is unsuccessful in eliminating the pathogens from the deep seated intrabony defects. Surgical modes of periodontal treatment along with the PRF are much popular these days to accomplish periodontal regeneration which is the final goal of periodontal therapy (3). Studies have already established the additional benefits of PRF when used as an adjunctive with the surgical ways of treating periodontal diseases. PRF has steadily been displaying regenerative potential; it is simple, handy and reasonable biomaterial compared with bone grafts.(4). Like PRF, ample number of studies are showing successful outcomes with the adjunctive usage of herbal products along with the surgical procedures in treating periodontitis. This is because of no side effects and the therapeutic benefits, for example Aloe vera, Tea tree oil and Cranberry (5). Cranberry (CRN) (Vaccinium

macrocarpon) extract, has been used in the nonsurgical periodontal treatment described in many studies but there have been no studies till date, where CRN extract as an adjunctive has been used in the surgical periodontal treatment for treating intrabony defects.

The food industry has taken up the privilege of honouring Cranberry as the top most fruit on basis of healthy ingredients in it. The bioactive flavonoids all together with flavanols, anthocyanins and proanthocyanidins really displays its highest potential in health wellbeing.

The colonization of the biofilm and the adhesion to proteins by the red complex pathogens in the gingival sulcus is hindered by the non-dialyzable fraction of Cranberry (NDM). This results in the depletion of the bacterial coaggregation in periodontitis. Even the gingipain activity, the activity related to the fibrinogen attachment to various proteins of the *P.gingivalis* and trypsin like activity of the other organisms are heavily detained and thus the hindrance facilitated by the bacterial proteinases are devastated. (6)

In our present study, PRF was used as a control site. It enhances hard and soft tissue healing while protecting surgical and grafted site as it has strong fibrin architecture and slow release of growth factors which forms a resorbable natural bioactive membrane. Various classes of gingival recession, intrabony defects (IBDs) and periapical lesions have been treated with PRF in periodontics. (7).

But, however PRF lacks the antimicrobial property unlike Cranberry, which fails to remove the periopathogens such as *P. gingivalis*, *F.*

nucleatum and T. forsythia completely from the deep pockets, even though it can accelerate healing process. (9)(10) However, though Cranberry possess antimicrobial property, but it has never been used in periodontal regenerative surgery for treating intrabony defects. (8,11).

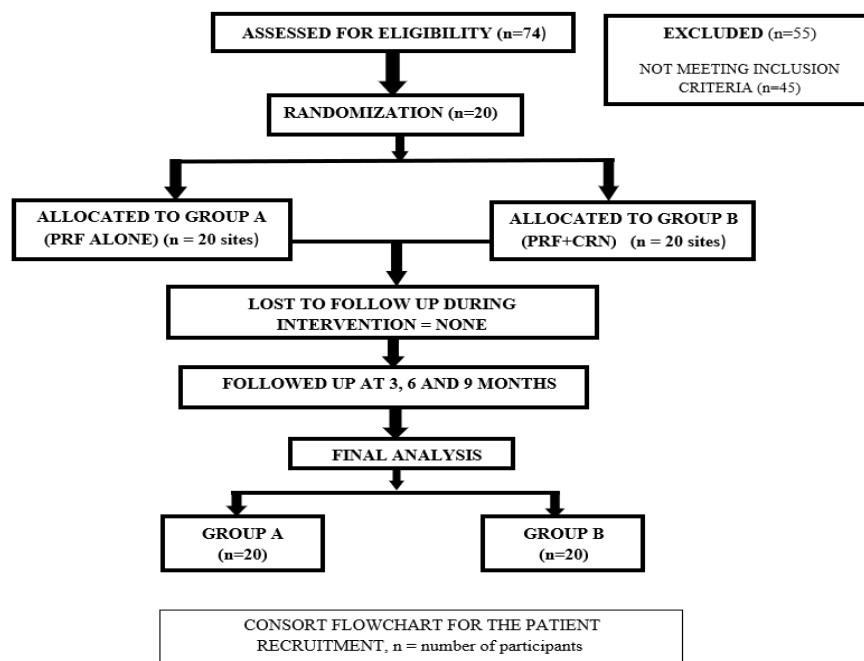
The purpose of the present study is to find the synergetic effects of cranberry with PRF if any in the treatment of chronic periodontitis. It was evaluated by assessing the enhancement in the clinical parameters along with the gain in radiological parameters in case of intrabony defects seen in chronic periodontitis.

MATERIALS AND METHOD

This current study was a double-blind, randomised controlled trial, which was conducted amongst the patients visiting the Department of Periodontics and Oral Implantology, IDS, SUM Hospital, S“O”A deemed to be University, Bhubaneswar, Odisha. The study was accepted, approved, and followed in accordance to ethical guidelines of Helsinki Declaration of 1975, as revised in 2000. The

ethical committee of IMS and Sum Hospital, S“O”A deemed to be University approved the study with IHEC no: /DMR/IMS.SH/SOA/180308. Periodontal assessment was done by recalling the patients who had followed very well the maintenance phase as advised by us. The size of the sample was at least 17 sites in the respective group which was valued to achieve 80 % power to detect mean difference of 1 mm in a two-tailed comparative test between the groups ($P \leq 0.05$) making the total no of sites required to be 34 sites. A plan for enrolment of 20 sites in respective group were recruited considering the possibility of drop-outs.

Total twenty individuals were selected with the inclusion criteria's and then were randomly allocated to the concerned groups via lottery system with the blind method. The study was carried out from April 2018 to August 2019. All surgical procedure was done by the same operator who was blinded to the allocation. Every individual signed a written informed agreement and was explained before time to their inclusion in the study. The individuals were designated on the source of the following norms.



The inclusion and exclusion norms for the study were as follows: To meet the requirements for inclusion, the contributors had to be with the age

range of 35-55 years with no systemic diseases. And the Probing pocket depth in the range of 5-7 mm after phase 1 therapy, with bilateral intra

bony vertical defect along with the radiographic evidence of vertical bone loss. Exclusion criteria were history with medically compromised status, pregnant and lactating women, allergic if any to medication, smokers, undesirable oral hygiene status, cases undergone periodontal surgeries.

All the contributors were sumptuously elucidated about the need, importance, and process of the study, and informed written agreement was attained from them after guaranteeing secrecy and privacy.

After screening of hundred subjects, twenty subjects were nominated on the source of selection norms. All subjects were arbitrarily divided into two groups with using lottery system such as Group A:Control site(n=20 sites) open flap debridement followed by assignment of PRF alone in the intrabony defects and Group B:Test site: (n=20sites) open flap debridement followed by placement of PRF infused with Cranberry extract in the intrabony defects.

The collected data at baseline, three months, six months and nine months postoperative were tabulated and analysed. The software used for the statistical analysis was SPSS (version 20, SPSS, Inc., Chigago, IL, USA). The statistical tests used were Paired Student's T test - for intra-group comparison, and unpaired Paired Student's T test - for intergroup comparison between control and test groups.

Once the PRF was prepared, commercially available Cranberry extract containing 100% juice concentrate (unsweetened) was procured

(Van Dyk's by Nature; Nova Scotia, Canada). Cranberry extract was kept in a fridge at a temperature of 10 degree to 18 degree Celsius. For infusion of Cranberry extract, freshly prepared PRF was suspended in 10 ml of Cranberry extract in a sterile dappen dish for 10 minutes.

Plaque index, (12) Gingival index (13), Probing pocket depth, Relative attachment level, Radiographic parameters like Defect Depth was calculated (From CEJ to apex of the radiographic defect), Defect Area: (Area between the CEJ of adjacent teeth and the apex of the radiographic defect), Defect Fill percentage: (Defect Area at Baseline - Post-operative Defect Area) X 100 divided by the Defect Area at baseline. The radiographic parameters assessed using an open-source Software program (ImageJ). All these parameters were measured at baseline, after 06 months and after 09 months post-operatively.

The RadioVisioGraphy Imaging System was used to record the radiological parameters at the baseline, at 03 months and 06 months by means of bisecting line angle technique. To add to the accuracy part in the bone fill linear measurement, standardized radiographic metal per unit square centimetre grid along with the dental films were used. The Defect Depth was measured digitally where the reference point remains the CEJ. The chosen flap procedure was the open flap debridement for easy accessibility to place PRF enriched Cranberry into the intrabony defect for treating Chronic Periodontitis.

Control Site Photographs



Figure 1: OCCLUSAL STENT AT THE SITE OF SURGERY



Figure 2: PD AND RAL AT BASELINE



**Figure 3: CREVICULAR
INCISION AT THE SITE OF
SURGERY**



**Figure 4: FLAP
REFLECTION SHOWING
INTRABONY DEFECT AT
THE SITE OF SURGERY**



**Figure 5: PRF PLACED AT
THE SITE OF DEFECT**



**Figure 6: FLAP
APPROXIMATED AND
SUTURE PLACED**



**Figure 7: COE-PACK
PLACED**



**Figure 8: 1 MONTH
FOLLOW UP**



**Figure 9: PD AND RAL AT
3 MONTHS FOLLOW UP**



**Figure 10: PD AND RAL AT
06 MONTHS FOLLOW UP**

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Figure 11: PD AND RAL AT 06 MONTHS FOLLOW UP

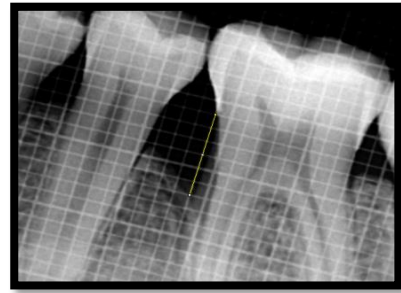


Figure 12: DEFECT DEPTH AT BASELINE

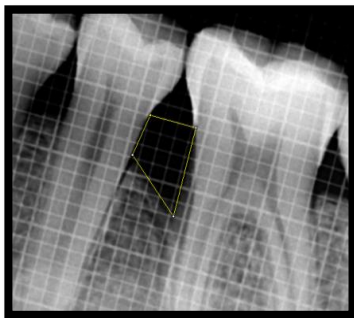


Figure 13: DEFECT AREA AT BASELINE

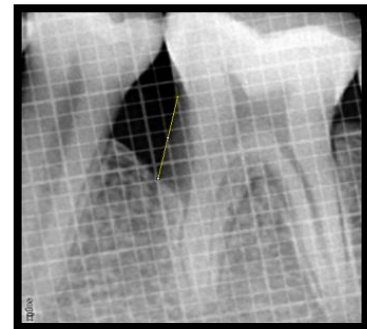


Figure 14: DEFECT DEPTH AT 06 MONTHS FOLLOW UP

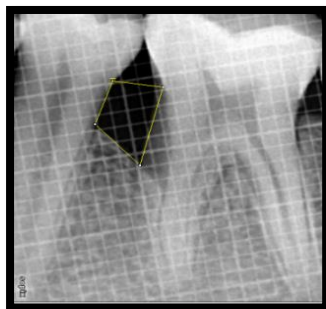


Figure 15: DEFECT AREA AT 06 MONTHS FOLLOW UP

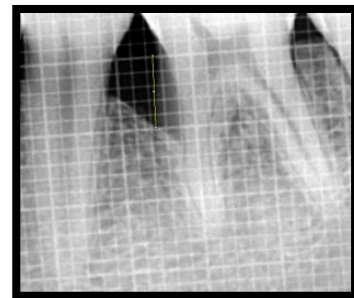


Figure 16: DEFECT DEPTH AT 09 MONTHS FOLLOW UP

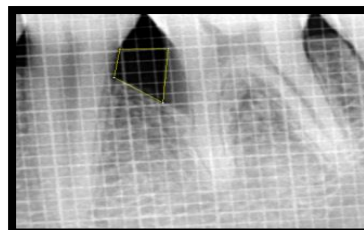


Figure 17: DEFECT AREA AT 09 MONTHS FOLLOW UP

Test Site Photographs



Figure 18: OCCLUSAL STENT AT THE SITE OF SURGERY



Figure 19: PD AND RAL AT BASELINE



Figure 20: CREVICULAR INCISION AT THE SITE OF SURGERY



Figure 21: FLAP REFLECTION SHOWING INTRABONY DEFECT AT THE SITE OF SURGERY



Figure 22: PRF INFUSED WITH CRN PLACED AT THE SITE OF DEFECT



Figure 23: FLAP APPROXIMATED AND SUTURE PLACED

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Figure 24: COE-PACK PLACED



Figure 25: AT 01 MONTH FOLLOW UP



Figure 26: PD AND RAL AT 03 MONTHS FOLLOW UP

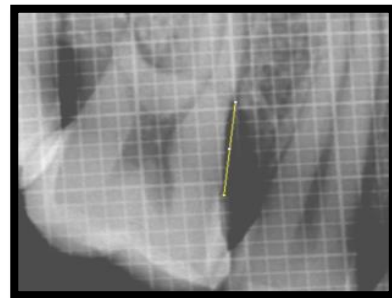


Figure 27: DEFECT DEPTH AT BASELINE

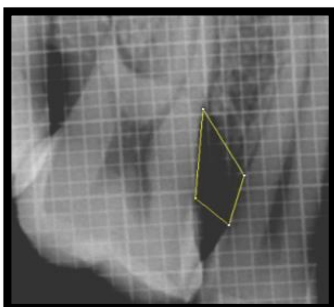


Figure 28: DEFECT AREA AT BASELINE

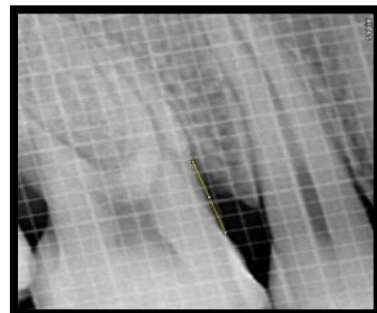


Figure 29: DEFECT DEPTH AT 06 MONTHS FOLLOW UP

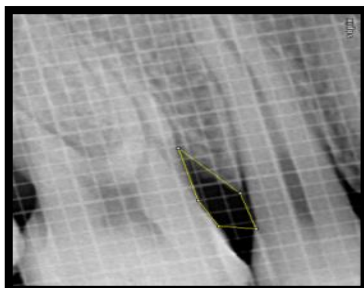


Figure 30: DEFECT AREA AT 06 MONTHS FOLLOW UP

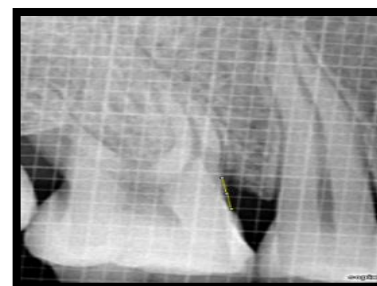


Figure 31: DEFECT DEPTH AT 09 MONTHS FOLLOW UP

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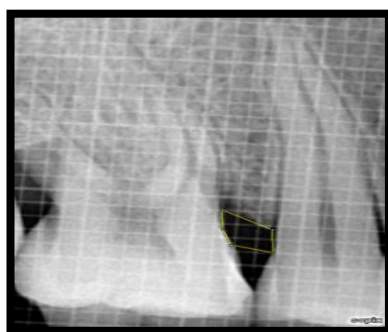


Figure 32: DEFECT AREA AT 09 MONTHS FOLLOW UP

TABLE 1: The baseline parameters of the included patients in both the groups

Parameters	GROUP A (PRF) MEAN ± SD	GROUP B (PRF+CRN) MEAN ± SD
PPD (AT BASELINE) (in mm)	6.60 ± .43	6.50 ± .33
RAL (AT BASELINE) (in mm)	12.50 ± 1.2	12.30 ± .99
FMGI (AT BASELINE)	0.875 ± .02	.925 ± .03
FMPI (AT BASELINE)	.899 ± .04	.833 ± .03
DD (AT BASELINE) (in mm)	3.560 ± .23	3.630 ± .24
DA (AT BASELINE) (in mm ²)	12.972 ± 1.33	13.447 ± 1.53

PPD- Probing Pocket Depth; RAL-Relative Attachment Level; FMGI: Full-mouth Gingival Index; FMPI: Full-mouth Plaque Index; DD-Defect Depth; DA-Defect Area

TABLE 2: Intergroup comparison of periodontal and radiological parameters at various time intervals in both the groups.

Parameters		Baseline		3 months		6 months		9 months	
		PRF	PRF+ CRN	PRF	PRF+ CRN	PRF	PRF+ CRN	PRF	PRF+CRN
PPD	N	20	20	20	20	20	20	20	20
	Mean	6.60	6.50	5.00	4.20	4.60	2.30	3.90	2.50
	SD	0.940	1.051	0.649	0.894	1.046	0.657	0.852	0.827
	Sgf	0.753	0.753	0.003	0.003	<0.001	<0.001	<0.001	<0.001
RAL	N	20	20	20	20	20	20	20	20
	Mean	12.50	12.30	10.80	9.70	10.40	8.30	9.70	8.30
	SD	1.051	0.923	1.361	0.923	1.789	0.923	1.658	1.031
	Sgf	0.527	0.527	0.005	0.005	<0.001	<0.001	0.003	0.003
GI	N	20	20	20	20	20	20	20	20
	Mean	0.875	0.925	0.700	0.725	0.500	0.600	0.425	0.500
	SD	0.236	0.257	0.153	0.291	0.162	0.170	0.164	0.198
	Sgf	0.527	0.527	0.736	0.737	0.065	0.065	0.201	0.201
PI	N	20	20	20	20	20	20	20	20
	Mean	0.899	0.833	0.676	0.618	0.551	0.482	0.487	0.437
	SD	0.293	0.304	0.193	0.225	0.196	0.151	0.200	0.164

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	Sgf	0.489	0.489	0.389	0.389	0.220	0.221	0.394	0.394
DD	N	20	20	-	-	20	20	20	20
	Mean	3.560	3.630	-	-	2.610	2.180	2.460	1.990
	SD	0.560	0.533	-	-	0.421	0.307	0.418	0.180
	Sgf	0.688	0.688	-	-	<0.001	<0.001	<0.001	<0.001
DA	N	20	20	-	-	20	20	20	20
	Mean	12.972	13.447	-	-	6.981	4.842	6.218	3.991
	SD	4.187	3.942	-	-	2.191	1.341	2.072	0.723
	Sgf	0.714	0.714	-	-	<0.001	<0.001	<0.001	<0.001
DF%	N	-	-	-	-	20	20	20	20
	Mean	-	-	-	-	44.349	63.411	50.254	68.837
	SD	-	-	-	-	15.095	5.894	14.274	6.7673
	Sgf	-	-	-	-	<0.001	<0.001	<0.001	<0.001

*P<0.001 Significant. Sgf-Significant. PPD- Probing Pocket Depth; RAL-Relative Attachment Level; FMGI: Full-mouth Gingival Index; FMPI: Full-mouth Plaque Index; DD-Defect Depth; DA-Defect Area;Df%-Defective Fill

It shows that the difference was statistically significant at 03 months,06 months and 09 months in the mean PPD and RAL between both the groups. The difference was statistically

significant in the mean DD, DA and DF% at 06 and 09 months between both the groups in the periodontal parameters such as the mean PPD and RAL

TABLE 3: Intragroup comparison of periodontal and radiological parameters at different time intervals in both the groups.

Parameters		Baseline to 03 Months		Baseline to 06 Months		Baseline to 09 Months		03 Months to 06 Months		06 Months to 09 Months	
		PRF	PRF+C RN	PRF	PRF+ CRN	PRF	PRF+C RN	PRF	PRF+ CRN	PRF	PRF+ CRN
PPD	Mean	1.600	2.300	2.000	4.200	2.700	4.000	0.400	1.900	0.700	-0.200
	SD	0.503	0.657	0.918	1.005	0.801	0.795	0.681	0.852	0.657	0.768
	Sgf	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	0.017	<0.001	<0.001	0.258
RAL	Mean	1.700	2.600	2.100	4.000	2.800	4.000	0.400	1.400	0.700	0.000
	SD	0.657	0.821	1.165	1.451	0.894	1.376	0.681	1.142	0.657	0.918
	Sgf	<0.001	<0.000	<0.001	<0.000	<0.001	<0.000	0.017	<0.000	<0.001	1.000
GI	Mean	0.175	0.200	0.37500	0.325	0.450	0.425	0.200	0.125	0.075	0.100
	SD	0.164	0.153	0.206	0.164	0.251	0.200	0.191	0.172	0.164	0.125
	Sgf	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	0.004	0.005	0.002
PI	Mean	0.222	0.214	0.347	0.350	0.411	0.395	0.124	0.135	0.064	0.044
	SD	0.140	0.127	0.265	0.280	0.277	0.274	0.164	0.185	0.093	0.054
	Sgf	<0.000	<0.000	<0.000	<0.000	<0.000	<0.000	0.003	0.004	0.006	0.002
DD	Mean	-	-	0.950	1.4500	1.100	1.6400	-	-	0.150	0.1900
	SD	-	-	0.459	0.3380	0.492	0.4524	-	-	0.082	0.1917

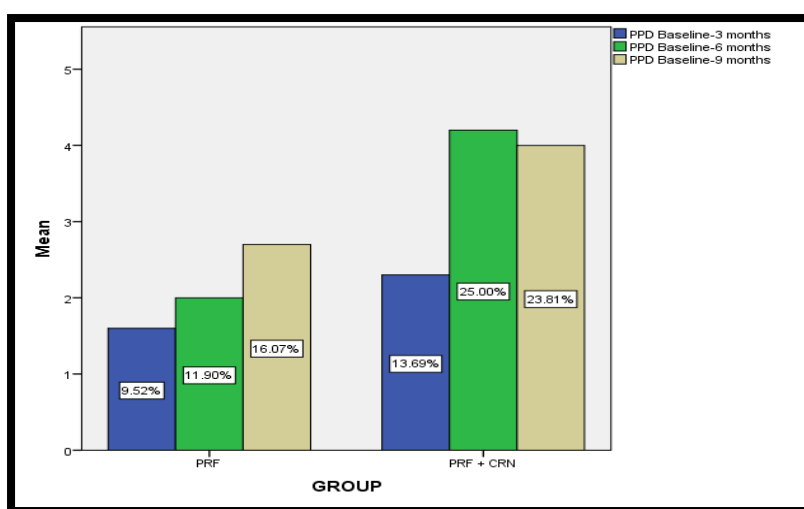
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	Sgf	-	-	<0.001	<0.001	<0.001	<0.001	-	-	<0.001	<0.001
DA	Mean	-	-	5.991	8.605	6.754	9.456	-	-	0.763	0.851
	SD	-	-	3.385	3.006	3.501	3.616	-	-	0.397	0.895
	Sgf	-	-	<0.001	<0.001	<0.001	<0.001	-	-	<0.001	<0.001

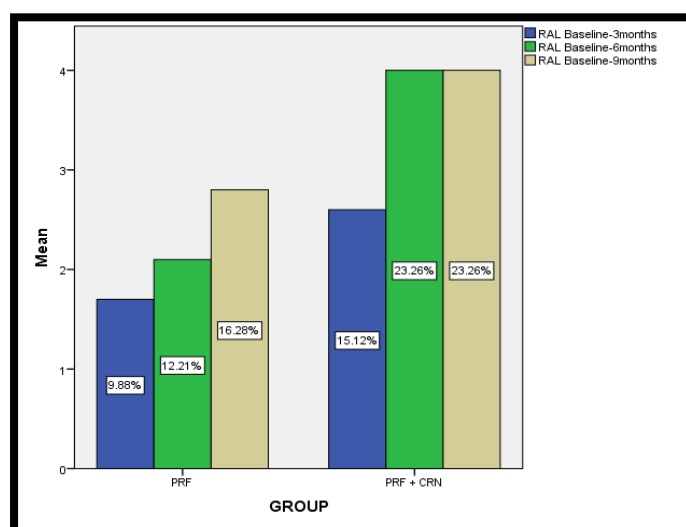
*P<0.001 Significant. Sgf-Significant. PPD- Probing Pocket Depth; RAL-Relative Attachment Level; GI: Gingival Index; PI: Plaque Index; DD-Defect Depth; DA-Defect Area.

It shows that there was a statistically significant difference in the mean PPD and RAL from three to six months followed by six to nine months in the control group. However, in the tested group, statistically significant difference in the mean

PPD, RAL was observed from three to six months only. Also, a statistically significant difference in the mean of the DD and DA from six to nine months was observed in the tested group.

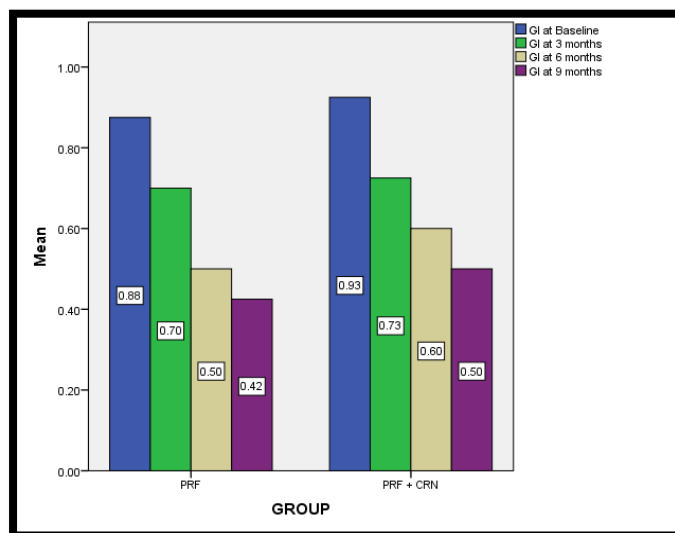


GRAPH 1: It shows the Intergroup PPD difference (%) at different time intervals in both the group

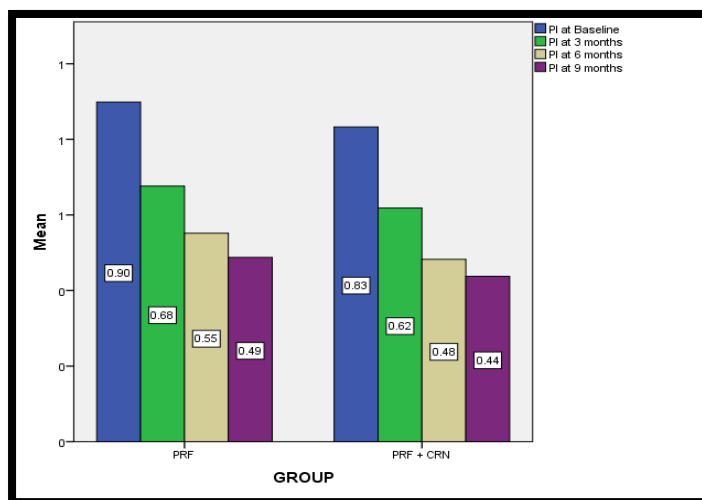


GRAPH 2: It shows the Intergroup comparison of RAL at different time intervals in both the groups

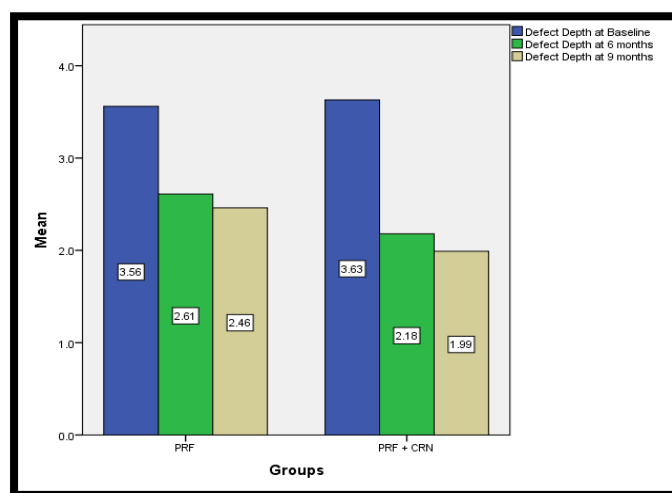
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GRAPH:3 It shows GI at different time intervals in both the groups.



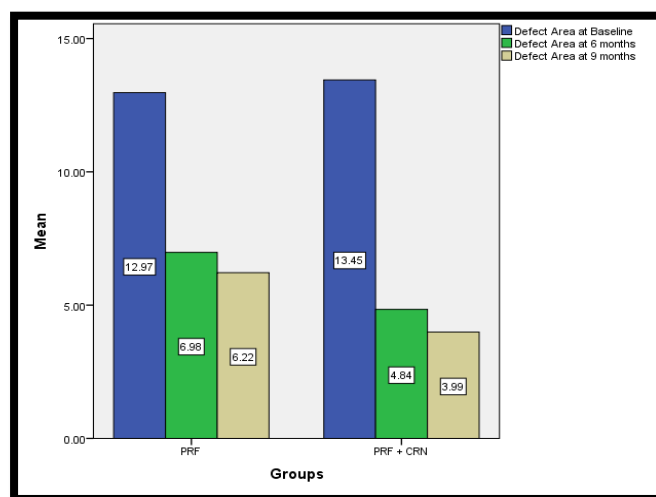
GRAPH 4: Intergroup comparison of PI at different time intervals in both the groups



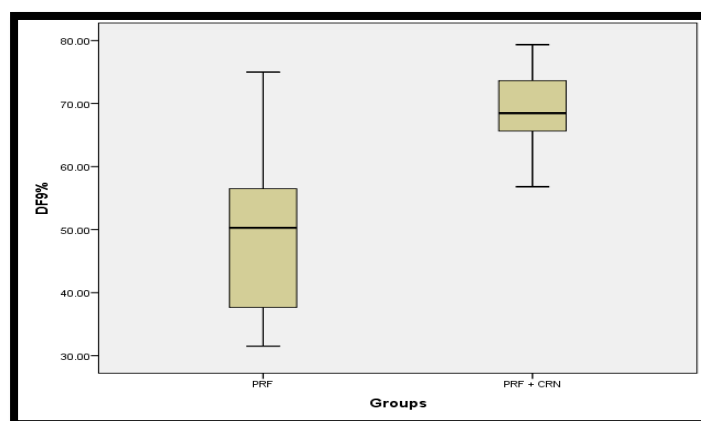
GRAPH 5: Intergroup comparison of DD at different time intervals in both the groups

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GRAPH 6: Intergroup comparison of DA at different time intervals in both the groups.



GRAPH 7: It shows the Intergroup comparison of DF% at 9 months in both the group

DISCUSSION

This randomised controlled study comprises of twenty patients with intrabony defects because of chronic periodontitis. They were treated with PRF enriched with Cranberry with follow up period at three, six and nine months respectively.

According to Nayak et al (03,04) PRF contains several growth factors which helps in periodontal regeneration with various degree of success. Our present study showed statistically significant difference at all the follow up periods in terms of the clinical parameters when compared with the baseline. Therefore, this study is agreeing with the literature with Nayak et al and also with the study conducted by Ajwani et al (14, 04) showing comparative evaluation of PRF versus only open

flap debridement in the treatment of two and three wall intrabony defects.

Ajwani et al shows statistically significant difference at nine months when compared from baseline for PI, SBI, PD and RAL and also observed statistically significant in gain when the defect was filled with PRF by open flap debridement and alone OFD. (14,17)

Another study, by Thorat et al (15,16), observed statistically significance in the clinical attachment level with PRF with OFD and alone OFD, which matches our present study.

The improvement in the clinical parameters (PI, PD, CAL, SBI, GML) was observed in the present study which was also reported in several

studies carried out by Chatterjee et al, Martande et al and Sharma et al (16-19)

Chadwick et al, (20) could observe a drop in the defect depth and defect area in the intrabony defects caused by chronic periodontitis, however a gain in the defect fill with PRF compared with the DFDBA at the follow up period of six and nine months respectively which supports our present study.

Ganesh et al (21) observed a reduction in the defect depth and bone fill percentage in case of OFD with PRF and alone OFD. The concluding part here was the adjunctive usage of PRF in the conventional open flap debridement could be a better option in treating intrabony defects due to its synergetic effects. This is very much in consistent with our present study when assessed radiographically (21).

Reduction in intrabony defect depth and gain in bone fill when treated with PRF in intrabony defect was observed which is in consistent with our present study along with the study by Bajaj et al, Kumar et al and Rosamma et al, (11, 21, 22).

In the present study, there was a statistically significant difference in plaque index at three, six and nine months when treated with PRF enriched with Cranberry with an intent to treat intrabony defects in chronic periodontitis. This supports the in-vitro study conducted by Labrecque et al, which states, cranberry non-dialyzable fraction is a potent hindrance of biofilm formation by *P.gingivalis*, but does not affect the development or viability of bacteria. (10).

The reduction of PI in the treated site also in agreement with the other study carried out by Yamanaka et al, (23), in an vitro study, which found a phenol fraction from cranberry juice in concentration of 250 and 500 µg/ml resulted in a significant drop of the formation of biofilm of the red complex pathogens.

It was observed from the study by Bodet et al (25, 27), the NDM fraction from the cranberry blocks the capability of *P.gingivalis* by degrading its protein contents which stops its reproduction (25). Along with it, also inhibits LPS -induced MMP-3 and MMP-9 production which are

known for the destructive enzymes in periodontal disease. This study hence supports our present study showing statistically significant reduction in PPD, RAL, GI and PI for the treated group when compared with the control. Also, statistically significant in the radiographic parameters with defect depth and defect area and defect percentage fill at six and nine months follow up) in the treated group.(28)

Since there are no studies reported for the comparison of autologous PRF and cranberry extract in the treatment of intrabony defects, therefore a straight assessment with other studies was not possible.

Therefore, the results obtained in the present study shows cranberry extract has an adjunct effect when used along with PRF in the treatment of intrabony defect when compared with PRF alone. Keeping in mind the present study results, it is considered that the cranberry extract can be a boon in terms of therapeutic option in the treatment of chronic periodontitis.

The limitation of the Cranberry from the previous studies was found that the pre-formed biofilm formed was not successfully broken down to hinder the bacterial growth. However, they effectively inhibited the formation of *Porphyromonas gingivalis* and *Fusobacterium nucleatum* at a concentration equal to or > 62.5 µg/ml. (09, 24). The periodontopathogen proteinases is affected by the cranberry NDM fraction in a dose dependent manner inhibiting the gingipain activities of *Porphyromonas gingivalis*, the trypsin – like activity of *Tannerella forsythia* and the chymotrypsin – like activity of *Treponema denticola*

However, the limitations of the present study include advanced imaging techniques such as CBCT and CADIA which could have been used in place of RVG for assessing appropriate defect dimensions. Another limitation of the present study says that further studies may be carried out using varying concentration of cranberry extract along with other autologous platelet concentrates such as PRP, injectable-PRF, PRGF etc. as an adjunct to surgical intervention.

CONCLUSION

In recent years, there have been many clinical studies on cranberry extract used in the treatment of nonsurgical periodontal therapy but till date, there has been no such clinical trial using cranberry extract in surgical treatment of periodontal disease. Therefore, to our knowledge, this is the first kind of its study to evaluate and compare the synergetic effect of platelet rich fibrin (PRF) infused with cranberry extract versus the use of platelet rich fibrin alone in the treatment of chronic periodontitis, in both clinical as well as radiological parameters.

Taking into consideration the present study limitations, it may be resolved that an adjunctive use of cranberry extract with PRF revealed significantly improvement in the clinical and radiographic parameters in management of chronic periodontitis.

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