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Comparative Evaluation to Assess the Effect of SRP With or Without Human Placental Extracts as Local Drug Delivery in Treatment of Localized Periodontal Pocket- A Randomized Controlled Clinical Trial

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Abstract

Background: Periodontal disease is one of the most prevalent global chronic disorder. Pathology affecting the structure surrounding teeth results in inflammation initiated by bacterial aggregation & alteration in their profile. Conventional periodontal therapeutics has focused on the control of etiologic agents, thereby promoting healing & repair of tissues. Delivery of therapeutic agents into the local milieu act as drug reservoirs which could alter pathogenic flora & promote its repair & wound healing. **Aim & Objective:** In an effort to develop a novel therapy, the present study aims to compare clinical soft tissue parameters around periodontal pockets treated with & without human placental extracts delivered locally. **Materials & Method:** In 10 patients of chronic periodontitis, bilateral localized periodontal pockets of 4-6 mm depth were included. Each site was randomly allocated to group 1 & group 2,where in group 1, scaling & root planing(SRP) was done while in group 2,Placentrex Gel (Human placental extracts) adsorbed on absorbable gelatin matrix (Abgel) used as a vehicle was delivered as an adjunct to SRP . Clinical parameters were recorded & re- evaluated after one month for both the treatment groups . Statistical analysis was carried out to evaluate the effect of Placentrex gel as an adjunct to SRP in treatment of periodontal pockets, Mann Whitney & Paired t test were done. **Results:** There was a statistically significant improvement in clinical parameters with notable difference in probing depth reduction & gain of clinical attachment level in the treatment group subjected to SRP & Placental extract delivery. **Conclusion:** Clinical variables showed a greater efficacy of SRP & adjunctive use of placental extracts as compared to conventional treatment by SRP thereby underlying placental extracts usage in the management of periodontal disease condition

Keywords: Human placental extracts, Periodontal Pockets, Periodontal disease.

INTRODUCTION

Periodontal Disease is one of the most prevalent global chronic disorder. Pathology affecting the structure surrounding teeth results in inflammation initiated by bacterial aggregation & alteration in their profile [1]. Conventional periodontal therapeutics has focused on the control of etiologic agents thus promoting healing & repair of tissues [2]. Delivery of therapeutic agents into the local milieu act as drug reservoirs which could alter pathogenic flora & promote its repair & wound healing.

Over the years main stay of wound therapy has been anti-microbials that exerts a control over the infection but has no direct role on tissue regeneration, new vessel formation, epithelialisation leading to the closure of wound. There is a lacuna of medications that directly brings about wound healing, among which are Human Placental extracts - obtained from fresh term healthy human placentae tissues containing : Fibronectin Type III like peptide; fragments of nucleotides PDRN (polydeoxyribonucleotide), NADPH (Nicotinamide adenine dinucleotide) etc; aminoacids-glutamate; a water-soluble peptide with CRF (Corticotropin releasing factor) like activity .

It has been well substantiated that wound healing is a process where different events operate in overlapping phases of inflammation, proliferation with the foundation for the subsequent rebuilding of healing tissue. In proliferation phase, a filament or template with tissue matrix forms initially made up of fibrinogen and fibronectin [3-5].

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Human Placental extracts claims to directly facilitates the process of wound healing through these active biomolecules . It has been reported earlier that human fibronectin type III peptide also has high efficacy of stimulating cell migration and wound repair. [6] In the periodontal milieu as a potential enhancer of wound healing placental extracts could be a promising novel therapy.

Based on Fluorescent screening,'Human Placental Extracts' have content of biologically active NADPH facilitating nitric oxide mediated wound healing, NitrousOxide helps in debriding necrotic tissues, killing bacteria & promoting re-epithelialisation [7, 8]

An in-vitro study by Akagi & co-workers, an increased type I collagen production &increased anti-inflammatory activities by the effect of human placental extracts on human gingival fibroblasts have been demonstrated. Also, it hinders the IL-6 (osteoclastic) &IL-8 secretion, thus exhibiting an osteogenetic & angiogenic potential [9].

The present study with a split mouth design was directed to analyse the effect of Scaling and Root planing (SRP) alongwith human placental extracts on clinical soft tissue parameters recorded in patients of chronic periodontitis versus the conventional treatment by SRP only.

MATERIALS & METHOD

The present double blinded,split mouth randomized clinical trial was conducted as per the Helsinki guidelines, both examiner and patients were not known of the treatment intervention in test and control sites, ethical clearance for the study was obtained from the institutional ethical committee with the IEC Ref.No.Director-PG Studies/ITSCDSR/L/2018/102 . [10] Verbal & written informed consent was obtained from all the patients. Ten Patients (five male & five female) reporting to the Department of Periodontics, I.T.S Dental College, Hospital & Research Centre, Greater Noida, Uttar Pradesh of age range 20-45 years, with 20 or more number of natural teeth having bilateral suprabony pocket of 4mm-6mm were included in the study.

Exclusion criteria: included patients with known systemic conditions like Diabetes, hypertension, atherosclerosis and other conditions known to affect periodontal status adversely, patients suffering from aggressive periodontitis, pregnant and lactating women, known deleterious habits like alcohol consumption, tobacco, any form of periodontal therapy in past six months,& antimicrobial therapy in past 3 months.

Each site was randomly allocated by random sampling (generated by random.org)[11] to group 1 (test sites) & group 2 (control sites),where in group 1 subgingival scaling & root planing with ultrasonic scaler (woodpecker UBS-J Piezoelectric scaler), along with 1ml of human placental extracts gel (Placentrex – the original research product of Albert David Limited, India, a drug obtained from fresh term healthy human placentae) (Fig.1) adsorbed in 30 beads of gelatin foam

(Abgel, Sri Gopal Krishna Labs,Pvt.Ltd. India)(Fig.2) of 1sq.mm were placed into the suprabony pockets of 4mm-6mm locally with the the help of a cannula or syringe (fig.3) and gel was inserted with the help of a probe to fully fill the sulcus to the deepest point (fig.4) & coepak was placed and patients were recalled after seven days to remove the coePak. . While in group 2, subgingival scaling & root planing was performed, the pocket was allowed to heal with secondary intention. Both the groups were barred from probing for six weeks.

Following clinical parameters were assessed at baseline and reevaluated after six weeks period at both the sites of the two treatment arms: Plaque index (Silness &Loe) 1964 [12] ; Gingival index (Loe &Sillness 1963) [13]; Pocket probing depth (PPD) [14]; Relative attachment level(RAL) [14]

Technique to ascertain the Probing Pocket Depth (PPD) and Relative attachment Level (RAL) at the treatment sites : A customized acrylic stent was fabricated for each patient for providing a reproducible insertion axis for the probe. The stent was grooved in an occluso-apical direction for the above mentioned purpose. The following clinical parameters were recorded to the nearest millimeter with the help of a Hu Friedy UNC 15 probe.

Measurements were taken from stent to deepest probing depth to record Probing pocket depth (PPD) while Relative Attachment level (RAL) were recorded by subtracting the length of deepest probing depth from stent by the length from stent to cemento-enamel junction (fig.5,6).

Statistical Analysis

All statistical calculation were performed through SPSS for Windows (Statistical product & service solution 2010, IBM inc. Chicago version 21.0). Mean values with std. deviation were used for data interpretation. Mann Whitney U test, Wilcoxon Paired rank sum test & Paired t test were used for comparative analysis of data.

RESULTS

Each of the 10 patients ((20 sites) with mean age of 33 years, 5 males & 5 females completed the study. Both treatment arms showed improvement in site specific GI & PI scores, but improvement was not statistically significant between the groups from baseline to one month (Table 1& 2).

Table 1: Comparison of mGI between test and control groups

GI		N	Mean	Std. Deviation	
Pre	Test site	10.00	2.08	0.42	0.655, NS
	Control site	10.00	2.06	0.41	
Post	Test site	10.00	1.01	0.30	1.000, NS
	Control site	10.00	1.01	0.30	

Table 2: Comparison of mPI between test and control groups

PI		N	Mean	Std. Deviation	
Pre	Test site	10.00	1.70	0.39	0.317, NS
	Control site	10.00	1.78	0.36	
Post	Test site	10.00	1.16	0.12	1.000, NS
	Control site	10.00	1.16	0.12	

Clinical parameters MPPD & mRAL also showed no differences in both groups at baseline, but there was a significant reduction in MPPD & mRAL gain at 6 weeks ($p<0.005$) in test group (group 1) (Table 3 & 4).

Table 3: Comparison of MPPD between test and control groups

MPPD		N	Mean	Std. Deviation	
Pre	Test site	10.00	5.00	0.67	0.009, S
	Control site	10.00	4.60	0.52	
Post	Test site	10.00	2.70	0.67	
	Control site	10.00	3.80	0.92	

Wilcoxon paired rank sum test

Table 4: Comparison of mRAL between test and control groups

RAL		N	Mean	Std. Deviation	
Pre	Test site	10.00	9.90	0.88	0.007, S
	Control site	10.00	9.60	1.07	
Post	Test site	10.00	8.00	1.15	
	Control site	10.00	9.00	1.33	

Wilcoxon paired rank sum test

Comparative evaluation of all clinical parameters is listed below (Table-5).

Table 5: Intergroup comparison of absolute reduction in MPPD, RAL gain, GI & PI

Absolute reduction in	N	Test sites		Control sites		P value
		Mean	Std. Deviation	Mean	Std. Deviation	
MPPD	10.00	2.30	0.67	0.80	1.03	0.006, S
RAL	10.00	1.90	0.99	0.60	1.17	0.009, S
GI	10.00	1.07	0.31	1.05	0.31	0.655, NS
PI	10.00	0.54	0.37	0.62	0.38	0.317, NS

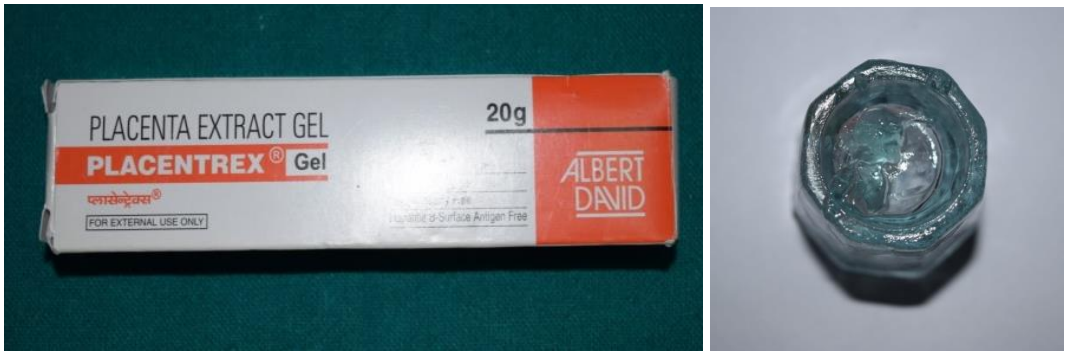

Figure 1: Human Placental Extracts(Placentrex) in gel form

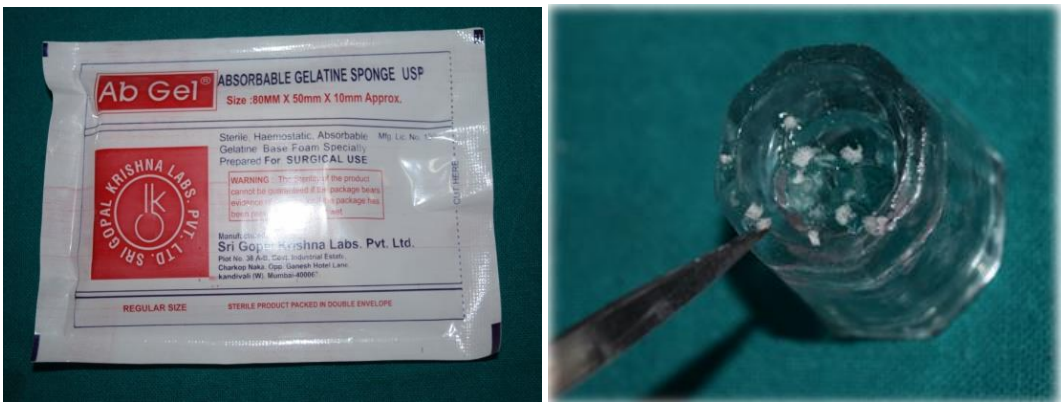

Figure 2: 1 ml PLACENTREX is adsorbed in 30 beads of ABGEL 1sq.mm

Figure 3: In-situ gel mixture carried in syringe

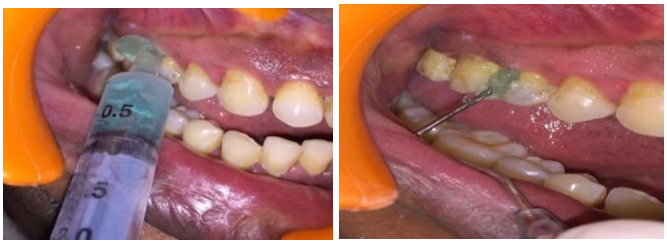

Figure 4: PLACENTREX is locally delivered to the periodontal pocket. Gel was inserted with the help of a probe to fully fill the sulcus to the deepest point

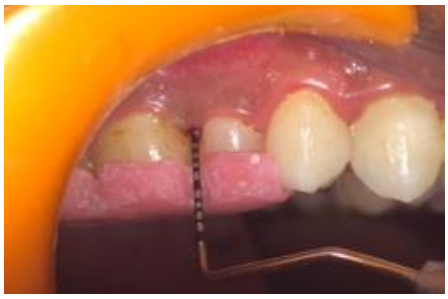

Figure 5: Pre-Op RAL=(8-5)mm=3mm PPD = 8mm with stent as reference point. (PPD=4mm without stent as reference point, here reference point was gingival margin)

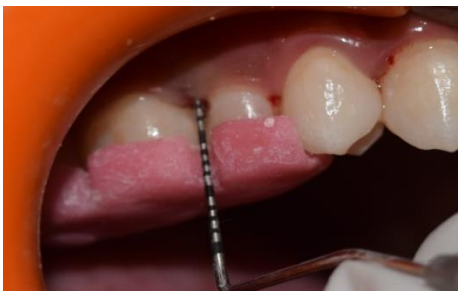

Figure 6: Post-Op RAL=(6-5)mm=1mm PPD=6mm with stent as a reference point. (PPD=2mm without stent as reference point, here reference point was gingival margin)

DISCUSSION

Periodontal inflammation of the supporting tissues of the teeth is usually a progressively destructive change leading to loss of bone and periodontal ligament characterized by an extension of inflammation from gingiva causes deepening of gingival sulcus into the adjacent bone and ligament.[15] Biologic treatment in periodontics are evolving at a rapid pace where newer modalities like BMPs, platelet rich concentrates are widely used to promote wound healing.

The present study was first of its kind with the used protocol, where the effect of human placental extracts application in adjunct to non-surgical periodontal therapy were evaluated on clinical parameters like PD and RAL in moderate periodontitis patients. Ten Patients with two suprabony pockets of 4-6mm of depth;=usually responsive to non surgical periodontal therapy i.e Scaling & Root Planing (SRP) were taken at the baseline, both the sites received SRP while one of the site received human placental extracts as an adjunct and soft tissue parameters like GI,PI,PD &RAL were evaluated again after six weeks permitting adequate time for both epithelial and connective tissue healing, so that one can accurately assess the periodontal condition at the end of Phase I therapy. Gingival inflammation usually decreases or is eliminated within 3 to 4 weeks after removal of calculus and local irritants [14].

To increase the substantivity of placental extracts within the pocket, it was made adsorbed to ABGEL (Absorbable Gelatin Sponge USP) -A non-toxic, non-allergenic, non-immunogenic, and non-pyrogenic, hemostat, already gamma-sterilized. The sponge is easily cut to fit the bleeding surface usually, here thus was easily used to fit within the periodontal pocket.
The gelatin sponge containing human placental extracts gel was inserted firmly in the pocket,where it became fixed within a short period of time.

AbGel can be left in situ and it gets fully absorbed. It usually **absorbs** 40-50 times, its weight of whole blood and adheres easily to the bleeding site. Its uniform porosity guarantees a favourable haemostasis. When implanted *in vivo*, it is completely absorbed within 3-5 weeks thereby it solved the purpose as a suitable carrier for placental extracts gel in this study.

It was observed that human placental extracts were well tolerated by all the subjects with no reported adverse effects like allergy, burning sensation swelling or discoloration etc.

It was noted that mean GI & PI scores were improved in both the groups however failed to reach statistical significance difference between group1 and group 2.However,clinical parameters like PD & RAL showed no differences in both groups at baseline, but there was statistically significant reduction in PD & RAL gain at 6 weeks in group 1.

The results are in corroboration with some observations of the study by Calvarano *et al* (1989) [16] in 15 patients with different chronic periodontitis, who had been treated with topical and intramuscular application of placental extract close to the typical therapy & the results, reached after two months, had been satisfactory, whether for the inflammation or for the distrophic forms of periodontal disease.

Akagi *et al* (2016) [9] also demonstrated that human placental extracts increased collagen type-1 production, linking to the regenerative capabilities of periodontal tissue, on primary human gingival fibroblasts *in vitro*.

Additional studies including a bigger sample size are required to further elucidate the benefits and shortcomings of using human placental extracts in periodontal treatment, though its uses for many other odontostomatological disease has been well established. For instance, placental extracts have also been used in the management of radiation-induced oral/oropharyngeal mucositis and especially in controlling subjective symptoms [17]. We postulate that placentrex aids in initiating a healing response.

To the best of our knowledge this trial is the first *in vivo* investigation for the treatment of periodontal diseases by human placental extracts sustained over time with no reported complications like allergies, burning sensations etc. Thus, characterization of various components

presents in placental extracts and correlating them with their therapeutic actions provides the future avenues for various studies.

CONCLUSION

The treatment was effective in the patients treated with SRP and placental extracts as an adjunct, clinical variables like PPD & RAL showed statistically significant improvement as compared to conventional treatment by SRP thereby underlying placental extracts usage in the management of periodontal disease condition. It was thus concluded that placenta is a valuable drug clinically applicable in the odonto stomatological field. Identification of biologically active components in placental extracts, which play significant role in wound healing also needs to be addressed.

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Nil.

Conflict of Interest

The authors declare no conflict of interest.

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