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Efficacy of Intra-Pocket Application of Two Antimicrobial Agents as an Adjunct to Mechanotherapy of Chronic Periodontitis (a Comparative Study)

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Key words
intra-pocket antimicrobial , mechanical treatment, chronic periodontitis.

Abstract

Numerous studies have been performed to evaluate the effectiveness of the use of locally delivered antimicrobials as an adjunct to mechanotherapy in treatment of chronic periodontitis. Some studies were resulted in improved clinical outcomes and others were not. The aim of this study is evaluation of the efficacy and safety of subgingival application of a (10 mg metronidazole gel), (1% chlorhexidine collagen gel) and (CHLOSITE® GHIMAS, Italy) gel which is a combination of two chlorhexidine formulations: 0.5% chlorhexidine digluconate and 1.0% chlorhexidine dihydrochloride), as an adjunct to mechanical treatment (scaling and root planing) (SRP) of chronic periodontitis. A total of 120 sites from 15 patients with age range of (24-55 years), who had periodontal pockets measuring 5-9 mm and had been diagnosed as chronic periodontitis cases, were selected for the study. The 4-quadrant split-mouth design was used in this study. The pocket sites in each patient were randomly assigned to 4 groups (30 sites for each):
(Group A) GA=(SRP) only.
(Group B) GB=(SRP) + 10 mg metronidazole gel.
(Group C) GC=(SRP) + 1% chlorhexidine collagen gel.
(Group D) GD=(SRP) + CHLOSITE®
Clinical parameters including (plaque index PI), (gingival index GI), (gingival bleeding index) GBI, (probing pocket depth PPD) & (clinical attachment level CAL) were measured and recorded at baseline before any treatment at (day 0) then the treatment was performed at the same day, The clinical parameters were also recorded at (day 30) & (day 90), in the selected sites of the four groups. The results of this study obviously showed a statistically significant reduction of all clinical parameters in all groups at (day 30 & day 90) from the base line (day 0). GD=(SRP) + CHLOSITE® revealed a reduction of the clinical parameters than groups (A, B and C) and the differences were highly statistically significant.

Introduction

Chronic periodontitis is a highly prevalent disease affects many adult and young populations, sometimes it is severe enough to cause tooth loss. Periodontal diseases are initiated by subgingival periodontal pathogens in susceptible periodontal sites [(1)]. Periodontal disease is an infectious disease that results in destruction and degradation of the periodontal tissues by the local action of periodontopathogenic microorganisms.

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These microorganisms release substances that strictly destroy periodontal tissues, in addition to inducing tissue damage by inflammatory and immunologic responses of the host [2]. The treatment of periodontal disease is based on pathogenic microbiota reduction by scaling and root planing. However, mechanical therapy used alone may fail to eliminate pathogenic bacteria that are placed into the soft tissue, and also in inaccessible areas to periodontal instruments, such as furcation area and root depression [3]. The bacteria in the subgingival area are organized in a complex microbial biofilm. These biofilms are matrix-enclosed bacterial populations that are adherent to each other and/or surfaces or interfaces [4,5]. These microbial plaques are extraordinarily persistent, difficult to eliminate, and play a vital role in periodontal disease [6]. Physical disruption of microbial plaque through hand or powered instrumentation is an effective way of eliminating biofilms. However, reinfection of periodontal pockets from recolonization of putative bacteria can occur within 60 days after mechanical therapy [7,8].Therefore, there is a demand for treatment strategies aiming primarily at suppressing or eliminating specific periodontal pathogens include local and systemic administration of antimicrobials [9]. After systemic intake of antimicrobial drug and in order to obtain an effective concentration of the antimicrobial drug which would reach the microorganisms in the periodontal tissues, repeated intake is required over a prolonged period in addition to the risks of side effects of systemic administration of antibiotics [10]. Sigusch, et al. (2001) reported that the administration of systemic antibiotics, even when preceded by complete removal of supra and subgingival irritants, did not lead to satisfactory overcomes with regard to the reduction of probing depth, to the clinical attachment gain, as well as to bacterial elimination, unless a re-instrumentation of the affected sites would be performed in an additional session [11]. So that, the advantage of a locally delivered drug is that it can be placed adjacent to disease sites in the periodontium, leaving other parts of the body unaffected. Another biggest benefits of any locally delivered drug is that it does not require patient compliance for regular drug intake. The clinicians placed the drug, which releases the antimicrobial agent for an extended period of time at a steady pharmacological level [12-14]. Among the antimicrobial agents, metronidazole, doxycycline, minocycline, chlorhexidine, stannous fluoride and others have been used by subgingival application with gel forms or other sustained-release local delivery systems (varnishes, chips or fibers). However, studies on antimicrobial agents gels are often contradictory in terms of improvement in clinical parameters. Chlorhexidine (CHX) is one of the most favorable choices among all the disinfectants currently in use. Chlorhexidine binds strongly to bacterial cell membranes. At low concentration, (CHX) increased permeability with leakage of bacterial intracellular components including potassium. At high concentration, chlorhexidine causes precipitation of bacterial cytoplasm and cell death. In addition, it is a broad-spectrum bactericidal agent against both Gram (+) and (−) bacteria. Its propensity to bind to the surface of tissues offers a long-lasting antimicrobial effect [15]. Its mechanism of action includes reduction pellicle formation, alteration of bacterial adherence to teeth, and alteration of bacterial cell walls which causes cell lysis [16] . A new xanthan-based syringable gel system: CHLOSITE® (GHIMAS, Italy), has been introduced recently. This gel contains a unique combination of two chlorhexidine formulations: 0.5% chlorhexidine digluconate and 1.0% chlorhexidine dihydrochloride. Metronidazole is bactericidal to anaerobic organisms and is believed to disrupt bacterial (DNA) synthesis in conditions with a low reduction potential. It is effective against anaerobes such as Porphyromonas gingivalis and Prevotella intermedia. Metronidazole has been used systemically and locally to treat necrotizing ulcerative gingivitis (NUG) and aggressive periodontitis. Locally, it has been used subgingivally as monotherapy and the results were similar

to SRP alone [4] . Metronidazole is applied locally in viscous consistency to the pocket, where it is liquidized by the body heat and then hardens again, forming crystals in contact with water. As a precursor, the preparation contains metronidazole-benzoate, which is converted into the active substance by esterases in gingival crevicular fluid [4,8]. In numerous studies, metronidazole gel and chlorhexidine gel have been used as an adjunct to mechanical treatment SRP with controversy and conflicting results were found, therefore, the present study was carried out to evaluate the efficacy and safety of local application of metronidazole gel & 1% chlorhexidine collagen gel and (CHLOSITE® the new xanthan-based chlorhexidine) as an adjunct to (SRP) in the treatment of chronic periodontitis and compare this treatment modality with (SRP) alone.

Materials and Methods

A total number of 15 patients aged 24-55 years diagnosed with chronic periodontitis and having pocket depths ranging from 5 to 9 mm as well as radiographic evidence of bone loss, were selected for the study from the private clinic of the researcher. The patients were willing to take part in this study and maintain follow-up visits regularly.

Exclusion Criteria for Patient Selection

1-Patients having systemic diseases like diabetes mellitus, hypertension, bleeding disorders, pregnancy and lactation.
2- Patients who have had periodontal treatment in last six months.
3- Antibiotic therapy within 6 months prior to treatment. 4- Patients with medical or dental therapy scheduled or expected to occur during the course of this study that could have an impact on the subjects ability to complete the study.

A total number of 120 sites from 15 patients were selected for the study. The patients having non-adjacent interproximal sites (to avoid carry-across or spillover effects). The duration of the study was for 90 days for each patient. For all patients, general, oral and full mouth periodontal examination was carried out. On screening day (day 0), patient evaluation and the study variables were recorded at baseline day (day 0) before treatment to provide baseline data.

The Following Parameters were Recorded

Plaque index (PI), Gingival index (GI), Gingival bleeding index (GBI), Probing pocket depth (PPD) & clinical attachment level (CAL). The pocket sites were grouped and treated as follows:
Group A (GA) - Comprised of 30 sites; only SRP was done at the baseline visit.
Group B (GB) - Comprised of 30 sites; SRP + (10 mg metronidazole benzoate gel Metrogyl) was injected subgingivally at the baseline visit.
Group C (GC) – Included 30 sites; SRP + (1% chlorhexidine collagen gel) was injected subgingivally at the baseline visit.
Group D (GD) – Composed of 30 sites; SRP + CHLOSITE® gel was locally applied at the baseline visit.
During 21 days, the patients in groups B,C&D were submitted to weekly subgingival delivery which started at the first visit after SRP (0, 7, 14, 21 days). The irrigated areas were isolated with cotton rolls and the tissues were air dried. Subgingival delivery was performed with a plastic disposable syringe & curved thin plastic needle. This procedure continued until the pocket was completely filled. After insertion of the local drug delivery system, the patients were advised not to eat hard food that could traumatize the gingiva. They were also advised not to brush the treated areas for 12 hours or to floss or use interproximal cleaning devices for ten days. The four groups were again examined on the 30^{th} & 90^{th} day. During these visits, all clinical parameters, were measured and recorded again. During the study period, the patients were instructed to continue regular tooth brushing and interdental cleansing. They were also instructed not to use any mouth wash during the study period.

Statistical Analysis

Mean values and standard deviations were calculated from the samples for each study group. Mean values were compared by Student's independent *t*-test/Student's paired *t*-test wherever appropriate. The proportion of positivity of the gingival bleeding index was compared between test groups by Pearson's chi-square test. In the present study, $P < 0.05$ was considered as the level of significance. The difference was considered as significant when the P-value is < 0.05.

Results

Table 1 shows the mean values & standard deviation of the (PI) in the 4 groups of the study and it is obvious that the mean values of (PI) in GA, GB, GC and GD were similar at base line (day 0) with no significant difference among them. The mean values of (PI) in GA, GB, GC and GD at day 0 were 2.52, 2.44, 2.41 and 2.3 respectively. While at day 30 the mean values of (PI) were 1.49, 1.02, 1.0 and 0.78 for GA, GB, GC and GD respectively. In GD the mean value of (PI) was reduced significantly more than other groups. At day 90, the mean values of (PI) were 0.49, 0.26, 0.27 & 0.02 for GA, GB, GC and GD respectively. In GD the mean value of (PI) was decreased significantly more than other groups at day 90.Table 2 reveals that the mean values of (gingival index GI) in GA, GB, GC and GD at base line were 2.19, 2.11, 1.98 & 2.23 with no significant difference at P-value < 0.05. At day 30 the mean values of (GI) in GA, GB, GC & GD were 1.52, 1.10, 0.98 & 0.55 respectively. The mean values of (GI) at 30 day were reduced significantly in the 4 groups of the study mostly in GD. At day 90, the mean value of (GI) was 0.96, 0.32, 0.25 & 0.08 for GA, GB, GC and GD respectively, with significant reduction at P-value < 0.05 at day 90. Table 3 shows that the percentage values of (gingival bleeding index GBI) in the 4 groups at day 0 were (100%). At day 30 the percentage values of (gingival bleeding index GBI) in GA, GB, GC & GD were 70%, 52%, 47%, & 23% respectively. with significant difference mostly in GD at P-value < 0.05. At day 90, the percentage values of (gingival bleeding index GBI) in GA, GB, GC & GD were 37%, 28%, 20%, & 4% respectively, with highly significant difference in GD at P-value < 0.001. Table 4 demonstrates that the mean values of (probing pocket depth PPD) at day 0 for GA, GB, GC & GD, were similar, 7.8 mm, 7.71 mm, 7.98 mm, & 7.81 mm respectively with no significant difference at P-value < 0.05. At day 30 the mean values of (PPD) in GA, GB, GC & GD were 4.9 mm, 3.47 mm, 3.98 mm, & 3.28 mm respectively. The PPD was decreased in all groups of the study significantly mostly in GD. At day 90, the mean values of PPD were 4.1 mm, 3.19 mm, 3.05 mm, & 2.0 mm in GA, GB, GC & GD respectively & highly significant difference in GD at P-value < 0.001. Table 5 demonstrates that the mean values of (clinical attachment level CAL) at day 0 for GA, GB, GC & GD, were similar, 8.21 mm, 8.11 mm, 8.18 mm, & 7.99 mm respectively with no significant difference at P-value < 0.05. At day 30 the mean values of (CAL) in GA, GB, GC & GD were 6.9 mm, 5.67 mm, 5.55 mm, & 4.58 mm respectively. The PPD was decreased in all groups of the study significantly mostly in GD. At day 90, the mean values of PPD were 4.9 mm, 3.89 mm, 3.95 mm, & 3.10 mm in GA, GB, GC & GD respectively & highly significant difference in GD at P-value < 0.001. Tables 6&7 illustrate the clinical parameters difference in each group according to time intervals. The results reported that all the clinical parameters were reduced as the time progressed in the 4 groups. A comparison between (day 0 and 30) & between (day 0 and 90) for all the clinical parameters in each group is shown in (table 5). Tables 8&9 reveal the comparison of clinical parameters difference between each 2 groups according to time intervals (day 30 & day 90). The results reported that all the clinical parameters were reduced significantly in GB & GC from GA. The clinical parameters were decreased in GD from GA and the difference was highly significant at P-value < 0.001. The clinical parameters difference between GB & GC was not significant at P-value < 0.05. The clinical parameters were reduced

significantly in GD**,** from GB & GC at P-value < 0.05.

Discussion

Traditional therapies such as tooth brushing, flossing, subgingival irrigation, and mechanical debridement are successful for patients with mild periodontal diseases. However, as the periodontal pocket deepens, the patient's home care procedures as well as professional debridement loses effectiveness, making local drug delivery a viable option. Local administration of antimicrobial agents within periodontal pockets has emerged as an adjuvant factor to conventional mechanical therapy, specifically to sites with periodontitis that have not provided remission towards the initial treatment [(7)]. The addition of local delivery can also help to maintain or control the disease among maintenance visits [(17)]. Advances in the technology of drug delivery systems have resulted in a number of site-specific, controlled release methods. Local delivery systems offer the advantages of high concentrations at the target site with reduced dosage, fewer applications, and high patient acceptability**.** Thus, adjunctive use of local drug delivery may provide a beneficial response, especially in specific areas where conventional forms of therapy might fail [(18)]. The local drug delivery systems are especially indicated for patients in supportive treatment, medically compromised patients who cannot undergo surgical therapy, localized refractory sites, and failing implants. They are also indicated prior to regenerative surgery to improve the predictability by reducing the bacterial load [(19,20)]. In many studies, metronidazole gels and chlorhexidine gels were used separately, (only in separated studies), but not in one study, and conflicting outcomes were found therefore we have carried out this study to assess the effectiveness of metronidazole gel, chlorhexidine collagen gel and a new xanthan-based chlorhexidine (CHLOSITE®) which contains a unique combination of two chlorhexidine formulations: 0.5% chlorhexidine digluconate and 1.0% chlorhexidine dihydrochloride, as an adjunct to SRP, and to compare these treatment modalities with the results obtained by SRP **alone.** In the present study, all of the clinical parameters were improved significantly in all study groups. The PI, GI, GBI & PPD were reduced significantly on day 30 and day 90 in the four groups. The significant reductions observed in plaque and gingival scores from baseline could be attributed to the recording of these parameters before SRP at the baseline visit. Lower plaque and gingival index scores observed in the test groups may also be the result of the antiplaque and antibacterial role of chlorhexidine that may have leaked out of the pockets [(19)]. Group D showed a reduction in all clinical parameters throughout the study and this reduction was significantly higher than the other 3 groups of the study. These findings may be explained by the fact that the combination of the two formulations of CHX had given a potentiation and augmentation of bactericidal effect of the mixture in addition to increased duration of antibacterial action. On the other hand Group B & Group C in which the SRP was accompanied by local application of (metronidazole benzoate gel) & (chlorhexidine collagen gel) respectively have shown an improvement in all clinical parameters more than Group A (SRP alone) and the difference was statistically significant at P-value < 0.05.Studies of subgingival application of 1 or 2% chlorhexidine gel have been performed. In some studies no significant improvement was reported [(20)]. Chlorhexidine digluconate (CHX) has demonstrated to have substantivity with regard to enamel and oral mucosa. Nevertheless, current studies have indicated that this substantivity can have a short term, with antimicrobial activity of only 24 hours. Clinical evidences related to subgingival irrigation with CHX have shown the inefficiency of this application [(11)]. The explanation of the loss of significant improvement by application of chlorhexidine in some studies may be attributed to the low frequency of administration because only one application of gel was used [(22,23)]. Another explanation could be low doses or

concentrations in relation to the minimum inhibitory concentration (MIC) or minimum bactericide concentration (MBC), described in an in vitro study [24]. On the other hand, some authors reported an improvement in the clinical parameters with chlorhexidine gel irrigation [25,26], or a reduction in the percentage of bacteria after one subgingival application [27]. The collagen gel was chosen as a vehicle for the application of chlorhexidine because it possesses adhesive properties that promote a slow release of the chlorhexidine, increasing the substantivity and the duration of the bactericidal activity of the drug [28]. The xanthan-based chlorhexidine gel is supplied with a special needle having a blunt tip and a lateral opening. This facilitates the application of the gel without traumatizing or damaging the periodontal tissues. Xanthan is a naturally occurring, biocompatible saccharidic polymer that forms a three-dimensional pseudoplastic reticulum when in contact with water. Chlorhexidine digluconate is liberated in the first day, and achieves a concentration greater than 100 μg/mL. This concentration is maintained for an average of 6-9 days, and is much more than the minimum inhibitory concentration (MIC) for chlorhexidine (0.10 μg/mL). Chlorhexidine dihydrochloride is released in the following days, and maintains the bacteriostatic and bactericidal concentrations for at least 2 weeks and prevents re-colonization[29]. In a study by Jolkovsky et al. [30], the importance of the periodicity of the irrigation as an adjunctive technique was demonstrated because the constant renovation of the fluid or gel facilitates the exit of substances of the subgingival area after the irrigation. Although the observation period was short, the results encourage the use of chlorhexidine irrigation in combination with SRP [31].

Griffiths et al (2000) compared the clinical effects of subgingival scaling (SRP) alone with SRP plus subgingival application of 25% metronidazole gel, in patients with chronic periodontitis. They reported that both treatments effectively reduced the signs of periodontitis. However, at each follow-up visit, reduction in PPD, CAL and BOP after the combined treatment was greater than for SRP alone [32]. The results of this study are in agreement with the results of the present study. Rudhart et al (1998) and Hitzig et al (1994) performed clinical studies that have resulted in a significant difference in the improvement of clinical parameters when SRP was combined with metronidazole, as compared to SRP alone [33,34]. The findings of the present study are also in accordance with these studies. However, similar studies comparing SRP with metronidazole gel used as an adjunct to mechanotherapy, showed that no significant difference in the results achieved in terms of a reduction of probing pocket depth [35].

Conclusions

All of the study groups where were displayed a statistically significant reduction in all the clinical parameters. A degradable, subgingivally placed drug delivery system containing antimicrobial agents as locally delivered gels (CHLOSITE® the new xanthan-based chlorhexidine), (metronidazole 10 mg) and (1% CHX collagen) applied with mechanotherapy, is a safe and efficient adjunct to scaling and root planing in the treatment of chronic periodontitis. CHLOSITE® demonstrated a statistically significant improvement more than other groups.

Table (1):- Mean PI values in all groups at different time intervals.

PI	Group A		Group B		Group C		Group D	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Day 0	2.52*	±0.48	2.44*	±0.37	2.41*	±0.23	2.3*	±0.42
Day 30	1.49**	±0.61	1.02**	±0.31	1.0**	±0.26	0.78**	±0.21
Day 90	0.49***	±0.01	0.26	±0.12	0.27	±0.02	0.02***	±0.01

*NS: No significant difference at P value < 0.05.
**S:Significant difference at P value < 0.05.
***HS: Highly Significant difference at P value < 0.001.

Table (2):- Mean GI values in all groups at different time intervals.

GI	Group A		Group B		Group C		Group D	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Day 0	2.19*	±0.90	2.11*	±0.54	1.98*	±0.12	2.23*	±0.5
Day 30	1.52***	±0.39	1.1**	±0.33	0.98**	±0.21	0.55***	±0.15
Day 90	0.96***	±0.15	0.32	±0.44	0.25	±0.01	0.08***	±0.04

*NS: No significant difference at P value < 0.05.
**S: Significant difference at P value < 0.05.
***HS: Highly Significant difference at P value < 0.001.

Table (3):- GBI scores of all groups at different time intervals.

GBI	Group A	Group B	Group C	Group D
Day 0	100%*	100%*	100%*	100%*
Day 30	70%***	52%	47%	23%***
Day 90	37%***	28%	20%	4 %***

*NS: No significant difference at P value < 0.05.
**S: Significant difference at P value < 0.05.
***HS: Highly Significant difference at P value < 0.001.

Table (4):- Mean values of PPD of all groups at different time intervals.

PPD	Group A		Group B		Group C		Group D	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Day 0	7.8*	±1.2	7.71*	±0.54	7.98*	±1.12	7.81*	±1.5
Day 30	4.9**	±1.12	3.47	±1.33	3.98	±1.21	3.28**	±1.0
Day 90	4.1***	±0.9	3.19**	±0.44	3.05	±0.11	2.0***	±0.3

*NS: No significant difference at P value < 0.05.
**S: Significant difference at P value < 0.05.
***HS: Highly Significant difference at P value < 0.001.

Table (5):- Mean values of CAL of all groups at different time intervals.

CAL	Group A		Group B		Group C		Group D	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Day 0	8.21*	±2.2	8.11*	±2.54	8.18*	±3.72	7.99*	±2.89
Day 30	6.9***	±1.48	5.67	±1.87	5.55	±1.01	4.58***	±1.32
Day 90	4.9***	±1.75	3.89	±0.74	3.95	±0.61	3.10***	±0.37

*NS: No significant difference at P value < 0.05.
***HS: Highly Significant difference at P value < 0.001.

Table (6):- Differences of the study indices of each group at different time intervals.

PI	Day 0 & 30	Sig of diff	Day 0 & 90	Sig. of diff.
Group A	2.52 & 1.49	S	2.52 & 0.49	HS
Group B	2.44 & 1.02	S	2.44& 0.26	HS
Group C	2.41 & 1.0	S	2.41 & 0.27	HS
Group D	2.3 & 0.78	HS	2.3 & 0.02	HS
GI	Day 0 & 30	Sig of diff	Day 0 & 90	Sig of diff
Group A	2.19 & 1.52	S	2.19 & 0.96	HS
Group B	2.11 & 1.1	S	2.11 & 0.32	HS
Group C	1.98 & 0.98	S	1.98 & 0.25	HS
Group D	2.23 & 0.55	HS	2.23 & 0.08	HS
GBI	Day 0 & 30	Sig of diff	Day 0 & 90	Sig of diff
Group A	100% & 70%	S	100% & 37%	HS
Group B	100% & 52%	S	100% & 28%	HS
Group C	100% & 47%	S	100% & 20%	HS
Group D	100% & 23%	HS	100% & 4%	HS

S: Significant difference at P value < 0.05.
HS: Highly Significant difference at P value < 0.001.

Table (7):- Differences of PPD & CAL of each group in different time intervals.

PPD	Day 0 & 30	Sig. of diff.	Day 0 & 90	Sig. of diff.
Group A	7.80 & 4.90	S	7.80 & 4.10	HS
Group B	7.71 & 3.47	S	7.71 & 3.19	HS
Group C	7.98 & 3.38	S	7.98 & 3.05	HS
Group D	7.81 & 3.28	S	7.81 & 2.0	HS
CAL	Day 0 & 30	Sig. of diff.	Day 0 & 90	Sig. of diff.
Group A	8.21 & 6.9	S	8.21& 4.9	HS
Group B	8.11 & 5.67	S	8.11 & 3.89	HS
Group C	8.18 & 5.55	S	8.18 & 3.95	HS
Group D	7.99 & 4.58	S	7.99 & 3.10	HS

S: Significant difference at P value < 0.05.
HS: Highly Significant difference at P value < 0.001.

Table (8):-Comparison between each pair of groups of the study indices at different time intervals.

PI	DAY 30	P-Value	Significance	DAY 90	P-Value	Significance
GA & GB	1.49 & 1.02	P < 0.05	Sig.	0.49 & 0.26	P < 0.05	Sig.
GA & GC	1.49 & 1.0	P < 0.05	Sig.	0.49 & 0.27	P < 0.05	Sig.
GA & GD	1.49 & 0.78	P < 0.001	H . Sig.	0.49 & 0.02	P < 0.001	H . Sig.
GB & GC	1.02 & 1.0	P > 0.05	N . Sig.	0.26 & 0.27	P > 0.05	N . Sig.
GB & GD	1.02 & 0.78	P < 0.05	Sig.	0.26 & 0.02	P < 0.05	Sig.
GC & GD	1.0 & 0.78	P < 0.05	Sig.	0.27 & 0.02	P < 0.05	Sig.
GI	DAY 30	P-Value	Significance	DAY 90	P-Value	Significance
GA & GB	1.52 & 1.10	P < 0.05	Sig.	0.96 & 0.32	P < 0.05	Sig.
GA & GC	1.52 & 0.98	P < 0.05	Sig.	0.96 & 0.25	P < 0.05	Sig.
GA & GD	1.52 & 0.55	P < 0.001	H . Sig.	0.96 & 0.08	P < 0.001	H . Sig.
GB & GC	1.10 & 0.98	P > 0.05	N . Sig.	0.32 & 0.25	P > 0.05	N . Sig.
GB & GD	1.10 & 0.55	P < 0.05	Sig.	0.32 & 0.08	P < 0.05	Sig.
GC & GD	0.98 & 0.55	P < 0.05	Sig.	0.25 & 0.08	P < 0.05	Sig.
GBI	DAY 30	P-Value	Significance	DAY 90	P-Value	Significance
GA & GB	70% & 52%	P < 0.05	Sig.	37% & 28%	P < 0.05	Sig.
GA & GC	70% & 47%	P < 0.05	Sig.	37% & 20%	P < 0.05	Sig.
GA & GD	70% & 23%	P < 0.001	H . Sig.	37% & 4%	P < 0.001	H . Sig.
GB & GC	52% & 47%	P > 0.05	N . Sig.	28% & 20%	P > 0.05	N . Sig.
GB & GD	52% & 23%	P < 0.05	Sig.	28% & 4%	P < 0.05	Sig.
GC & GD	47% & 23%	P < 0.05	Sig.	20% & 4%	P < 0.05	Sig.

Table (9):-Comparison between each pair of groups of PPD & CAL at different time intervals.

PPD	DAY 30	P-Value	Significance	DAY 90	P-Value	Significance
GA & GB	4.90 & 3.47	P < 0.05	Sig.	4.10 & 3.19	P < 0.05	Sig.
GA & GC	4.90 & 3.98	P < 0.05	Sig.	4.10 & 3.05	P < 0.05	Sig.
GA & GD	4.90 & 3.28	P < 0.001	H.Sig.	4.10 & 2.0	P < 0.001	H.Sig.
GB & GC	3.47 & 3.38	P > 0.05	N.Sig.	3.19 & 3.05	P > 0.05	N.Sig.
GB & GD	3.47 & 3.28	P < 0.05	Sig.	3.19 & 2.0	P < 0.05	Sig.
GC & GD	3.98 & 3.28	P < 0.05	Sig.	3.05 & 2.0	P < 0.05	Sig.
CAL	DAY 30	P-Value	Significance	DAY 90	P-Value	Significance
GA & GB	8.21 &5.67	P < 0.05	Sig.	8.21 & 3.89	P < 0.05	Sig.
GA & GC	8.21 &5.55	P < 0.05	Sig.	8.21 & 3.95	P < 0.05	Sig.
GA & GD	8.21 &4.58	P < 0.001	H.Sig.	8.21 & 3.10	P < 0.001	H.Sig.
GB & GC	5.67& 5.55	P > 0.05	N.Sig.	3.89 & 3.95	P > 0.05	N.Sig.
GB & GD	5.67 & 4.58	P < 0.05	Sig.	3.89 & 3.10	P < 0.05	Sig.
GC & GD	5.55 & 4.58	P < 0.05	Sig.	3.95 & 3.10	P < 0.05	Sig.

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