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Evaluation of the Effectiveness of Chlorhexidine Gluconate Gel on Periodontal Parameters and Fusobacterium Nucleatum Pathogen in Periodontitis Patients

Mohand Falah Abdullah [(1)] *
Alaa Omran [(2)]

[(1,2)] College of Dentistry, University of Baghdad, Baghdad, Iraq.

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***Corresponding Author:**
Email: mhnd.dt@gmail.com

Master student. College of Dentistry, University of Baghdad, Baghdad, Iraq.

Abstract

Background: Periodontal disease, a prevalent oral disease affecting 10-15% of adults globally, leads to tissue damage and bone loss. Fusobacterium nucleatum, a bacterium from the Bacteroidaceae family, significantly contributes to this disease. Chlorhexidine, a powerful antibacterial agent. It is believed to be the gold-standard for conventional periodontal treatment due to its effectiveness in eliminating periodontal pathogenic bacteria.

Aim of study: Estimate the effictiveness of chlorhexidine gluconate gel in the nonsurgical management of periodontitis patients.

Methods: by employing single-blinded, split-mouth randomized clinical trial. It included ten attending patients diagnosed with generalized unstable periodontitis. A split-mouth design was used, and 15 test and 15 control sites were selected. every subject had two locates selected: a control locate that received subgingival debridement with placebo gel and an experiment locate that received subgingival debridement with chlorhexidine gel. Clinical parameters Levels were measured for full dentition.

Results: Bleeding on probing sites significantly decreased after treatment in the CHX group. Pocket probing depths, clinical attachment levels, also bacteria found to be significantly reduced after treatment in both groups. A statistically significant strong positive correlation has been identified regarding bacteria and periodontal probing depth, and a positive correlation has been identified regarding bacteria and clinical attachment level.

Conclusion: Treatment with chlorhexidine gluconate gel can lower Fubacterium nucleatum bacterial count in periodontal pockets and significantly decrease bleeding on probing and clinical attachment scores within the locates treated with chlorhexidine gluconate.

Introduction:

Periodontal disease (PD), a common dental inflammation that disturbs the supporting structure that surround the teeth. It encompasses gingivitis and periodontitis [1]. With a prevalence ranging from 20% to 50%, PD was the eleventh most common prevalent disease worldwide [2, 3]. Periodontitis is characterized by gingival recession, periodontal tissue degeneration, and alveolar bone loss, which is an inflammatory condition [4]. This inflammatory disease is caused by pathogenic bacteria and is distinguished by the way the pathogens interact with the host cells. Pathogenic bacteria eradication is by the host's native or aquired immune reaction. The periodontal tissue degradation is a consequence of dysbiosis, characterized by an imbalance in the microbial flora and host immune response[5]. Fusobacterium nucleatum (f. nucleatum) is one of the most researched bacteria linked to periodontal disease. It is a prominent microorganism that is a member of the Bacteroides family [6]. In order to sustain mechanical root surface debridement by local and systemic chemical agent delivery, deep pockets necessitate the use of an adjuvant antibacterial agents. One advantage of local application of chemical agents in diseased pockets is that it minimizes the amount of drug exposed to the entire body while sustaining adequate intensity of the drug at the recipient diseased pocket [7]. Chlorhexidine (CHX), a cationic bisbiguanide, has a wide range of effects on dermatophytes, yeasts, gram + and gram - pathogenic bacteria alongside several lipo-philic viruses [8]. With the application of CHX in the prevention or treatment of PD it plays a crucial role in dentistry and is widely recognized as the "gold standard" antiseptic agent [9]. CHX is extensively utilized and tested antiseptic and it is regarded as the gold standard because of its high bactericidal capability, its capacity to inhibit proteolytic activities, and its ability to reduce matrix metalloproteinase activities in a wide range of oral bacteria [10].Dental plaque is significant causative factor in the advancement of periodontitis. The need for using antimicrobial treatment in conjunction with mechanical debridement is necessary when complete removal of plaque is not possible using debridement only. The most used and studied antimicrobial drug, CHX, has a therapeutic effect that is likely due to both its substantive and antibacterial qualities [11] [12]. This study aims to estimate the efficacy of chlorhexidine gluconate gel in non-surgical management of periodontitis cases by measuring clinical periodontal parameters and evaluating f.nucleatum subgingival load. The novelty researched in this study is to ascertain the efficacy of chlorhexidine gel on f. nucleatum. Despite the fact that many researchers studied the chlorehexine's bactericidal ability on periodontal pathogenic bacteria, studies particularily investigate its impact on f.nucleatum in literature is considered very scarce.

Material And Methods

Study design and settings: This study is a single blinded split-mouth randomized clinical trial conducted at Al-Sadr Specialized Dental Center during a period of seven months from February to September 2023. The protocol approval was given by the Ethics committee, College of Dentistry, University of Baghdad was under the Reference number :820, Project number :820623, Date :23\5\2023.

Study population: The study included 10 patients diagnosed with generalized unstable periodontitis (stage I-III periodontitis) selected from patients seeking periodontal treatment. Periodontitis cases was demarcated when interdentally clinical attachment level is measureable at two or more non-adjoining teeth, or clinical attachment level is equal or exceeding 3 mm with pockets measured more than 3 mm is evident with at least two teeth [13].

A split-mouth design was used, and 15 test and 15 control sites were selected. Each patient had two sites selected: one was a monitor locate that received subgingival instrumentation debridement with placebo

gel, while the other was a test site that received mechanical debridement and chlorhexidine gel (Perio Kin 0.2%)

Periodontal parameters: Clinical Attachment Level (CAL), Plaque Index (PI), Bleeding on Probing (BOP), and Periodontal Probing Depth (PPD), have been measured for full dentition. A graded periodontal probe (William probe, Osung USA, Houston, USA) was used to perform a complete mouth checkup. The probe marks are 1,2,3,5,7,8,9, and 10 mm. it measures six locations for each tooth (mesio-buccal, buccal, disto-buccal, mesio-lingual, lingual, and disto-lingual), with an exception for PI, which were examined on four surfaces.

Clinical examination: examination for each patient started by the PI, which was performed using a plaque disclosing agent for the purpose of detecting presence or absence of dental plaque. To record BOP scores by using the periodontal probe by light force insertion to the periodontal pocket depth, the force should be ceased when a little obstruction was felt. Six surfaces of each tooth were surveyed so the spot that showed bleeding when probed was scored 1, and the surface that did not show bleeding was scored 0. CAL and PPD were measured at the same time. PPD measuring was calculated starting the marginal gingiva up to the deepest point of the periodontal pocket, whereas CAL measuring would be from the cemento-enamel junction (CEJ) the pocket's deepest point. In this step, the periodontitis stage was identified by detecting the tooth with the highest CAL.

Clinical intervention: A single-blind, split-mouth design clinical trial was conducted. The included sites with existing pockets measured 5-7 mm with total number of the test and control pockets were 30. Commercially available preparations of chlorhexidine gel (PerioKin 0.20% Chlorhexidine DG, Laboratories KIN, Spain gel) was used in this study. There were three visits in the clinical intervention which were:

1. Patient's provisional visit: taking detailed clinical scores (PI, BOP, PPD and CAL), doing gross scaling for the entire set of teeth, ideal brushing and flossing awareness.
2. Starting visit: by means of a periopaper, a plaque sample was collected from inside the pocket, and the pockets were treated normally with subgingival mechanical debridement, as well as the administration of the CHX gel and placebo gels in the pockets. A 5ml one-use syringe fitted out with a dull 25-gauge needle was utilized, and the syringe placed in the deepest point of the pocket.
3. **Second visit:** (Three months following the first visit): Measuring the clinical parameters (PLI, BOP, CAL and PPD), as well as collecting of subgingival bacterial biofilm within the exact treated pockets for laboratory quantification procedure.

Quantification of F. nucleatum via quantitative real time Polymerase Chain Reaction (qPCR)

- ✓ **Kits and Primers** Tables (1) and(2)
- ✓ **DNA Extraction:** separation of bacterial DNA from salivary samples was done following the protocol of ABIOpure Extraction
- ✓ **Primer preparation:** Lyophilized primers thawed to provide an ultimate concentration of 100pmol/µl to be a standard solution. The preparation of the primers' working solutions was formulated by the addition 10 µl of the standard solution to 90µl water to acquire primers' working solutions of 10pmol/µl.
- ✓ **Absolute quantification by the standard curve (SC):** This is a scheme that utilizes a dilution sequence of familiar prototype duplicate number in the qPCR assay.
- ✓ **Reaction Setup and Thermal Cycling Protocol:** Table (3)

Statistical analysis: The data introduced as means, ranges and standard deviations. Shapiro Wilk test used to test the normality distribution of the quantitative variable. Paired t-test has been utilized to

associate the continuous variables prior to and following the intervention. Wilcoxon sig rank test: non-parametric test check the difference between two related points. McNemar test is a statistical test used for two related readings with dichotomous variable. A level of P-value reduced than 0.05 has been regarded as significant.

Results:

This study's population included ten contributors that have demographic features dispersed through gender and age. The studied subjects involved: two females 20 %, eight males 80 %. The male proportion exceeded the female proportion Figure (1). Contributors' age range was between 19 and 30 in years. The age mean range was 22.8. The standard deviation (SD) for the age was 3.584. Using Shapiro Wilk test, periodontal parameters are normally distributed among groups and visits at p value >0.05 (table 4). Regarding PI, no significant change detected after intervention in either group at ($P \geq 0.05$) (table 5). BOP sites were significantly reduced following intervention for CHX group (P=0.004). Significant change has not been detected with placebo group at (P=0.07) (table 6). Results regarding PPD, CAL, and bacteria as shown in tables (7,8 and 9) demonstrate a significant reduction after intervention in comparison to prior intervention within the groups ($P < 0.05$). Associations concerning bacteria and PD, CAL are presented in table (9). Statistically significant strong positively correlated bacteria with PD (r=0.73, P=0.001), while bacteria was moderately positively correlated with CAL (r=0.456, P=0.011).

Discussion

The main efficient chemotherapeutic drug and it is considered cornerstone for reducing oral biofilm is CHX. In dentistry, CHX products like as rinses, gels, microchips, and resins are prescribed (14). It has rapid antibacterial and antifungal effect and it is effective even yet at lower doses [15]. According to the European Federation of Periodontology, people with periodontitis stages 1-3 may benefit from CHX as a form dispensed in site with a sustained-release as a supplement to sub gingival debridement [16]. Although there are many studies that study the association between chlorhexidine effect on bacterial species that cause periodontitis, there are scarce number of papers that discuss the impact of chlorhexidine on f. nucleatum [17].

Regarding plaque index, the statistical analysis does not show any significant difference when comparing the intervention samples and the control samples. This conclusion indicates that the efficiency of plaque reduction for both groups is affected primarily by the efficiency of the subgingival debridement and the oral hygiene measures regardless of the therapeutic material used adjunctive to the original treatment. These readings support the preceding studies [18-20] that also detected a decline in plaque index after periodontal non-surgical intervention. Though, a conflicting result has been stated in one more study [21]. In this study, BOP sites were significantly lessened after CHX intervention group; whereas placebo group does not show significant change. This study was agreed with other studies conducted in Italy 2021 [22] and in India 2021 [21]. It is commonly known that CHX exhibits anti-inflammatory properties on gingival tissue at concentrations of 0.1% and 0.2%. Because BOP measures inflammation, the anti-inflammatory impact of CHX on the studied sites resulted in a lower BOP score [9].

Considering PPD score in this study, it is slightly lower in locations remedied by CHX than in placebo gel intervention sites and this is agreed with studies conducted in Italy 2021 [22] and 2004 [23]. It is also agreed with a study conducted in Iraq in 2013 [24] . In the contrary to this study a number of studies disagrees with the results. One systematic review [25] and the following studies disagrees with our study [26]. A possible explanation could be that the mechanical debridement has a significant role in reducing the depth of the pockets, and that the CHX gel may not have been penetrated all the way down to the periodontal pockets. PPD is a crucial parameter for assessing improvements in periodontal health, but it has several drawbacks, including the rate at which

gingival crevicular fluid flows and the capacity of bacteria to resist the effects of CHX. Numerous investigations have shown that CHX gel has, at most, a minimal impact on the depth of the periodontal pocket [25].

The most important parameter measured in this study is CAL. The study shows a significant reduction with all groups, although the intervention group takes further shift comparing to the placebo group. CAL is the parameter that measures the severity of periodontitis because it is considered more objective parameter than PPD due to its fixed point of measurement and the scores are less impacted by the gingival level of inflammation [27]. The possible explanation for the outcomes of the conducted study is that since CHX gel affects gram+ bacteria a higher degree than gram- bacteria, it works better on shallow pockets than deep pockets [15] also Deep pockets could be difficult for mechanical debridement to reach, and CHX gel works better on root surfaces clear of dental plaque [16, 25]. These reasons explain the effect of CHX gel on CAL as it affects shallow and deep pockets and healing sites after treatment.

This result indicates that treatment with CHX gel can lower f.nucleatum bacterial count in periodontal pockets. The effect of CHX gel was studied on multiple pathogenic bacteria and was found to have antimicrobial effect on pathogenic bacteria [28]. There are limited in vivo studies in literature that tested the effect of CHX on f. neauclatum. A related clinical trial study indicated that a 0.1% concentration of CHX solution considerably reduced the amount of f. nucleatum, which was consistent with the results of this investigation [29]. In conclusion, treatment with CHX gel can lower f.nucleatum bacterial count in periodontal pockets by monitoring the effect using RT-PCR and causes significant decrease in the BOP and CAL scores in the sites treated with CHX gel in comparison to the BOP scores before treatment. Future trials with bigger sample sizes and extended periods of time are required for the validation of the efficacy of CHX gel as an adjunctive to periodontal therapy. An attempt should be made to determine the efficacy of the experimental substance in relation to other materials.

Limitation of this study: First limitation was the small sample size due to the difficulty of recruiting the patient and obtaining the consent from them. Second, this study that it involves only unstable periodontitis, gingivitis and stable periodontitis were excluded in this study and these groups can be included in future studies, also systemic conditions like diabetes was excluded and can be included in future studies. Third, PCR is technically sensitive and demanding procedure which could be associated with possibility of reporting false negative results. It requires special laboratory tools and a trained technician to eliminate the chances for any technical errors. Fourth, the use of a single concentration of CHX and testing a single pathological bacterium was also a downside for this study. We recommend to use new materials in addition to chlorhexidine and test more periodontal pathogens in addition to F.nucleatum

Conclusion:

As concluded by the outcomes of the current study, CHX gel demonstrates efficacy in reducing Fusobacterium nucleatum counts within periodontal pockets. Chlorhexidine (CHX) gel significantly reduced bleeding on probing (BOP) scores in the treated pockets. Also, the treatment with chlorhexidine (CHX) gel did not result in a statistically significant lessening in probing pocket depth (PPD) scores at the treated sites.in contrary the treatment resulted in a statistically significant lessening in clinical attachment loss (CAL) in the treated pockets.

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Conflicts of interest:
The authors claim to have no conflicting interests.

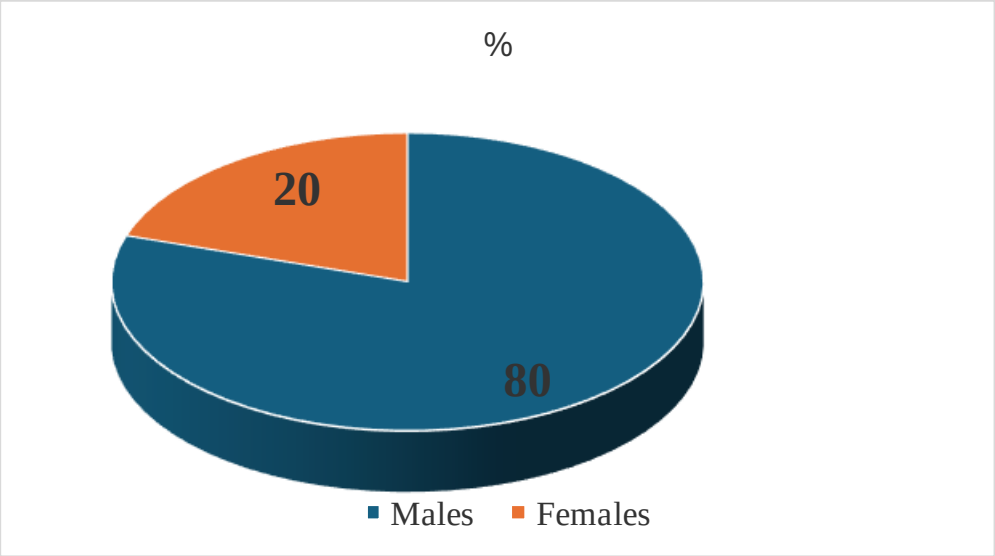

Figure (1): gender ratio of the study

Table 1: Primer Kits

Kits
GoTag qPCR Master Mix, Nuclease Free Water.
ABIOpure™ Total DNA
Absolute Ethanol
Primers

Table 2: Primers

Primer Name	Sequence `5-3`	Annealing Temp. (˚C)
F. nucleatum-F	AGCAGCCGCGGTAATACG	60
F. nucleatum-R	GCGCTTTACGCCCAATAAATC	

Table 3: Real Time PCR Program

Steps	°C	m: s	Cycle
Initial Denaturation	95	05:00	1
Denaturation	95	00:20	40
Annealing	60	00:20 Acquiring on Green	

Table 4: Normality test of studied variables (Shapiro-Wilk)

			Groups					
			Placebo			CHX- gel		
			Statistic	df	P value	Statistic	df	P value
Baseline		PPD	0.885	15	0.056	0.887	15	0.060
Treatment		PPD	0.882	15	0.052	0.890	15	0.067
Baseline		CAL	0.886	15	0.058	0.918	15	0.182
Treatment		CAL	0.891	15	0.069	0.885	15	0.056
Baseline		Bacteria	0.818	15	**0.006**	0.713	15	**0.000**
Treatment		Bacteria	0.911	15	0.142	0.790	15	**0.003**

Table 5: PI distribution among groups& visits

Visits	Groups	Cats.	N.	%	Fisher exact p value
Before	Placebo	Absence	12	80.00	0.999 NS
		presence	3	20.00	
	CHX- gel	Absence	13	86.67	
		presence	2	13.33	
Treatment	Placebo	Absence	13	86.67	0.999 NS
		presence	2	13.33	
	CHX- gel	Absence	14	93.33	
		presence	1	6.67	
Placebo	Before-Treat.	MC-NE mare's test	0.999 NS		
CHX-gel	Before-Treat.	MC-NE mare's test	0.999 NS		

Table 6: BOP distribution among groups & visits

Visits	Groups	Cats.	N.	%	Fisher exact p value
Before	Placebo	Absence	3	20.00	0.598 NS
		presence	12	80.00	
	CHX- gel	Absence	1	6.67	
		presence	14	93.33	
Treatment	Placebo	Absence	9	60.00	0.999 NS
		presence	6	40.00	
	CHX- gel	Absence	10	66.67	
		presence	5	33.33	
Placebo	Before-Treat.	MC-NE mare's test	0.070 NS		
CHX-gel	Before-Treat.	MC-NE mare's test	**0.004 Sig.**		

Table 7: PPD distribution among groups & visits

Groups		Baseline	Treatment	Paired T test	P value	Cohen effect size
Placebo	Min.	4.000	2.000	5.104	**0.000**	1.318
	max.	6.000	5.000			
	Mean	4.667	3.400			
	±SD	0.617	0.910			
CHX- gel	Min.	4.000	2.000	6.904	**0.000**	1.783
	max.	10.000	5.000			
	Mean	5.400	2.733			
	±SD	1.454	0.884			
Paired T test		1.111	1.167			
P value		0.276	0.253			

Table 8: CAL distribution among groups & visits

Groups		Baseline	Treatment	Paired T test	P value	Cohen effect size
Placebo	Min.	2.000	1.000	5.735	**0.000**	1.481
	max.	5.000	3.000			
	Mean	3.933	2.467			
	±SD	1.280	0.743			
CHX-gel	Min.	2.000	1.000	5.809	**0.000**	1.500
	max.	9.000	3.000			
	Mean	4.733	1.733			
	±SD	1.944	0.799			
Paired T test		1.331	2.603			
P value		0.194	**0.015**			

Table 9: Bacterial distribution (1=Inter-comparison, 2=Intra-comparison)

Groups		Baseline	Treatment	Wilcoxon sign rank	P value	Effect size
Placebo	Min.	49070	44200	2.605	**0.009**	0.475 medium
	max.	3000000	1230000			
	Median	487500	146300			
	Mean rank1	14.37	18.73			
	Mean rank 2	11.00	7.23			
CHX- gel	Min.	70550	6590	3.408	**0.001**	0.622 large
	max.	7287000	548100			
	Median	691200	89400			
	Mean rank1	16.63	12.27			
	Mean rank 2	8	0			
Wilcoxon sum rank		0.705	2.012			
P value		0.481	**0.044**			

Table 10: periodontal parameters and bacterial correlation

Groups	Vars.	rsp	P value
Placebo	bop	0.189	0.500
	PLI	0.227	0.416
	PPD	0.128	0.650
	CAL	0.406	0.133
CHX- gel	bop	0.012	0.994
	PLI	0.062	0.827
	PPD	0.018	0.950
	CAL	0.069	0.806

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