

Treatment of periodontal diseases by the local drug delivery system using 1% chlorhexidine gel: A randomized clinical trial

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Abstract: The idea of the local drug delivery system is getting popular nowadays to treat gingivitis and periodontitis. The method of delivering the drug locally is quite easy and requires minimal intervention. This delivery system not only treats the periodontal diseases effectively but also prevents the side effects linked with the use of the drugs which are used orally for longer periods to cure these diseases. Chlorhexidine (CHX) is being widely used to treat these conditions because of its broad spectrum anti-bacterial effect and is found to be more effective in lowering plaque formation. The aim of this study was to appraise the effect of the local drug delivery system by using 1% CHX gel in patients with periodontal diseases. 1% CHX gel was prepared and its physicochemical characteristics were then assessed. Clinical parameters and inflammatory salivary biomarkers were evaluated in two groups of patients. Group I: standard treatment group. Group II: gel treatment group. These parameters were evaluated before treatment and after 4 weeks of treatment. 1% CHX gel was highly effective in reducing gingivitis and periodontitis by using the local drug delivery system which allowed the drug to retain into the periodontal pocket for prolong period of time.

Keywords: Local drug delivery system, chlorhexidine, gingivitis, periodontitis.

INTRODUCTION

The most widely recognized reason for the obliteration of gingiva and periodontium is bacterial plaque (Aimetti *et al.*, 2014). The preliminary standard treatment of gingivitis and periodontitis is scaling and root planning and counselling of patients for the maintenance of oral hygiene. In the advance stage of the disease sometimes surgical treatment is required (Rocha *et al.*, 2015). In order to decrease the surgical approaches for treating periodontitis, the idea of local drug delivery system was presented by Goodson *et al.* in 1979 along with the initial standard treatment. The retention properties of different devices such as gels, fibers, chips and mouthwashes gained the attention of researchers, doctors and specially periodontologists (Yadav *et al.*, 2015).

In periodontal diseases, conventional treatment alone does not eliminate the bacteria entirely because the scaling instrument does not reach deep in to the periodontal pockets. The bacteria then again multiply and form a complex biofilm. So, the local drug delivery system has the advantage that it helps in the complete removal of biofilm and eliminates bacteria from the deep periodontal pockets and infection sites (Ravishankar *et al.*, 2017). This system not only requires less intervention but also prevents the side effects linked with oral use of the drugs

which are prescribed for longer periods to treat gingivitis and periodontitis (Malathi *et al.*, 2014).

Preparations of chlorhexidine (CHX) are available in the market which ranges from 0.004% to 4% concentration. CHX is an important ingredient in oral rinses, gels, and toothpastes. It is bacteriostatic at low pH, but is bactericidal at pH 2 or more which precipitate the cytoplasmic contents, result in the bacterial cell death. It binds to the cutaneous and mucosal proteins producing continuous antibacterial effects without systemic absorption (Calogiuri *et al.*, 2013). In this study we made 1% CHX gel to evaluate its effects on patients of periodontal diseases by using the local drug delivery system.

MATERIALS AND METHODS

Preparation of 1% CHX gel

500 gm gel of 1% CHX was prepared by adding 5 ml of chlorhexidine gluconate solution in carbopol 940 gel. Methyl paraben, propyl paraben and EDTA were used as preservatives. Triethanolamine was added to modify the pH of the solution. Flavoring agent was included so that it was tolerable to the mouth. Distilled water was added to formulate the final preparation of 1% CHX gel (Garala *et al.*, 2013). The prepared gel was evaluated for its pH, spread ability, mucoadhesiveness, viscosity and syringe ability, before its application in to the oral cavity. Agar diffusion method was used to calculate the MIC of the

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gel. Total microbial count was also done for the quality assurance of the gel (Swain *et al.*, 2019).

Ethical approval

All the procedures performed on humans were according to the Helsinki declaration of 2013. The study was approved from the board of advanced studies and research, Karachi University, Sindh, Pakistan (BASR) and the Independent Ethics Committee of International Center for Chemical and Biological sciences ICCBS/IEC-029- HS2017/Protocol/1.0.

Participants

40 patients were selected from a dental OPD during the period of June 2018 to November 2018. The study was directed in the department of Pharmacology, University of Karachi, Sindh, Pakistan and HEJ research institute of chemistry, University of Karachi, Sindh, Pakistan. Patients who agreed to participate in the study signed the consent form. Medical and dental history was taken and clinical examination was done by using the standard dental examination kit in a clear light of the dental chair. Clinical parameters were estimated by using CPITN probe.

Study design

Randomized clinical control trial

Inclusion criteria

Patient eligibility criteria were all the patients having periodontal disease without any accompanying systemic diseases. Furthermore the patients included in the study were all above 20 years of age.

Exclusion criteria

The patients that were not included in the study were the ones that received any dental treatment in the last two years, patients that were on any medication or recreational drugs since the last six months, females that were pregnant along with mothers that were lactating and any patients that were age 20 or below.

In this study we grouped the patients in two sets

- I. Standard treatment group- patients received conventional periodontal treatment only
- II. Gel treatment group- received 1% CHX intra-crevicular gel application 48 hours after conventional treatment every week for the next four weeks. 25 gauge blunt needles were used to place the gel deep in to the periodontal pockets.

Measurement of clinical parameters

- I. Pocket depth: estimated by using CPITN probe (Varghese *et al.*, 2014).
- II. Clinical attachment level (CAL) (Mdala *et al.*, 2014).
- III. Tooth mobility: it is an important parameter for the research point of view. It was assessed by using the

handles of two dental instruments by applying pressure in the horizontal and vertical direction (Preshaw, 2015).

- IV. Plaque index (Pradeep *et al.*, 2017).
- V. Gingival index (Ranjan *et al.*, 2017).
- VI. Bleeding on probing: evaluated by manipulation of the tissue at the depth of the gingival sulcus with periodontal probe (Mombelli *et al.*, 2017).

Saliva sample collection of patients

The saliva samples were collected before starting the treatment and after the completion of treatment. The samples were collected according to standard saliva collection protocol (Nunes *et al.*, 2015). The samples after centrifugation were then freeze at -20°C.

Measurement of, TNF- α , PGE₂ and nitric oxide salivary level

The centrifuged clear fluid was assessed for tumor necrosis factor- α , prostaglandin E₂ and nitric oxide level by using ELISA kits (Poorsattar *et al.*, 2014; Gumus *et al.*, 2016; Machado *et al.*, 2018)

STATISTICAL ANALYSIS

Data was entered on SPSS version 21. Analysis was done by utilizing one way ANOVA pursued by Bonferroni test. P value of ≤ 0.05 was considered significant.

RESULTS

There was a very substantial reduction in periodontal pocket depth ($p \leq 0.001$) in the patients received gel treatment after scaling and root planning as compared to standard treatment group. Gain in CAL ($p \leq 0.001$) was also observed in the patients received gel treatment after scaling and root planning as compared to the group of patients received standard treatment. There is no significant reduction in tooth mobility after four weeks in both groups received standard treatment and gel treatment (table 1). Bleeding, plaque index and gingival index were also reduced in one month ($p \leq 0.001$) in the patients received gel treatment after scaling and root planning when compared to patients received standard conventional treatment (table 2).

Inflammatory mediators in the saliva of patients including TNF- α , PGE₂ and nitric oxide were decreased to significant levels in the patients received gel treatment after scaling and root planning as compared to standard treatment group which received only conventional standard scaling and root planning ($p \leq 0.001$) (table 3a,b,c).

DISCUSSION

Periodontal diseases, including gingivitis and periodontitis affect a number of people worldwide (Holde *et al.*, 2016). This affects the quality of life of an

Table 1: Measurement of pocket depth, attachment level and tooth mobility before and after treatment

Groups	PD		CAL		Tooth mobility	
	Before treatment	4 weeks after treatment	Before treatment	4 weeks after treatment	Before treatment	4 weeks after treatment
Standard treatment	3.90±0.83	3.77±0.95	3.79±0.55	3.57±1.00	0.70±0.67	0.70±0.67
1% CHX Gel	3.88±0.81	2.20±0.69***	4.01±0.8	2.34±0.68***	0.60±0.70	0.20±0.42

n= 20 for each group; *** p≤ 0.001 is significant in comparison to standard treatment Periodontal pocket depth= PD; Attachment level=CAL

Table 2: Measurement of bleeding on probing, plaque index and gingival index before and after treatment

Groups	BOP		PI		GI	
	Before treatment	4 weeks after treatment	Before treatment	4 weeks after treatment	Before treatment	4 weeks after treatment
Standard treatment	0.90±0.32	0.54±0.25	2.64±0.18	2.31±0.15	2.63±0.37	1.89±0.77
1% CHX Gel	0.85±0.32	0.05±0.11***	2.46±0.42	0.51±0.47***	2.28±0.41	0.45±0.39***

n= 20 for each group; *** p≤0.001 is significant in comparison to standard treatment Bleeding on Probing =BOP; Plaque index =PI; Gingival index =GI

Table 3a: Measurement of TNF- α , in saliva before and after treatment

Group	TNF- α (pg/ml)	
	Before treatment	After treatment
Standard treatment	75.26±1.62	62.67±1.43
1% CHX Gel	79.63±1.54	12.73±1.65***

n= 20 for each group; *** p≤ 0.001 is significant in comparison to standard treatment TNF- α = Tumor necrosis- α

Table 3b: Measurement of PGE₂ in saliva before and after treatment

Group	PGE ₂ (pg/ml)	
	Before treatment	After treatment
Standard treatment	95.78±2.15	93.6±2.36
1% CHX Gel	89.79±0.93	19.60±0.78***

n= 20 for each group; *** p≤0.001 is significant in comparison to standard treatment PGE₂= Prostaglandin E₂

Table 3c: Measurement of NO in saliva before and after treatment

Group	Nitric Oxide (μ mol/ml)	
	Before treatment	After treatment
Standard treatment	61.47±0.75	60.72±0.67
1% CHX Gel	63.28±2.38	23.67±2.12***

n= 20 for each group; *** p≤ 0.001 is significant in comparison to standard treatment Nitric Oxide= NO

individual due to pain, bleeding gums, loosening of tooth, and tooth loss. The prevalence of these diseases is growing due to increased consumption of refined diet and poor oral hygiene (Lertpimonchai *et al.*, 2017). It not only affects patients' daily routine work, but they also experience difficulty in chewing and ultimately led to alteration in their food choices (Lindmark *et al.*, 20018).

The concept of local drug delivery with the help of devices which increases intra pocket retention is getting popular nowadays (Yadav *et al.*, 2015). These devices deliver drug effectively in the periodontal pocket (Szulc *et al.*, 2018).

Different studies used 2% or higher concentration of gels to treat the clinical symptoms of periodontal diseases

(Fekrazad *et al.*, 2016; Rocas *et al.*, 2016) but this study showed high reduction in pocket depth, improved attachment level, gingival index and plaque index and decreased bleeding by using only 1% CHX gel in only four weeks. This shows that the local drug delivery system is exceedingly compelling in treating periodontal diseases even at low concentrations and shorter time period.

High levels of TNF- α is detected in saliva, gingival crevicular fluid (GCF) and in serum of patients with periodontitis (Gumus *et al.*, 2016; Ozer *et al.*, 2015). Our study showed that these high levels dropped down in the group that received gel treatment after four weeks as compared to the group which received only standard treatment procedures. Thus, the use of CHX preparation

in gel formulation by the local drug delivery system exhibited significant reduction in the level of TNF- α , consequently reducing infection and inflammation through its anti-inflammatory action.

PGE₂ is a highly sensitive salivary biomarker in predicting periodontal diseases (Ebersole *et al.*, 2015). The levels of PGE₂ were reduced with scaling and root planning, but when conventional periodontal treatment is combined with the application of CHX gel using the local drug delivery method, the reduction is highly significant.

Nitric oxide acts as an anti-bacterial agent and it supports vascular tone regulation in endothelium. The correct equilibrium between the free radicals and their scavengers is required in healthy people but in diseased patients, this balance is disturbed and there is an increased level of free radicals. This causes cell damage leading to advanced periodontitis, periapical inflammation and even cancer of oral cavity. Thus, it is also another important biomarker of inflammatory diseases, including periodontitis (Parwani and Parwani, 2015). The reduction in the level of NO after treatment with prepared anti-bacterial gel confirms its effectiveness in treating periodontal diseases.

The reduction in biochemical variables by the gel confirms a decrease in bleeding and plaque formation and increase in attachment level. This improvement is because of the anti-inflammatory and antibacterial effect of the gel which is muco-adhesive and utilizes the periodontal pocket to house the drug delivery system and thus the gel is able to release for a longer period of time (Aslani *et al.*, 2013; Sheshala *et al.*, 2019).

Although the researchers registered severe allergic reactions with CHX such as hives, bronchospasm, hypotension and anaphylactic shock (Bubenhofer *et al.*, 2015) but during this study no patient returned with any adverse effects after using CHX gel. So we recommend the use of CHX in different concentrations by using the local drug delivery system to treat gingivitis and periodontitis. The local drug delivery method is also useful in the manner that the drug marks only the disease site and concentrates in the periodontal pocket for long time period (Rocha *et al.*, 2015).

CONCLUSION

In accordance to our research the local drug delivery system is an effectual procedure for treatment of periodontal diseases and by using this system even 1% CHX gel is highly effective in reducing gingivitis and periodontitis. This system is more reliable, effective and control by the clinician as compare to the orthodox way of treatment. Within the limitations of the present research no clinical adverse effects were observed after the use of this local antimicrobial preparation. Therefore, we highly

suggested the use of local drug delivery system in treating periodontal diseases.

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