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Original Research Article

Evaluation of locally-administered controlled-release doxycycline hyclate gel in smokers and non-smokers in the management of periodontitis: An Indian study

Garima Singh[1,2], Shankar T Gokhale[2,3]*, Shiva Manjunath[2], Saad M Al-Qahtani[3], Raghavendra Reddy Nagate[3], Vatsala Venkataram[4], Betsy Joseph[3,5]

[1]Max Dental Care, Bareilly-243001, Uttar Pradesh, [2]Department of Periodontics, Institute of Dental Sciences, Bareilly-243006, Uttar Pradesh, India, [3]Department of Periodontics and Community Dental Sciences, College of Dentistry, King Khalid University, Abha–61471, Kingdom of Saudi Arabia, [4]Department of Pedodontics & Preventive Dentistry, KVG Dental College & Hospital, Sullia-574327, Karnataka, [5]Department of Periodontics, Saveetha Dental College and Hospitals Saveetha Institute of Medical and Technical Sciences, Chennai, India

For correspondence:* ***Email:* *sgokhale@kku.edu.sa;* ***Tel:*** *00966-581573072*

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Abstract

Purpose: *To assess the clinical and biological effect of locally-administered controlled-release 10 % doxycycline hyclate gel in smokers and non-smokers for the management of periodontitis.*
Methods: *Forty periodontitis patients were enrolled in this study from December 2012 to February 2013 at the Department of Periodontology and Implantology of the Institute of Dental Sciences and Dental Unit of Rohilkhand Medical College, Bareilly, Uttar Pradesh (UP), India. For each patient, probing pocket depth (PPD), clinical attachment level (CAL), plaque index (PI), gingival index (GI), and sulcular bleeding index (SBI) were recorded. Changes in microbial counts were assessed by measuring colony-forming units (CFU) of three major periodontal pathogens. Clinical and microbial parameters were recorded at baseline and one month after scaling and root planing plus controlled local drug delivery of 10 % doxycycline hyclate gel in smokers and non-smokers.*
Results: *A statistically significant change ($p < 0.01$) in PPD was observed among smokers between baseline (4.26 ± 0.12mm) and re-evaluation at one month (3.20 ± 0.11) with a change of 24.88 %. A statistically significant difference was found between smokers and non-smokers in PPD at the end of a 1-month re-evaluation ($p < 0.05$). None of the other parameters showed improvement in smokers following treatment.*
Conclusion: *These results indicate that 10 % doxycycline hyclate gel, when administered locally into the periodontal pocket, shows clinical and microbial improvement, among smokers and non-smokers, in the management of periodontitis. Therefore, 10 % doxycycline gel is potentially an effective therapeutic strategy in the management of periodontitis.*

Keywords: *Controlled-release, Doxycycline hyclate gel, Topical gel, Smokers, Periodontitis, COVID-19*

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INTRODUCTION

Periodontal disease is an immune-inflammatory and infectious disease of the periodontium caused by dental biofilm. Although scaling and root planing (SRP) is still regarded as the ideal treatment for nonsurgical periodontal therapy, certain conditions such as deep periodontal pockets, refractory sites, and furcation involvement have shown unpredictable and inconsistent results with SRP alone. The use of antimicrobial agents in nonsurgical treatment improves the clinical outcomes and suppress the bacterial recolonization of incompletely debrided roots [1]. This has encouraged numerous authors to explore the possibilities of direct application of antimicrobial agents (local drug delivery-LDD) into the periodontal pockets [2]. Gels containing chlorhexidine, doxycycline, metronidazole, and enamel matric derivative; microspheres and ointments containing minocycline and tetracycline fibres are among the various locally applied antimicrobials investigated].

Locally delivered antimicrobial agents have the advantages of attaining higher concentration (up to 100-fold higher than systemic drug regimen) of the antimicrobial agent in the diseased sites, the need for a one-time application only, and absence of systemic adverse effects [3]. There are many advantages of LDDs, such as improved patient compliance, reduced risk of antimicrobial drug resistance, and fewer adverse drug reactions. Atridox® (Atrix Laboratories, Inc., Fort Collins, Colorado) comprises 10 % doxycycline and poly-DL-lactide and N-methyl-2-pyrrolidone mixture a bioabsorbable and flowable form. FDA approves it for local application into the periodontal pockets. Doxycycline exerts sustained antimicrobial effect on anaerobic periodontal pathogens [4], cytoprotective action and a broad range of anti-inflammatory effects such as inhibition of matrix metalloproteinase (MMP) host-derived tissue-destructive enzymes, hydrolase suppression (a-amylases), and cytokines (factor-alpha / TNF-a, IL-1b, IL-6 tumor necrosis). Doxycycline also scavenges, inhibits the metabolites of reactive oxygen and prevents or decreases the pathological degradation of tissue seen in periodontal disease [5]. This forms the basis of various studies conducted using doxycycline in managing deep periodontal pockets, furcations, and supportive periodontal therapy [6].

Smoking adversely affects treatment outcomes of various periodontal therapies such as scaling and root planing, guided tissue regeneration, mucogingival surgeries, and dental implants. There are numerous reports of detrimental effects of smoking on the subgingival microbiota and periodontal bacteria prevalence [7,8]. Some recent studies indicate that locally delivered antibiotics in conjunction with nonsurgical periodontal therapy may benefit smokers (9,10). Although several randomized controlled trials and systematic reviews have been done to comprehensively evaluate the efficacy of local application of antimicrobial adjuncts in smokers, the best controlled local drug delivery (CLDD) system remains unanswered [1,2,9-10]. Therefore, the study aims to assess the effect of locally administered controlled-release 10% doxycycline hyclate gel in smokers and non-smokers for the reduction of probing pocket depth (PPD), clinical attachment level (CAL), plaque index (PI), gingival index (GI) and sulcular bleeding index (SBI), along with changes in colony-forming units (CFU) of three major periodontal pathogens in periodontitis. The null hypothesis was that there was no change in the clinical and microbiological parameters following the controlled released local drugs application between smokers and non-smokers with periodontitis.

METHODS

Study design

Forty patients diagnosed with periodontitis were enrolled in this study that was conducted over three months (December 2012 to February 2013) at the outpatient unit of the Department of Periodontology and Implantology of Institute of Dental Sciences and Dental Unit of Rohilkhand Medical College, Bareilly, Uttar Pradesh (UP), India. Participants who met the eligibility criteria of the study were all adults aged 18 and above.

The study was done as per the Declaration of Helsinki (as amended in Edinburgh, 2000). It was approved by the Institutional Ethics Committee (IEC) of the Institute of Dental Sciences and Dental Unit Rohilkhand Medical College, *vide* IEC approval no. IDC/ETHCC/12/08(11). The study was registered with the Clinical Trial Registry of India (CTRI REF/2020/11/038185). The study protocol was explained to all the participants, and their informed consent was obtained before the commencement of the study. The study was conducted at the Department of Periodontology and Implantology of the Institute of Dental Sciences, Bareily, India. The gel preparation of doxycycline hyclate, a tetracycline derivative, was formulated at the Department of Pharmaceutical Technology of Rakhspal Bahadur Institute of Pharmacy (Bareilly), India.

Samples

These study participants were selected using a systematic random sampling method from the list of patients diagnosed with periodontitis at the OPD from December 2012 to February 2013. They were categorized into non-smokers (n = 20) and smokers (n = 20) based on smoking history. All participants who took part in this trial fulfilled the criteria of chronic periodontitis according to the AAP 1999 classification and were age- and gender-matched. The inclusion criteria for the patient selection were (a) patients in the age group of 18 - 60 years, (b) untreated chronic periodontitis with a minimum of four periodontal pockets per quadrant, (c) pockets with probing depth 4 to 6 mm. Patients with systemic diseases, who had received antibiotics during the previous three months, or who had received antiseptic/ antiplaque agents in the last three months, and patients who had undergone periodontal treatment the last six months, were excluded from the study.

Sample size calculation

Sample size (n) was calculated using Eq 1.

$$n = \frac{2(Standard\ deviation)^2}{(Effect\ size)^2}(Z_{\alpha/2} + Z_{1-\beta})^2 \quad \ldots (1)$$

where $Z_{\alpha/2}$ = 1.96, $Z_{1-\beta}$ = 1.28 are respectively the 95 % confidence value obtained from the standard normal distribution. At least 17 subjects were needed to detect a significant difference in PPD after intervention with an effect size of 0.50 and a standard deviation of 0.45 from the pilot study using ten patients. To compensate for the dropouts, 10 % of n is added to get the final sample size. Hence, the final minimum sample size in each group was n = 20.

Procedure

The periodontal status of each patient was recorded using probing pocket depth (PPD), clinical attachment level (CAL), gingival index (GI), sulcular bleeding index (SBI), and plaque index (PI) were assessed before and after application of the 10% doxycycline gel. All examinations were done using a mild force by a single examiner all through the study duration. The PPD and CAL were assessed with the help of the Hu-Friedy UNC-15 probe at six sites per tooth at baseline and one month. The mean values of the PPD and CAL were calculated of the treated tooth and used for further analysis. Ten patients were examined twice with a difference of 24 hours before the study to assure intra-examiner calibration. It was accepted if the readings at the baseline and 24 hours were similar to 1 mm at the 95 % level.

Following initial examination and treatment planning, both groups received scaling and root planning, followed by the application of 10 % doxycycline hyclate gel into the deep pockets. All the clinical data at the baseline and during follow-up visits were recorded by an experienced periodontist (GS) blinded to the study procedure. On the other hand, the treatment (SRP and CLDD) was carried out by another experienced periodontist (SG).

Formulation of 10 % doxycycline hyclate gel

An anhydrous solution was used as a carrier which was needed to protect the stabilization of doxycycline hyclate. A stable biodegradable controlled-release gel formulation of 10 % doxycycline hyclate was developed in the laboratory of Rakhspal Bahadur Institute of Pharmacy (Bareilly), Department of Pharmaceutical Technology. Glycerol monooleate (GMO) gel is a biodegradable and durable solution that is syringe-administered and converted in the periodontal pocket into a semi-solid shape, attaches to the mucosa, and is well-contained in the periodontal pocket. Five per cent of sesame oil was combined with 95 per cent of the melted GMO at 60-70 °C. This was done by continuous stirring to prepare doxycycline hyclate gel in the GMO and sesame oil mixture. Ten per cent of doxycycline hyclate (Figure 1) was applied to the vehicle before a homogenous gel was obtained. This was done only after the vehicle had attained room temperature. The 10 % doxycycline hyclate gel was then filled into syringes that were ready for clinical use (12).

Figure 1: a) Doxycycline hyclate powder in raw form (PHR1145-Fluka-*SIGMA ALDRICH*®); b) GMO-Glyceryl-mono-oleate (Estosoft-GMO®); c) Laboratory formulated sustained release 10 % doxycycline hyclate

Microbiological analysis

Before recording clinical parameters, subgingival plaque samples were collected from the selected sites before and after treatment to evaluate the

changes in numbers and proportions of the primary periodontal pathogens, i.e., *Prevotella intermedia*, *Porphyromonas gingivalis*, and *Tannerella forsythia*. Plaque samples from patients were collected using sterile area-specific Gracey curettes (Hu Friedy)® in a previously fumigated minor operation theatre. The samples were transferred into vials containing Robertson Cooked Meat Medium (RCM) and were incubated at 37 °C for 24 - 72 hours. The antimicrobial effectiveness of biodegradable controlled-release 10 % doxycycline hyclate gel was recorded using conventional culture methods and specific biochemical tests for each bacterium.

Porphyromonas gingivalis, Prevotella intermedia and *Tanerella forsythia* were cultured on selective media using a standard protocol. The total number of colony-forming units (CFU) was determined based on serial dilution from 10^{-1} to 10^{-3} on selective media. Finally, each bacteria's count was determined typical colony and bacterial morphology in 10^{2} CFU on MHA (Muller Hinton Agar)/millilitre (Figure 2).

Figure 2: a) Anaerobic Transport Medium-Robertson Cooked Meat Medium; b) Samples were incubated at 37 °C for 27-72 hours; c) Colony Forming Unit (CFU) on Muller Hinton Agar

After one week of mechanical debridement, patients were scheduled for root planing and local drug delivery application. On the scheduled appointment after root planing with area specific Gracey curettes, the above mentioned 10 % doxycycline gel was inserted into the bases of the pockets using a special syringe with a blunt cannula. The end of the blunt cannula was moved coronally to fill the pocket, and the excess gel was removed using a curette or wet cotton pellet. The site was covered with a periodontal dressing (Coe-Pak®) to prevent the medication from being flushed out of the pocket (Figure 3). Patients were advised to use 0.2 per cent of chlorhexidine rinses and refrain from brushing the test tooth for one week. After one week, the patients reviewed for any discomfort such as transient discomfort, erythema, transient resistance, allergy following treatment, and visual examination to record any soft tissue changes after removal periodontal dressing. After one month, all patients were recalled for a check-up and further evaluation.

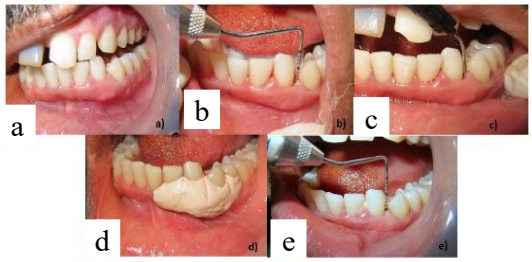

Figure 3: a) Pre-operative view; b) Probing Pocket depth at baseline; c) Placement of the drug with blunt cannula syringe; d) Placement of periodontal dressing (Coe-pak®); e) Probing Pocket depth postoperatively

Statistical analysis

Data on various parameters from smokers and non-smokers were subjected to statistical treatment using SPSS version 23.0. Since data distribution was non-normal and the sample size in each group is less than 30, non-parametric statistical tests were employed. Data are presented as mean ± standard error (SE). Comparisons between the groups were made by the Mann-Whitney *U* test, while Wilcoxon's signed-rank test was used for intragroup comparisons. Calculated *p*-value less than 0.05 were considered to be statistically significant.

RESULTS

All the forty patients recruited completed the study. The patients reported no adverse effects or complaints during the study. Table 1 shows a comparison of PPD and CAL in both test and control groups at baseline and re-evaluation after one month.

Table 1: PPD and CAL in test and control groups at baseline and re-evaluation after one month

Variable		Smoker (n=20)	Non-smoker (n=20)	*P*-value
PPD	Baseline	4.26 ± 0.12	4.24 ± 0.12	0.925
	After 1 month	3.20 ± 0.11	3.50 ± 0.12	0.038*
	% Change	24.88	17.45	0.242
	P-value	0.000**	0.001**	
CAL	Baseline	4.32 ± 0.12	4.37 ± 0.14	0.765
	After 1 month	3.59 ± 0.11	3.75 ± 0.11	0.301
	Change (%)	16.90	14.19	0.344
	P-value	0.000**	0.001**	

***Significant at p < 0.01, *significant at p < 0.05*

A statistically significant change ($p < 0.01$) of 24.88 % in the PPD was observed among smokers between baseline (4.26 ± 0.12mm) and re-evaluation at one month. Similarly, in non-smokers also, a 17.45 % change in the PPD between baseline (4.24 ± 0.12) and re-evaluation at one month (3.50 ± 0.12) was observed, which was statistically significant ($p < 0.01$). Similarly, a statistically significant difference was found between smokers and non-smokers in PPD at the end of a 1-month re-evaluation ($p < 0.05$). A significant difference was found in terms of the average CAL of smokers and non-smokers evaluated at baseline and re-evaluation ($p < 0.01$). For smokers, the average CAL at baseline was 4.32 ± 0.12, and it significantly reduced to 3.59 ± 0.11 after one month (16.90%), while for non-smokers, CAL changed from 4.37 ± 0.14 to 3.75 ± 0.11 with a 14.19 % change when compared with the baseline. No significance was noticed between smokers and non-smokers based on the baseline, re-evaluation, and per cent change in CAL ($p > 0.05$).

Table 2 shows changes in PI, GI, and SBI observed in smokers and non-smokers at baseline and re-evaluation after one month. No significant difference was observed between smokers and non-smokers ($p > 0.05$), although the changes within each group were statistically significant. There was a considerable change in the average GI of smokers during baseline to a one-month re-evaluation ($p < 0.01$). For smokers, the average GI at baseline was 1.55 ± 0.06, and it significantly reduced to 0.64 ± 0.08 after one month (58.71 %). Similarly, there was a significant change in the mean GI of non-smokers at baseline to a one-month re-evaluation ($p < 0.01$). For non-smokers, the average GI at baseline was 1.86 ± 0.07, and it significantly reduced to 0.66 ± 0.08 on re-evaluation after one month (64.52 %). No statistically significant difference was demonstrated between smokers and non-smokers based on the re-evaluation and per cent change in GI ($p > 0.05$).

There is a significant change in smokers' average SBI at baseline to a one-month re-evaluation ($p < 0.01$). For smokers, the average SBI at baseline was 1.25 ± 0.16, and it significantly reduced to 0.15 ± 0.07 after one month (88.00%). Similarly, there was a significant change in the average SBI of non-smokers during baseline to a re-evaluation ($p < 0.01$). For non-smokers, the average SBI in baseline was 2.11 ± 0.14, and it significantly reduced to 0.14 ± 0.05 after one month (93.36 %). No significance was observed between smokers and non-smokers based on the one-month re-evaluation and per cent change in GI ($p > 0.05$).

Table 2: PI, GI, SBI in test and control groups at baseline and re-evaluation after one month

Variable		Smoker	Non-smoker	*P*-value
PI	Baseline	1.84 ± 0.10	1.89 ± 0.05	0.645
	After 1 month	0.73 ± 0.06	0.60 ± 0.07	0.143
	Change (%)	60.33	68.25	0.060
	P-value	0.000**	0.000**	
GI	Baseline	1.55 ± 0.06	1.86 ± 0.07	0.001
	After 1 month	0.64 ± 0.08	0.66 ± 0.08	0.715
	% Change (%)	58.71	64.52	0.400
	P-value	0.000**	0.000**	
SBI	Baseline	1.25 ± 0.16	2.11 ± 0.14	0.001
	After 1 month	0.15 ± 0.07	0.14 ± 0.05	0.654
	Change (%)	88.00	93.36	0.949
	P-value	0.000**	0.000**	

***Significant at p < 0.01*

Table 3 shows changes in the microbial CFUs after the application of the CLDD gel. There is a significant change in the average CFUs of *P. intermedia* in smokers during baseline to a re-evaluation ($p < 0.01$). For smokers, the average CFU counts related to *P. intermedia* at baseline was 0.84 ± 0.12, and it significantly reduced to 0.56 ± 0.09 upon re-evaluation (33.33 %at). Similarly, there was a significant change in average *P. intermedia* CFUs of non-smokers over time ($p < 0.01$). For non-smokers, the average CFU counts related to *P. intermedia* at baseline were 1.09 ± 0.10, and it significantly reduced to 0.66 ± 0.09 after re-evaluation (39.45 %).

There is a significant change in the average CFUs of *P. gingivalis* of smokers during baseline to a one-month re-evaluation ($p < 0.01$). For smokers, the mean *P. gingivalis* CFUs at baseline was 0.83 ± 0.14, and it significantly reduced to 0.67 ± 0.15 after one month (19.28%). Similarly, a significant change was observed in the average CFU counts of *P. gingivalis* in non-smokers during baseline to a re-evaluation ($p < 0.01$). For non-smokers, this average CFU counts of *P. gingivalis* at baseline was0.79 ± 0.14, and it significantly reduced to 0.40 ± 0.09 (49.37 %).

Table 3: Colony-forming units of both test and control groups at baseline and re-evaluation after one month

Parameter	Test	Smoker	Non-smoker	*P*-value
Prevotella intermedia	Baseline	0.84 ± 0.12	1.09 ± 0.10	0.295
	after 1 month	0.56 ± 0.09	0.66 ± 0.09	0.309
	Change (%)	33.33	39.45	0.255
	P-value	0.002**	0.000**	
Porphyromonas gingivalis	Baseline	0.83 ± 0.14	0.79 ± 0.14	0.978
	after 1 month	0.67 ± 0.15	0.40 ± 0.09	0.307
	Change (%)	19.28	49.37	0.052
	P-value	0.002**	0.001**	
Tannerella forsythia	Baseline	0.62 ± 0.12	0.73 ± 0.14	0.645
	after 1 month	0.40 ± 0.11	0.38 ± 0.10	1.000
	Change (%)	35.48	47.95	0.279
	P-value	0.002**	0.000**	

***Significant at p < 0.01*

A statistically significant change in the average CFU counts of *T. forsythia* among smokers ($p < 0.01$) was observed. For smokers, the average *T. forsythia* CFU at baseline was 0.62 ± 0.12, and it significantly reduced to 0.40 ± 0.11 after one month (35.48%).

Similarly, for non-smokers, the average *T. forsythia* CFU at baseline was 0.73 ± 0.14, and it significantly reduced to 0.38 ± 0.10 after one month (47.95%). Table 4 shows the percentage changes in clinical and microbial parameters among smokers with periodontitis after one month.

Table 4: Change in clinical and microbial parameters among smokers with periodontitis after 1 month

Variable	Smoker (n=20)	Non-smoker (n=20)	Difference (%)
PPD	24.88	17.45	10.43
CAL	16.90	14.19	2.71
PI	60.33	68.25	-7.92
GI	58.71	64.52	-5.81
SBI	88.00	93.36	-5.36
Pi	33.33	39.45	-6.12
Pg	19.28	49.37	-30.09
Tf	35.48	47.95	-12.47

DISCUSSION

Smoking not only negatively impacts the occurrence but also the development and treatment outcome of periodontal disease. This study evaluated the efficacy of locally administered controlled-release 10 % doxycycline hyclate gel to improve clinical and microbial parameters among smokers with periodontitis compared with non-smokers. Literature shows unanimously that, relative to non-smokers, smokers have a greater vulnerability, higher incidence, and faster development of periodontal disease [13]. Treatment of periodontitis poses more significant challenges in smokers since smokers tend to lose more teeth and have a less favourable response to therapy than non-smokers. However, the mechanisms involved remain uncertain. An LDD-order drug release kinetics is enabled in controlled-release drug delivery since the reservoir of the antimicrobial agent is kept away from the local removal mechanisms once it is placed in the periodontal pocket. This helps in maintaining a consistently high concentration of the drug in the periodontal pocket. Moreover, after application, the concentration of CLDD significantly exceeds the minimum inhibitory concentration (MIC) and persists at high levels in the site for 7 to 14 days (6). Therefore, local application of 10% doxycycline hyclate gel in periodontal pockets was used in this study.

A significant clinical benefit was observed in our study following the application of10% doxy in smokers. They exhibited greater PPD and CAL reduction compared to non-smokers after one month. Many similar reports have been published [6,14]. A shift from periodontitis to clinical health can be attributed to doxycycline's local application's numerous therapeutic effects [15]. Doxycycline suppresses periodontal pathogens by its anti-collagenase, anti-inflammatory and anti-metalloproteinase properties. This improves clinical parameters, including substantial reductions in BOP, suggesting that adjunctive treatment with doxycycline is more effective than mechanical debridement alone [16]. Variability in results may be due to many reasons, such as using automated probes [10] and different doxycycline gel concentrations such as 8.5 % [17]. The flowable nature of the polymer gel fills and conforms to the pocket morphology. It transforms into a wax-like substance after contact with the sulcular fluid, which could have also been a beneficial factor in enhancing the study's primary outcome measure.

Smokers tend to show less favourable results than non-smokers with periodontitis [18]. This

could be because PPD in non-smokers showed a more significant difference than in smokers following SRP alone. In the present r study, the resolution of gingival inflammation and sulcular bleeding was marginally in non-smokers following 10 % doxycycline gel, although this difference was not statistically significant. These results are in line with the previous reports of improved treatment results in non-smokers [19]. Studies show that the orogranulocytic migratory rate is directly associated with GI and is not susceptible to plaque or calculus. It is proposed that oPMNs accumulate in periodontal tissue in smokers rather than migrating via the gingival crevice. They expel their constituents, contributing to increased deterioration of connective tissue components (20). Moreover, the enhanced oxidative burst of polymorphonuclear leukocytes, reactive oxygen species production, and lipid peroxidation play a role in healing tissues in smokers.

In terms of microbial pathogens, a more remarkable improvement was observed among non-smokers than smokers. However, there were significant intra-group changes in both groups following treatment with the doxy gel. This may be attributed to the critical regrowth of pathogenic species after treatment [18]. It is clinically relevant to understand the dynamics of subgingival recolonization of periodontal pathogens in smokers as this group responds poorly to SRP. It is noteworthy that smokers showed an improvement that was 30.09 % less than non-smokers.

The present study shows that smokers have different treatment response patterns and healing dynamics than non-smokers following 20 % doxycycline gel and SRP. This indicates the need for a more stringent treatment regimen for smoking patients for a better treatment outcome and a reduced risk of further developing periodontal disease. Another possibility is that since the 10 % doxycycline gel was only locally applied into periodontal pockets, periodontal pathogens present within the adjacent gingival connective tissues and on the tongue, tonsils, and buccal mucosa would not have been eliminated. This could be the reason for less significant improvement in microbial CFUs and secondary outcomes of clinical parameters such as GI, SBI, and PI in smokers. Simultaneous application of CLDD into the pocket and oral rinsing with the same drug in future studies can be a treatment option to improve the drug's clinical and microbial effects.

Among non-smokers, secondary clinical outcome measures such as GI, SBI, and PI are correlated with a more significant reduction of *P. gingivalis*. In other words, the lack of substantial improvement of GI and SBI in smokers in response to CLDD+SRP correlated with a similar kind of reduction in *P. gingivalis*. This could be explained on the basis that, by functioning as a possible community activist, *P. gingivalis* exerts a profound impact on the volume and composition of the oral microbiota, even at low abundance [21,22]. Since *P. gingivalis* exploits the host immune response by various techniques with various virulence factors (such as gingipains) and manipulating neutrophils, the more remarkable improvement in signs of inflammation non-smokers can occur possibly due to a more significant reduction of *P. gingivalis*.

The present study is relevant because of its practical advantages. Doxycycline is widely available, is cost-effective, and safe. Furthermore, the patients reported no adverse reactions such as transient discomfort, erythema, transient resistance, and allergy or pain. In contrast, Garrett *et al* [23] found that less than 1 % of the subject showed some adverse reactions. Keeping in mind the current scenario of COVID-19, doxycycline has been suggested as a potential agent in the treatment armamentarium because of its anti-viral and anti-inflammatory effects, broad microbiological coverage, and anti-collagenase effects [24]. The scientific community are yet to fully understand the deleterious periodontal impacts of the novel COVID-19 virus. This adds significance to the use of CLDD using doxycycline in the management of periodontitis during post-pandemic times.

A randomized controlled double-blinded multi-centric trial with a larger sample size is being planned to evaluate the effect of 10 % doxy gel in smokers. Subsequent studies would apply the new classification of periodontitis and a larger sample size to study this wonder drug's effect. Future research should focus on doxycycline molecular inclusions into β-cyclodextrin as it has shown promising results when used as a local drug delivery system in periodontitis. Similarly, drug-loaded films can be implemented as a potential control release device. This technique has been reported to induce an increase in water absorption and increase the weight loss of the films. Cost-effectiveness and patient-centred outcomes should be included in the upcoming studies as patient satisfaction is a critical component in any successful therapy.

CONCLUSION

A single application of locally administered

controlled-release 10 % doxycycline hyclate gel yields short-term clinical and microbial benefits for smokers and non-smokers in the management of periodontitis. Therefore, doxycycline gel is recommended in the management of periodontitis.

DECLARATIONS

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Conflict of interest

No conflict of interest is associated with this work. There was no external funding for this study.

Contribution of authors

We declare that this work was done by the author(s) named in this article. All the liabilities pertaining to claims relating to the content of this article will be borne by the authors. Conception and design of the study were done by ST Gokhale; acquisition of data by G Singh, RG Manjunath; analysis and/or interpretation of data by RR Nagate, SM Al-Qahtani, B Joseph. Drafting of the manuscript was by G Singh, ST Gokhale, B Joseph while revising the manuscript was by V Venkataram, RG Manjunath, RR Nagate, SM Al-Qahtani. All the authors approved the final draft of the manuscript.

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