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Original Article

Comparative Evaluation of the Efficacy of 10% Doxycycline Gel And 1% Chlorhexidine Digluconate Gel in the Disinfection of Sandblasted Acid-Etched Titanium Implant Surface Contaminated with Porphyromonas Gingivalis

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Abstract

The study evaluates the efficacy of 10% doxycycline gel and 1% chlorhexidine (CHX) gel in the disinfection of sandblasted acid-etched titanium implant surfaces contaminated with *Porphyromonas gingivalis*. Titanium implants were divided into two groups – Group A and Group B, which were further subdivided into three subgroups (A1, A2, and A3 and B1, B2, and B3). All the implants were contaminated with *P. gingivalis.* Group A was treated with 10% doxycycline gel, and Group B was treated with 1% CHX gel. After decontamination with antimicrobials, the residual viable *P. gingivalis* count was assessed using the culture method. At baseline, the mean values recorded for Group A and Group B were 120,000,000 colony-forming unit (CFU). On day 1, the mean values recorded were 3291.67 CFU (Group A1) and 0 CFU (Group B1). On days 3 and 7, the mean values for the remaining groups (A2, A3, B2, and B3) were 0 CFU. A single application of 1% CHX gel and multiple applications of 10% doxycycline gel were effective in achieving decontamination of implants. Hence, these gels could prove as cost-effective treatment modalities for peri-implantitis.

Key words: Anti-infective agents, Chlorhexidine, Doxycycline, *Porphyromonas gingivalis*

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Introduction

Oral health is an integral part of general health. A healthy dentition, efficient mastication, and ability to smile contribute to maintaining a patient's quality of life. Thus, with the advent of implant dentistry, replacing missing teeth became more appealing to the patients [1]. Although implants have demonstrated a very high clinical success rate, complications still pose challenges that need to be addressed [2]. These complications can be grouped as mechanical, technical, or biological [3, 4]. Biological complications constitute peri-implantitis, which is an infectious disease of the peri-implant tissues.

A systematic review of microbial biofilm profile of peri-implantitis concluded that the most common red-complex bacteria found in the peri-implantitis sites were *Porphyromonas gingivalis* [5]. The treatment modalities for peri-implantitis are broadly classified as nonsurgical and surgical approaches. Mechanical debridement, local drug delivery, laser, and

photodynamic therapy are nonsurgical methods of treating peri-implantitis, whereas the surgical approach includes resective and regenerative treatments. Antibiotic therapy can serve as an alternative treatment option where access is difficult, and the patient or the site is not suitable for surgical intervention [6].

Antimicrobials in combination with mechanical debridement, which have been evaluated till date, are 0.2% chlorhexidine (CHX), 10% hydrogen peroxide, 5% tetracycline HCL solution, 25% metronidazole, minocycline, and citric acid, and 14% doxycycline. Yet, no antimicrobial has proven 100% effective for decontaminating implants [7].

The rationale of this study is that decontamination of implants is of utmost importance in the healing of peri-implant defects to avoid untimely loss of the implant. Although peri-implantitis is caused by a complex microbiome, *P. gingivalis* forms one of the major components of peri-implantitis-related complex [8]. Hence, anti-infective agents should be tested against *P. gingivalis.* Among various antimicrobials, CHX has been extensively studied in the treatment of peri-implantitis at various concentration levels due to its high substantivity [9, 10]. However, it proved ineffective against *P. gingivalis* when used at lower concentrations like 0.05%–0.2% with a single application. Similarly, a study has shown that doxycycline produced short-term significant results in the treatment of peri-implantitis [11]. However, since no study has evaluated effectiveness of 1% CHX and 10% doxycycline against *P. gingivalis,* it is important to develop antimicrobial application protocols specifically targeting this primary pathogen and key colonizer in peri-implantitis. Therefore, to evaluate the effectiveness of antimicrobials against *P. gingivalis,* we intended to compare the efficacy of 10% doxycycline gel and 1% CHX gel in the disinfection of sandblasted acid-etched (SAE) titanium implant surface contaminated with *P. gingivalis.*

Materials and Methods

The present *in vitro* study was approved by the Ethical Committee and carried out in the department of periodontics, during the year 2018–2021.

A total of 72 SAE titanium implants were divided randomly into two groups. Group A, comprising 36 titanium implants, was treated with 10% doxycycline gel. Group B, comprising 36 titanium implants, was treated with 1% CHX gel. Each group was further subdivided into three subgroups comprising 12 implants as follows – A1, A2, A3, B1, B2, and B3.

Pharmacological excipients such as poloxamer (P407) and propylene glycol (PG), used for the formulation of doxycycline gel, were purchased from BASF Pharmaceuticals and Bangalore Fine Chemicals, respectively. Doxycycline was procured as a gift sample from Sisco Research Laboratories Private Limited.

Poloxamer gel was prepared by the cold method as described by Schmolka, 1972 [12]. A weighted amount of P407 was gradually added to cooled distilled water by maintaining it in an ice bath at 4ºC to form a 20% w/v solution of P407 and was stored in the refrigerator overnight for complete dissolution [13]. The resulting clear viscous solution was maintained at room temperature to form a gel. A weighted amount of doxycycline hyclate was incorporated into the P407 base to formulate gel with a 10% concentration. The consistency of the gel was adjusted by adding PG **(Figure 1)**. A commercially available CHX gel with a 1% concentration was stored at 4ºC **(Figure 2)**.

a b

Figure 1. Formulation of 10% doxycycline gel. (a) Poloxamer gel base stored in an ice bath at 4ºC; (b) Addition of doxycycline hyclate, propylene glycol, and benzalkonium chloride to poloxamer gel base

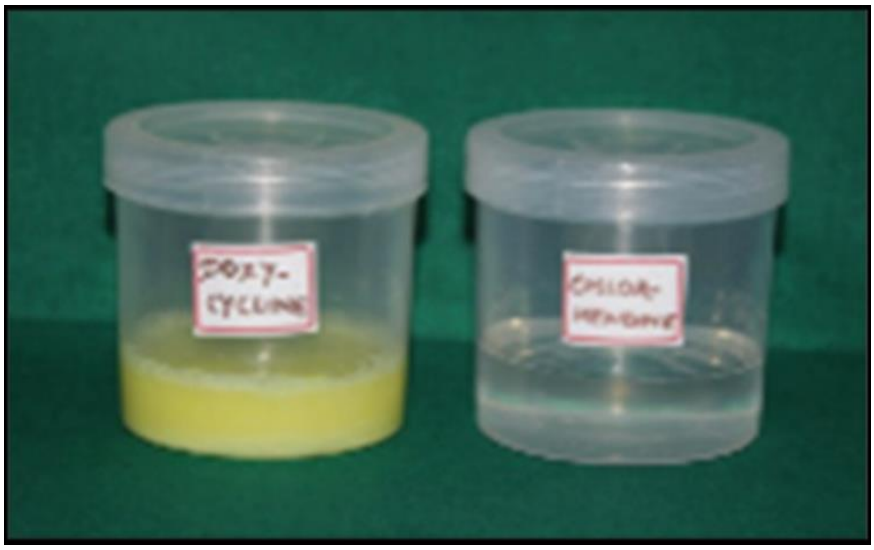
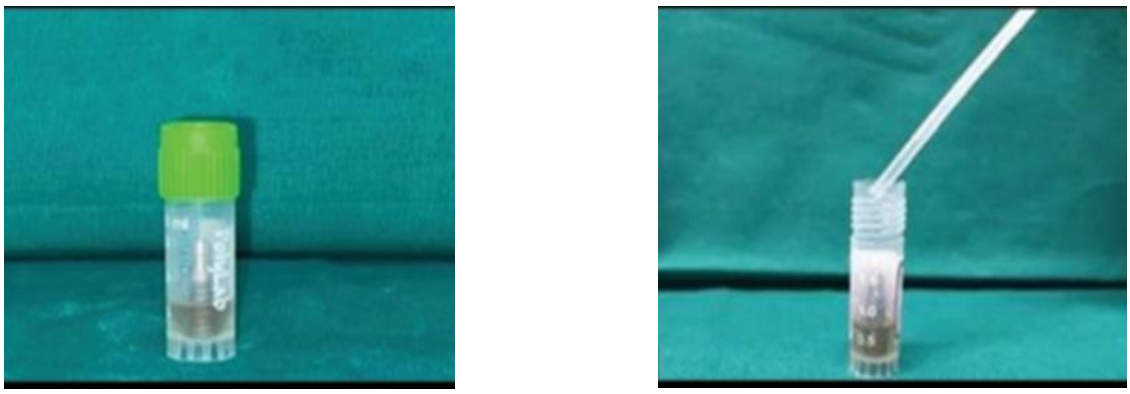


Figure 2. Antimicrobial gels used for treatment – 10% doxycycline gel and 1% chlorhexidine gel

The American Type Culture Collection (ATCC) 33277 strain of *P. gingivalis* was procured from HiMedia (KWIK-STIK™) in lyophilized form and preserved at 4ºC. Each KWIK-STIK contains a lyophilized microorganism pellet, an ampoule of hydrating fluid, and an inoculating swab. Recovery of the lyophilized cells was carried out according to ATCC guidelines.
Before inoculating the implants with *P. gingivalis*, they were sterilized in a dry autoclave at 121ºC for 15 min. Sterile plastic cryovials (2 ml capacity, 45 mm height × 11 mm diameter) were used to embed the implants. Thioglycolate (TG) agar (1%) was used as the culture medium and was autoclaved at standard pressure and temperature (120°C for 15 min, 1 bar).
The culture medium was allowed to cool until it reached a semisolid consistency. At this stage, sterile implants were embedded such that approximately half of the implants were submerged within the solidifying agar. After the agar had solidified, the exposed parts of the implants were contaminated by adding an aliquot (0.5 ml) of *P. gingivalis* suspension containing 1.2×10^8 bacterial cells **(Figure 3)**. All the vials were placed in an anaerobic chamber and incubated at 37ºC in a 5% CO_2 incubator for 48 h **(Figure 4)**.



a b

Figure 3. (a) Implant embedded in semisolid thioglycollate agar; (b) Addition of an aliquot containing *P. gingivalis* on implant

Figure 4. Vials containing *Porphyromonas gingivalis* contaminated implants placed in an anaerobic jar

On day 1, all the implants in Group A were treated with doxycycline gel using a syringe fitted with a blunt cannula and were allowed to stay in contact for about 3 min. Similarly, implants in Group B were treated with CHX gel which was left in contact for 10 min. Following the decontamination treatment, both the groups were thoroughly irrigated with sterile saline **(Figure 5)**.

a b

Figure 5. (a and b) Application of antimicrobial gel on implant

Implants from subgroups A1 and B1 were transferred into sterile microtubes containing 10 ml of TG broth. Each microtube containing an implant was vortexed for 60 s to allow bacteria to detach from the implant surface. Subsequently, the resulting bacterial suspension was serially diluted to 10^2 **(Figure 6)**. The diluted vortexed suspension was subsequently plated onto blood agar for colony-forming unit (CFU) analysis **(Figure 7)**. The inoculated blood agar plates were incubated at 37ºC in a 5% CO_2 incubator for 48 h. The remaining implants from subgroups A2, A3, B2, and B3 were returned to the incubator.

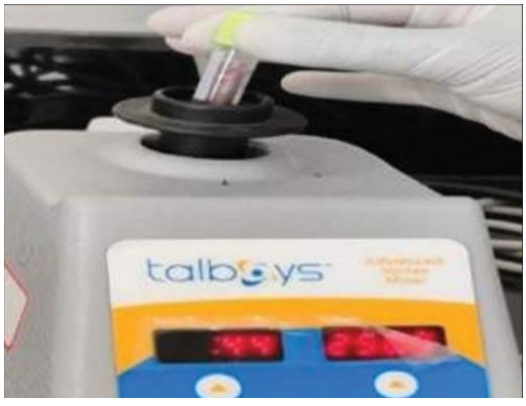


Figure 6. Vortexing of disinfected implants in 10 ml of thioglycollate broth for 60 s

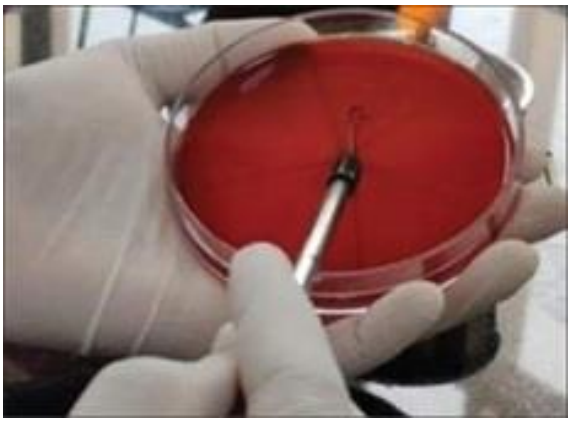
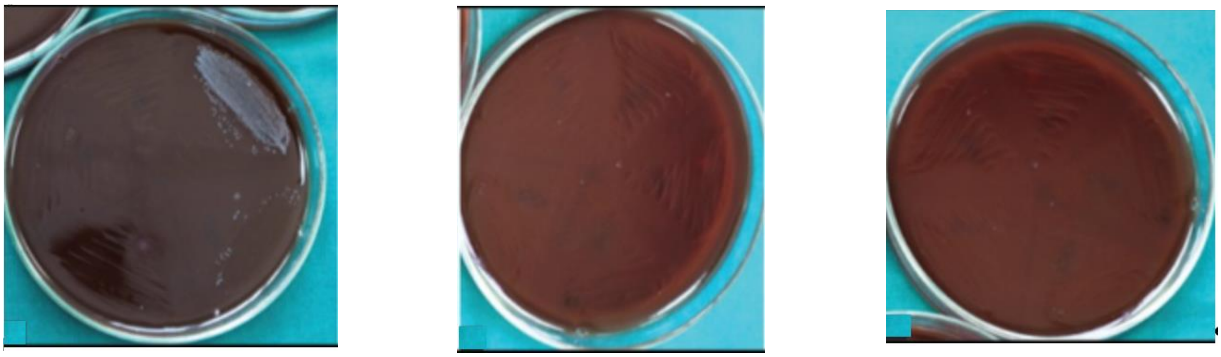


Figure 7. Vortexed broth cultured on blood agar

On day 3, antimicrobial gels were applied to the implants of subgroups A2, A3, B2, and B3, following the same protocol, employed on day 1. However, only implants from subgroups A2 and B2 were subsequently transferred to the sterile microtubes containing TG broth and vortexed. The resulting diluted suspension was plated onto blood agar medium and incubated at 37ºC in a 5% CO_2 incubator for 48 h. The implants in subgroups A3 and B3 were returned to the incubator.

On day 7, implants from subgroups A3 and B3 were treated with antimicrobial gels, similar to the procedure employed on day 1 and day 3. Followed by which, these implants were transferred to the TG medium to obtain a bacterial suspension. The diluted suspensions were plated onto blood agar and were incubated at 37ºC in a 5% CO_2 incubator for 48 h.

Following an incubation period of 48 h on days 1, 3, and 7, *P. gingivalis* colonies were identified on the blood agar and were manually counted using a magnifying glass **(Figures 8 and 9)**. The methodology of the study is illustrated in the flow chart **(Figure 10)**.



a b c

Figure 8. Colony-forming unit (CFU) of *Porphyromonas gingivalis* on blood agar for implants in subgroups A1, A2, and A3 treated with 10% doxycycline gel. (a) CFU for subgroup A1 implants; (b) CFU for subgroup A2 implants; (c) CFU for subgroup A3 implants

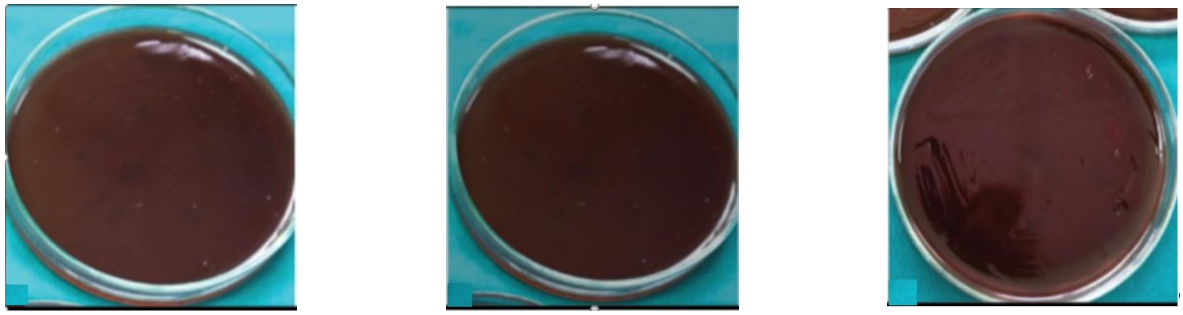


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Figure 9. Colony-forming unit (CFU) of *Porphyromonas gingivalis* on blood agar for implants in subgroups B1, B2, and B3 treated with 1% chlorhexidine gel. (a) CFU for subgroup B1 implants; (b) CFU for subgroup B2 implants; (c) CFU for subgroup B3 implants

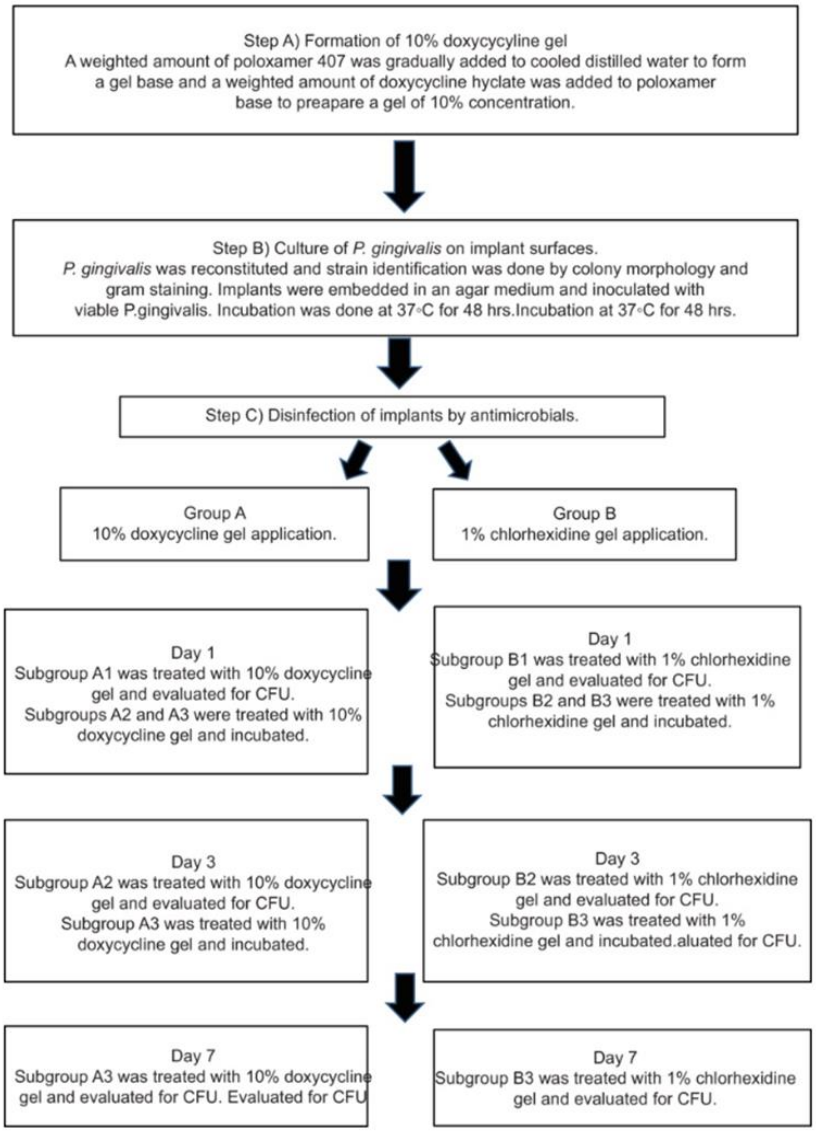

Figure 10. Study design flowchart

Results and Discussion

The mean CFU recorded at baseline for both Groups A and B was 1.2×10^8. On day 1, the mean CFU count for subgroup A1 was 3291.67, whereas no bacterial growth (0 CFU) was detected for subgroup B1. On days 3 and 7, the mean CFU values for the remaining subgroups – A2, B2, A3, and B3 were also 0.

Intragroup comparison among subgroups A1, A2, A3 and B1, B2, B3 was done using Friedman's test (for >2 observations). **Table 1** and **Figure 11** illustrates a statistically highly significant difference in CFU values between the baseline and subgroups A1, A2, and A3 ($P < 0.01$). Among these subgroups, CFU values were higher for A1 when compared with the CFU values of subgroups A2 and A3, with the differences being highly significant ($P < 0.01$). Similarly, Table 2 and **Figure 12** demonstratesa highly significant difference in the values between the baseline and subgroups B1, B2, and B3 ($P < 0.01$). However, the differences in CFU values among these subgroups were statistically nonsignificant ($P > 0.05$).

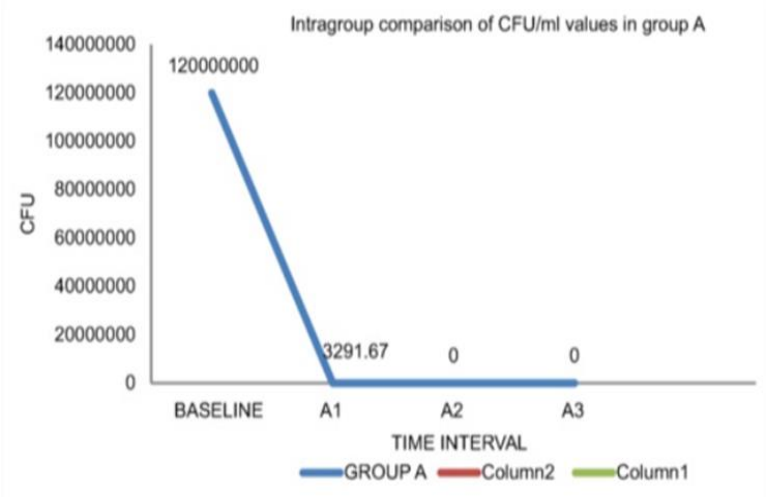

Figure 11. Bar Figure showing the difference between colony-forming unit count of *Porphyromonas gingivalis* retrieved from implants before and after treatment with 10% doxycycline gel for subgroups A1, A2, and A3. CFU – Colony-forming unit

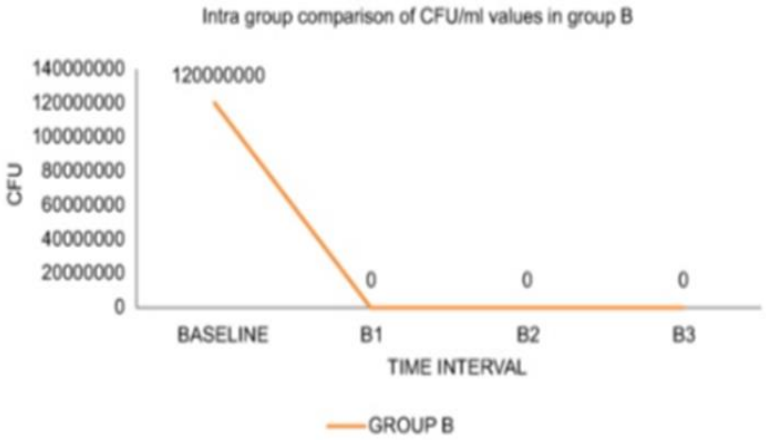

Figure 12. Bar Figure showing the difference between colony-forming unit count of *Porphyromonas gingivalis* retrieved from implants before and after treatment with 1% chlorhexidine gel for subgroups B1, B2, and B3. CFU – Colony-forming unit

Table 1. Colony-forming unit count of *Porphyromonas gingivalis* for Group A implants before and after treatment with 10% doxycycline gel

	n	Mean	SD	Minimum	Maximum	Median	Mean rank	$\chi 2$	*P* value of Friedman test
Baseline	36	120,000,000	0.000	120,000,000	120,000,000	120,000,000	4.00	33.545	0.000**
A1 (day 1)	12	3291.67	5451.34	0	20,000	2300.00	2.75		
A2 (day 3)	12	0.00	0.000	0	0	0.00	1.63		
A3 (day 7)	**12**	**0.00**	**0.000**	**0**	**0**	**0.00**	**1.63**		

SD – Standard deviation; *P* - Probability value, *n* - Sample size, $^{**}P < 0.01$ - Highly significant

Table 2: Colony-forming unit count of *Porphyromonas gingivalis* for Group B implants before and after treatment with 1% chlorhexidine gel

	n	Mean	SD	Minimum	Maximum	Median	Mean rank	$\chi 2$	*P* value of Friedman test
Baseline	36	120,000,000	0.000	120,000,000	120,000,000	120,000,000	4.00	36.000	0.000**
B1 (day 1)	12	0.00	0.000	0	0	0.00	2.00		
B2 (day 3)	12	0.00	0.000	0	0	0.00	2.00		
B3 (day 7)	12	0.00	0.000	0	0	0.00	2.00		

SD – Standard deviation; *P* - Probability value, *n* - Sample size, $^{**}P < 0.01$- Highly significant

Intergroup comparisons between Groups A and B were done using the Mann–Whitney *U*-test. **Table 3** demonstrates a statistically highly significant difference in CFU count between Groups A1 and B1 ($P < 0.01$) **(Figure 13)**. **Tables 4 and 5** illustrate a statistically nonsignificant difference in CFU values between Groups A2 and B2 and between Groups A3 and B3 ($P > 0.05$) **(Figure 13)**.

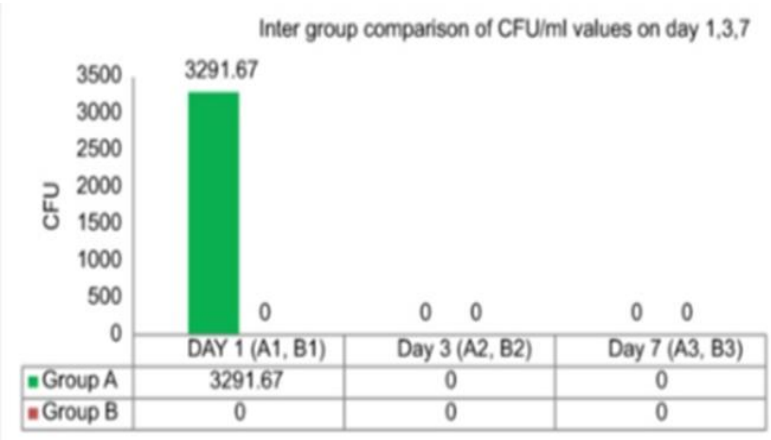

Figure 13. Bar Figure showing difference between colony-forming unit count of *Porphyromonas gingivalis* retrieved from doxycycline-treated implant groups (A1, A2, and A3) and chlorhexidine-treated implant groups (B1, B2, and B3). CFU – Colony-forming unit

Table 3. Colony-forming unit count of *Porphyromonas gingivalis* for implants in subgroups A1 and B1 treated with 10% doxycycline gel and 1% chlorhexidine gel, respectively

Groups	*n*	Mean	SD	Median	Mann-Whitney *U* value	*Z*	*P* value of Mann–Whitney *U*-test
A1 (day 1)	12	3291.67	5451.348	0	18.000	−3.585	0.000**
B1 (day 1)	12	0.00	0.000	0			

SD – Standard deviation; *P* - Probability value, *n* - Sample size, *Z* - Standard score, ***P* < 0.01- Highly significant

Table 4. Colony-forming unit count of *Porphyromonas gingivalis* for implants in subgroups A2 and B2 treated with 10% doxycycline gel and 1% chlorhexidine gel, respectively

Groups	*n*	Mean	SD	Median	Mann–Whitney *U* value	*Z*	*P* value of Mann–Whitney *U*-test
A2 (day 3)	12	0.00	0.000	0	72.000	−0.448	1.000#
B2 (day 3)	12	0.00	0.000	0			

SD – Standard deviation; *P* - Probability value, *n* - Sample size, *Z* - Standard score, #*P* > 0.05 - Nonsignificant

Table 5: Colony-forming unit count of *Porphyromonas gingivalis* for implants in subgroups A3 and B3 treated with 10% doxycycline gel and 1% chlorhexidine gel, respectively

Groups	*n*	Mean	SD	Median	Mann–Whitney *U* value	*Z*	*P* value of Mann–Whitney *U*-test
A3 (day 3)	12	0.00	0.000	0	72.000	0.000	1.000#
B3 (day 3)	12	0.00	0.000	0			

SD – Standard deviation; *P* - Probability value, *n* - Sample size, *Z* - Standard score, #*P* > 0.05 - Nonsignificant

Decontamination of implants by eliminating bacteria from the implant surface is necessary to treat peri-implant diseases. While this can be achieved through a combination of mechanical and chemical methods, numerous approaches evaluated in various *in vivo* studies have failed to demonstrate superior efficacy [14]. The present *in vitro* study evaluated the effectiveness of doxycycline and CHX with single and multiple applications for disinfection of implant surfaces contaminated with *P. gingivalis* strain.

Although *in vivo* systems constitute biofilm with varied microbial complexes, numerous studies have illustrated a strong association of red-complex bacteria with peri-implantitis [5]. In addition, Ghensi *et al.* [15] conducted a study that identified *P. gingivalis* as the most prevalent pathogen in peri-implantitis sites compared to control sites. *P. gingivalis* plays a vital role in determining the composition and the structure of the biofilm in peri-implant sites. The Arg- or Lys-gingipains produced by *P. gingivalis* can facilitate the growth and colonization of other species such as *Treponema denticola* and *Tannerella forsythia* [8]. Another important consideration is that the most commonly used implant surfaces, such as SAE surfaces, exhibit higher adhesion of *P. gingivalis,* followed by other organisms [16]. These findings suggest that *P. gingivalis* is one of the key colonizers in peri-implantitis, further emphasizing the need for formulation of therapeutic agents exhibiting great impact on this keystone pathogen for effective management of peri-implantitis.

The anti-infective agents used in this study were 10% doxycycline, a bacteriostatic antibiotic, and 1% CHX which is bactericidal at this concentration [17]. In the present study, 10% formulation of doxycycline hyclate was selected based on the predictable and successful outcome reported in previous studies by Ahamed *et al.* [18] and Javali and Vandana [19]. A study by Patianna *et al.* [20] reported the effectiveness of doxycycline gel when applied on the implants for a duration of 3 min. These findings served as the basis for the exposure time selected in the present study. Based on the efficacy of 1% CHX gel in studies reported by Renvert *et al.* [21] and Paolantonio *et al.* [22] a commercially available 1% formulation of CHX gel was evaluated in the present study. A 10-min duration of exposure of implants to CHX gel was adopted based on the

findings by Sbricoli *et al.* [23] who reported complete decontamination of implant surfaces accomplished within this time frame.

Anti-infective agents in solution form are rapidly excreted from gingival crevicular fluid, thereby necessitating a high initial concentration and repeated applications of the agents, to achieve sustained antimicrobial efficacy [24]. In contrast, gel formulations enhance the contact time of the therapeutic agent with the target surface, thus increasing its effectiveness. This was supported by a study conducted by Lollobrigida *et al.* [25] which concluded that antimicrobials employed in gel formulations exhibited superior efficacy than liquid formulations. These findings formed the basis for selecting antimicrobials in gel formulations in the present study.

The mean CFU count of *P. gingivalis* retrieved from implants treated with doxycycline gel was significantly lower than the baseline values. These results are in agreement with the findings of the study conducted by Patianna *et al*. [20] who reported a significant reduction of bacteria in test groups, treated with 14% doxycycline compared to control groups. In addition, an increase in the decontamination rate was observed on day 3 in comparison to day 1. These findings are in accordance with a study by Trajano *et al*. [26] who reported a significant improvement in the clinical parameters on day 60 compared to day 30 and baseline, and attributed this outcomes to subsequent reapplication of doxycycline gel. The significant reduction of mean CFU count for the implants treated with CHX group, observed on days 1, 3, and 7 compared to baseline, is consistent with the findings of Paolantonio *et al.* [22] who reported a reduced bacterial colonization in implants treated with 1% CHX in comparison to control groups, thus indicating effective antimicrobial activity of CHX at 1% concentration.

Wheelis *et al.* [27] studied the effects of various chemical agents on the surface texture and the elemental composition of two grades of titanium implants using two different decontamination methods. The study revealed that CHX at 1% concentration caused only discoloration of the implant surface without inducing corrosion. However, doxycycline at a concentration of 50% led to surface pitting, discoloration, and oxide layer removal. Energy dispersive spectroscopy (EDS) results revealed titanium content ranging from 0.06% to 0.85% in the swab samples. Moreover, nearly all the tested agents increased surface roughness of both titanium grades posttreatment. The study also put forth that decontaminating implants by immersive method will be suitable for more acidic chemicals. However, these findings were beyond the scope of the present study and require further assessment.

As no single-treatment modality or combination of approaches has proven successful in treating peri-implantitis, the objective of this study was to evaluate efficacy of antimicrobials against *P. gingivalis* and identify strategies that would accomplish complete disinfection of implant surfaces. The findings of the present study highlight that effectiveness of antimicrobial agents is largely influenced by the frequency of applications, thus emphasizing the need for tailoring both dosage and application intervals to the specific antimicrobial agent and clinical conditions. For instance, the efficacy of 1% CHX in a single application makes it an ideal therapeutic agent for implant surface decontamination during surgical interventions for peri-implantitis, as compared to 10% doxycycline gel, which may require repeated applications for optimal outcomes. In addition, the efficacy of locally applied antimicrobial gels, established in this study, could serve as a preferable alternative to systemic administration. Local antimicrobial application minimizes the risk of systemic side effects, improving patient compliance necessary for achieving successful treatment outcomes. Hence, if the results of this study are replicated in an *in vivo* system, a standardized protocol for chemical decontamination of implants could be established, aiding clinicians to effectively manage peri-implantitis.

Conclusion

The antimicrobials evaluated in this study effectively achieved complete decontamination of implant surfaces infected with *P. gingivalis,* although the number of applications required varied depending on the agent. CHX gel (1%) demonstrated immediate efficacy, with no viable bacterial colonies detected after the first application, and inhibited further bacterial growth on repeated applications. In contrast, 10% doxycycline gel significantly reduced CFU counts of viable *P. gingivalis* after a single application, but complete eradication was achieved on subsequent reapplications. However, as this study was done in an *in vitro* setup, further *in vivo* research is necessary to validate these findings in clinical settings. In addition, it is imperative to assess the effects of these antimicrobials on different implant surface characteristics to develop a standardized treatment protocol.

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Conflict of interest: None

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Ethics statement: None

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