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The Efficacy of Subantimicrobial Dose of Doxycycline in the Treatment of Periodontal Disease as Host Modulation

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Annotation: Periodontal disease is a chronic inflammatory condition where host-mediated tissue destruction plays a central role, and conventional therapies like scaling and root planing (SRP) often fail to fully address the underlying immune response. Despite evidence supporting host modulation therapy, the effectiveness of subantimicrobial dose doxycycline (SDD) in routine clinical settings remains under-investigated. This randomized, double-blind, placebo-controlled clinical trial evaluated 60 patients with moderate to severe chronic periodontitis, comparing outcomes between SRP combined with SDD versus SRP alone. Clinical parameters—probing depth, attachment level, and bleeding on probing—were assessed at baseline, 3 months, and 6 months. The study demonstrated that SDD significantly enhanced periodontal outcomes without notable adverse events. These findings support the integration of SDD as a safe and effective adjunct to SRP, offering a targeted approach to modulate the host response and potentially reduce the need for invasive surgical interventions in periodontal therapy.

Keywords: periodontal disease, subantimicrobial dose doxycycline, host

modulation, matrix metalloproteinases, scaling and root planing, chronic periodontitis, inflammation control.

Introduction

Periodontal disease is a chronic inflammatory condition that affects the supporting structures of the teeth, including the gingiva, periodontal ligament, and alveolar bone (1). It is initiated by the accumulation of bacterial plaque, which triggers a host immune response that destroys periodontal tissues. If left untreated, periodontal disease can progress to tooth loss and has been associated with systemic conditions such as cardiovascular disease, diabetes, and rheumatoid arthritis (2). The pathogenesis of periodontal disease involves a complex interplay between microbial pathogens and the host immune response, releasing pro-inflammatory cytokines, matrix metalloproteinases (MMPs), and other mediators contributing to tissue breakdown (3).

Traditional periodontal therapy focuses on the mechanical removal of bacterial plaque through scaling and root planing (SRP) (4). While SRP effectively reduces bacterial load, it often fails to address the host-mediated inflammatory response, which plays a critical role in tissue destruction. This limitation has led to the development of host modulation therapy (HMT), which aims to modulate the host immune response to reduce inflammation and promote tissue repair. One of the most studied HMT agents is subantimicrobial dose doxycycline (SDD), a tetracycline derivative that inhibits MMPs and reduces inflammation without exerting antimicrobial effects (5).

MMPs are a family of enzymes that degrade extracellular matrix components, including collagen and are upregulated in periodontal disease. By inhibiting MMPs, SDD helps to prevent tissue destruction and promote periodontal healing (6). Additionally, SDD has been shown to reduce the production of pro-inflammatory cytokines such as interleukin-1β (IL-1β) and tumor necrosis factor-alpha (TNF-α), further contributing to its anti-inflammatory effects. The use of SDD in periodontal therapy was first investigated in the 1990s. Since then, numerous studies have demonstrated its efficacy in improving clinical outcomes, such as probing depth (PD), clinical attachment level (CAL), and bleeding on probing (BOP) (7).

Despite the growing body of evidence supporting the use of SDD in periodontal therapy, further research is needed to evaluate its efficacy as an adjunct to SRP in patients with moderate to severe chronic periodontitis. This study aimed to investigate the clinical and immunological effects of SDD in the treatment of periodontal disease and assess its safety and tolerability.

Methodology

Study Design

This randomized, double-blind, placebo-controlled clinical trial was conducted over 6 months. The Institutional Ethics Committee approved the study protocol, and all participants provided written informed consent.

Participants

- **Inclusion Criteria:** Adults aged 30-60 years with moderate to severe chronic periodontitis (PD ≥ 5 mm, CAL ≥ 3 mm, and BOP at ≥ 30% of sites).
- **Exclusion Criteria:** Systemic diseases, antibiotic use in the past 6 months, pregnancy, or allergy to tetracyclines.

Sample Size

A total of 60 participants were recruited and randomly allocated into two groups:

1. **SDD Group** (n = 30): Received SDD 20 mg twice daily + SRP.
2. **Placebo Group** (n = 30): Received placebo + SRP.

Intervention

- All participants underwent full-mouth SRP at baseline.
- The SDD group received 20 mg of SDD twice daily for 3 months, while the placebo group received an identical placebo.

Clinical Parameters

The following parameters were measured at baseline, 3 months, and 6 months:

1. **Probing Depth (PD):** Measured in millimeters using a periodontal probe.
2. **Clinical Attachment Level (CAL):** Measured from the cementoenamel junction to the pocket base.
3. **Bleeding on Probing (BOP):** Recorded as the percentage of sites with bleeding.

Statistical Analysis

Data were analyzed using SPSS software (version 25). Paired t-tests and independent t-tests were used to compare within-group and between-group differences, respectively. A p-value < 0.05 was considered statistically significant.

Results

The study included 60 participants with moderate to severe chronic periodontitis, randomly allocated into the SDD group (n = 30) and the placebo group (n = 30). Baseline characteristics, including age, gender, mean probing depth (PD), mean clinical attachment level (CAL), and bleeding on probing (BOP), were comparable between the two groups ($p > 0.05$), indicating successful randomization (Table 1).

Table 1: Baseline Characteristics of Participants

Parameter	SDD Group (n = 30)	Placebo Group (n = 30)	p-value
Age (years)	45.3 ± 6.2	46.1 ± 5.8	0.62
Gender (Male/Female)	16/14	15/15	0.82
Mean PD (mm)	5.2 ± 0.8	5.1 ± 0.7	0.71
Mean CAL (mm)	4.8 ± 0.9	4.7 ± 0.8	0.65
BOP (%)	52.3 ± 10.4	50.8 ± 9.6	0.54

At 6 months, the SDD group showed significant improvements in all clinical parameters compared to the placebo group. The mean reduction in probing depth (PD) was 1.8 ± 0.5 mm in the SDD group compared to 1.0 ± 0.4 mm in the placebo group ($p < 0.001$). Similarly, the mean gain in clinical attachment level (CAL) was 1.5 ± 0.6 mm in the SDD group compared to 0.7 ± 0.3 mm in the placebo group ($p < 0.001$). The reduction in bleeding on probing (BOP) was also significantly more significant in the SDD group (35.2 ± 8.1%) compared to the placebo group (18.4 ± 6.3%, $p < 0.001$) (Table 2).

Table 2: Changes in Clinical Parameters at 6 Months

Parameter	SDD Group (n = 30)	Placebo Group (n = 30)	p-value
Mean PD Reduction (mm)	1.8 ± 0.5	1.0 ± 0.4	<0.001
Mean CAL Gain (mm)	1.5 ± 0.6	0.7 ± 0.3	<0.001
BOP Reduction (%)	35.2 ± 8.1	18.4 ± 6.3	<0.001

Adverse events were mild and infrequent in both groups. In the SDD group, 3 participants (10%) reported mild gastrointestinal discomfort, and 1 participant (3.3%) reported headache. In the placebo group, 2 participants (6.7%) reported mild gastrointestinal discomfort and 1 (3.3%) reported headache. No serious adverse events were reported in either group (Table 3).

Table 3: Adverse Events

Adverse Event	SDD Group (n = 30)	Placebo Group (n = 30)
Gastrointestinal discomfort	3 (10%)	2 (6.7%)
Headache	1 (3.3%)	1 (3.3%)
None	26 (86.7%)	27 (90%)

Discussion

The findings of this study demonstrate that subantimicrobial dose doxycycline (SDD) is an effective adjunct to scaling and root planing (SRP) in treating moderate to severe chronic periodontitis. The SDD group showed significantly more significant improvements in probing depth (PD), clinical attachment level (CAL), and bleeding on probing (BOP) compared to the placebo group at 6 months. These results align with the proposed mechanism of action of SDD, which involves the inhibition of matrix metalloproteinases (MMPs) and modulation of the host immune response. MMPs are enzymes that degrade extracellular matrix components, including collagen and are upregulated in periodontal disease. By inhibiting MMPs, SDD helps to stabilize the periodontal tissues and prevent further breakdown. Additionally, SDD has been shown to reduce the production of pro-inflammatory cytokines such as interleukin-1β (IL-1β) and tumor necrosis factor-alpha (TNF-α), which are key mediators of inflammation and tissue destruction in periodontal disease. This dual mechanism of action—MMP inhibition and immune modulation—makes SDD a valuable adjunct to conventional periodontal therapy.

The clinical significance of these findings cannot be overstated. The mean reduction in PD of **1.8 ± 0.5 mm** in the SDD group compared to **1.0 ± 0.4 mm** in the placebo group ($p < 0.001$) indicates a substantial improvement in periodontal pocket depth, a key indicator of periodontal health. Similarly, the mean gain in CAL of **1.5 ± 0.6 mm** in the SDD group compared to **0.7 ± 0.3 mm** in the placebo group ($p < 0.001$) reflects significant periodontal tissue regeneration. The reduction in BOP of **35.2 ± 8.1%** in the SDD group compared to **18.4 ± 6.3%** in the placebo group ($p < 0.001$) further underscores the anti-inflammatory effects of SDD. These improvements are clinically meaningful, as they contribute to stabilizing periodontal health and preventing disease progression. Deep periodontal pockets and persistent inflammation are well-established risk factors for disease progression and tooth loss, and the ability of SDD to address these issues highlights its potential as a transformative therapy in periodontal care.

The results of this study are consistent with previous research demonstrating the efficacy of SDD in periodontal therapy. For example, (8) conducted a randomized controlled trial (RCT) in which patients with chronic periodontitis were treated with SDD or placebo in addition to SRP. The study found that the SDD group showed significantly more significant reductions in PD and gains in CAL compared to the placebo group at 9 months. Similarly, (9) conducted a systematic review and meta-analysis of RCTs evaluating the efficacy of SDD in periodontal therapy. The review found that SDD significantly improved clinical outcomes, including PD, CAL, and BOP, when used as an adjunct to SRP. These findings are further supported by (10), who investigated

the effects of SDD on gingival crevicular fluid (GCF) levels of MMP-8 in patients with chronic periodontitis. The study found that SDD significantly reduced GCF levels of MMP-8, indicating a reduction in tissue destruction. These studies provide robust evidence supporting the use of SDD as a host modulation agent in periodontal therapy.

One of the key advantages of SDD is its favorable safety profile. This study showed mild and infrequent adverse events in the SDD and placebo groups. The most common adverse event in the SDD group was mild gastrointestinal discomfort, which was reported by 10% of participants. Headache was reported by 3.3% of participants in the SDD group. These adverse events were similar in frequency and severity to those reported in the placebo group, indicating that SDD is well-tolerated by patients. The safety and tolerability of SDD have been well-documented in previous studies. For example, (11) conducted a long-term safety study in which patients with periodontitis were treated with SDD for up to 18 months. The study found that SDD was well-tolerated, with no serious adverse events reported. Similarly, (12,13) conducted a study to evaluate the effects of long-term SDD therapy on the subgingival microflora. The study found that SDD did not exert significant antimicrobial effects, confirming its safety as a host modulation agent.

The clinical implications of these findings are significant. SDD offers a novel approach to periodontal therapy by targeting the host inflammatory response, a key driver of tissue destruction in periodontal disease. By modulating the host response, SDD can enhance the effects of conventional periodontal therapy and improve clinical outcomes. This is particularly relevant for patients with severe or refractory periodontal disease, where traditional therapies may be insufficient. The use of SDD as an adjunct to SRP can also reduce the need for more invasive treatments, such as periodontal surgery. By stabilizing the periodontal tissues and preventing disease progression, SDD can help to preserve the dentition and improve the quality of life for patients with periodontal disease. Additionally, the favorable safety profile of SDD makes it a suitable option for long-term use in patients with chronic periodontitis.

Despite the promising findings, this study has some limitations that should be acknowledged. First, the study had a relatively small sample size (n = 60), which may limit the generalizability of the findings. More extensive studies with diverse patient populations are needed to confirm these results. Second, the follow-up duration was limited to 6 months. Longer-term studies are needed to evaluate the durability of the clinical benefits of SDD and its effects on disease progression. Another limitation is the lack of microbiological and immunological data. While the study focused on clinical outcomes, future studies should include assessments of the subgingival microflora and levels of inflammatory markers to provide a more comprehensive understanding of the effects of SDD. Additionally, the study did not evaluate the cost-effectiveness of SDD. Future studies should include economic analyses to determine the cost-effectiveness of SDD as an adjunct to periodontal therapy.

Future research should address these limitations and explore new avenues for using SDD in periodontal therapy. More significant multicenter studies with longer follow-up durations are needed to confirm the efficacy and safety of SDD in diverse patient populations. Additionally, studies should investigate the effects of SDD in combination with other host modulation agents, such as anti-inflammatory drugs or biologics, to determine whether combination therapy can further enhance clinical outcomes. Further research is also needed to explore the potential benefits of SDD in managing systemic conditions associated with periodontal disease, such as cardiovascular disease, diabetes, and rheumatoid arthritis. Given the role of inflammation in these conditions, SDD may have potential applications beyond periodontal therapy. Finally, studies should investigate the effects of SDD on patient-reported outcomes, such as quality of life and patient satisfaction, to provide a more holistic assessment of its benefits.

In conclusion, this study supports the efficacy of subantimicrobial dose doxycycline (SDD) as a host modulation agent in treating periodontal disease. When used as an adjunct to scaling and

root planing, SDD significantly improves clinical outcomes, including probing depth, clinical attachment level, and bleeding on probing. The favorable safety profile of SDD further supports its use in clinical practice. These findings highlight the potential of SDD to transform the management of periodontal disease by addressing the host inflammatory response, which is a key driver of tissue destruction. Future research should focus on confirming these findings in more extensive, long-term studies and exploring new applications for SDD in periodontal and systemic health.

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