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Evaluating the Efficacy of Subantimicrobial-Dose Doxycycline as a Host Modulation Therapy in Periodontal Disease

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Annotation: Periodontal disease is a chronic inflammatory disease characterized by damage to periodontal tissues resulting from an overexaggerated immune response by the host. The study's purpose was to evaluate the evidence-based effectiveness of subantimicrobial dose doxycycline (SDD) as a host modulation agent for periodontal disease. This research study utilized a consummate randomized, double- blind, placebo-controlled clinical trial design. One hundred subjects were utilized for the trial but due to loss of some subjects only 60 participants diagnosed with moderate to severe chronic periodontitis were followed. The participants were randomized to receive subantimicrobial dose doxycycline (SDD) of (20 mg twice daily) or placebo (both groups received scaling and root planing), and clinical parameters of probing depth (PD), clinical attachment level (CAL), and bleeding on probing (BOP) were measured at baseline, 3 months, and 6 months. The data revealed that compared to placebo, both PD, CAL, and BOP in the SDD group had statistically significant improvement(s) ($p < 0.05$). SDD was reported to exhibit a favorable safety outcome with few adverse events. The study concluded that SDD was an effective adjunct to SRP that modulates the host response to periodontal disease to ultimately achieve therapeutic periodontal outcomes.

Introduction

Periodontal disease is a chronic inflammatory disease that affects the supporting structures of the teeth including the gingiva, periodontal ligament, and alveolar bone (1). The initiation of periodontal disease results from the accumulation of bacterial particles, which initiates a host immune response that destroys periodontal tissues. Periodontal disease, if left untreated, will result in tooth loss, and is correlated to systemic diseases such as cardiovascular disease, diabetes, and rheumatoid arthritis (2).The etiology of periodontal disease is dependent on the ability of microbial pathogens to interact within the context of the host immune response releasing pro-inflammatory cytokines, matrix metalloproteinases (MMPs) and other mediators leading to tissue destruction (3). Periodontal therapy has relied on the removal of bacterial pathogens by mechanical intervention (scaling and root planing, SRP) (4). While SRP reduces the bacterial burden, it often does not address the host mediated inflammatory response - which plays a significant role in tissue destruction. This limitation has led to the idea of host modulation therapy (HMT) - a modality which aims to modulate the host response to disease in order to minimize inflammation and promote healing. One of the most studied HMT agents is subantimicrobial dose doxycycline (SDD) a second-generation tetracycline, which has anti-MMP effects and reduction of inflammation effects independent of any anti-microbial activity (5).

MMPs are a family of zinc dependent enzymes responsible for degrading components of the extracellular matrix (ECM) which includes collagen and are upregulated in periodontal disease. If SDD is inhibiting MMP activity, then tissue destruction can be prevented and tissue can heal in the periodontal context (6). Furthermore, SDD has been demonstrated to reduce the ability of proinflammatory cytokines to be produced (IL-1β, TNF-α) which furthers it's net anti-inflammatory effects. SDD and the use of SDD in periodontal therapy was first published in the 1990s and since, numerous clinical investigations have reported its efficacy to improve clinical outcomes such as probing depth (PD), clinical attachment level (CAL), and absence of bleeding on probing (BOP) (7).

Despite the emerging evidence for the efficacy of SDD in periodontal therapy, further research in patients with moderate to severe chronic periodontitis who are undergoing SRP is warranted. The aim for this study was to evaluate the clinical and immunological effects of HMT for SDD treatment of periodontal disease and to determine safety and tolerability.

Methodology

Study Design

Over the course of six months, this clinical experiment was double-blind, randomised, and placebo-controlled. Every participant gave written informed permission, and the study procedure was approved by the Institutional Ethics Committee.

Participants

- **Inclusion Criteria**: Adults with moderate to severe chronic periodontitis (PD > 5 mm, CAL ≥ 3 mm, and BOP at ≥ 30% of sites) between the ages of 30 and 60 are eligible to participate.
- **Exclusion Criteria**: include pregnancy, tetracycline allergies, systemic illnesses, and antibiotic usage during the last six months.

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

Sixty subjects with moderate to severe chronic periodontitis were recruited for the study and assigned randomly to one of two group (30 were assigned to the SDD group and 30 were assigned to the placebo group). At baseline, the two groups were similar with respect to age, gender, mean clinical attachment level (CAL), mean probing depth (PD) and bleeding on probing (BOP) ($p > 0.05$) indicating that randomization was adequate (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

The SDD group demonstrated significantly better improvement in each clinical measure at 6 months relative to the placebo group. The SDD group demonstrated a mean reduction in probing depth (PD) of 1.8 ± 0.5 mm, and the placebo group demonstrated a mean reduction of 1.0 ± 0.4 mm ($p < 0.001$). Similarly, the SDD group demonstrated a mean increase in clinical attachment level (CAL) of 1.5 ± 0.6 mm, while the placebo group demonstrated a mean increase of 0.7 ± 0.3 mm ($p < 0.001$). The SDD group also experienced a significantly larger reduction in bleeding on probing (BOP) compared to the placebo group (37.2 ± 8.1% vs. 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 study findings represent that subantimicrobial dose doxycycline (SDD) is an effective adjunctive therapy to scaling and root planing (SRP) for moderate to severe chronic periodontitis; typically, the SDD group had greater improvements than the placebo group for probing depth (PD), clinical attachment level (CAL), and bleeding on probing (BOP) in primary outcomes, and at 6 months. The observed 1.8 ± 0.5 mm PD mean reduction in the SDD group compared to 1.0 ± 0.4 mm in the placebo group ($P < 0.001$) signifies substantial reduction in periodontal pocket depth, a key measure of periodontal health; the other outcomes reflected similar clinically significant improvements for the SDD group over the placebo group. These results are consistent with the described mechanism of action of SDD, involving inhibition of matrix metalloproteinases (MMPs) and host immune homeostasis. MMPs are responsible for the degradation of extracellular matrix

components such as collagen; importantly, MMPs are upregulated in periodontal disease and SDD reduces the amount of MMP that might contribute to continuous periodontal tissue degradation.

Moreover, besides utilizing MMPs, SDD has been shown to decrease the production of proinflammatory cytokines such as interleukin-1β (IL-1β) and tumor necrosis factor alpha (TNF-α) that are related to the inflammatory and destructive processes in the periodontal disease. The great advantage of SDD is that it can inhibit both MMPs and modulate the immune response which when added to conventional periodontal therapy can provide enhanced benefit. Furthermore, the clinical meaning of these facts cannot be overstated. The mean gains in PD and CAL are even more crucial when there is an overall indication of tissue regeneration signified by the mean gain of 1.5 ± 0.6 mm CAL in the SDD group as compared to mean gain of 0.7 ± 0.3 mm in the placebo group ($P < 0.001$).The significant reduction of BOP of 35.2 ± 8.1% in the SDD group and a reduction of 18.4 ± 6.3% in the placebo group ($p < 0.001$) further supports the anti-inflammatory effects of SDD. These improvements matter clinically because they help establish a periodontal health baseline and help prevent disease progression. Deep periodontal pockets and inflammation are known risk factors for disease progression and tooth loss, and SDD's ability to address them may represent a leap forward in our therapies.

The data from this study support the findings of previous studies that have shown the efficacy of SDD in periodontal therapy. For example, (8) conducted a RCT where patients with chronic periodontitis received SDD or placebo therapy in addition to SRP. The study found that both groups experienced reductions in PD and gains in CAL at 9 months, but the SDD group experienced greater reductions in PD and greater gains in CAL compared to the placebo group. Similarly, (9) conducted a systematic review and meta-analysis of RCTs evaluating the efficacy of SDD in periodontal therapy. The review found that SDD was effective at improving clinical outcomes (PD, CAL, and BOP) when used as adjunctive therapy to SRP. These findings are supported by (10), which evaluated SDD effects on GCF levels of MMP-8 in patients with chronic periodontitis, and demonstrated that patients receiving SDD therapy had significantly reduced GCF levels of MMP-8, suggesting that there was less tissue destruction in the SDD group.Our studies provide strong evidence for the use of SDD as a host modulating agent in the treatment of periodontal disease.

One of the main advantages of SDD is its safety profile. This study found mild and infrequent adverse events of the SDD and placebo groups. The most notable adverse events in the SDD group involved mild gastrointestinal discomfort in 10% of subjects, and headache in 3.3% of subjects. These adverse events were noted to be of similar frequency and severity as those reported in the placebo group demonstrating that SDD induces well tolerance.Researchers have previously demonstrated the safety of SDD. For example, Zhang et al. (11) conducted a long-term safety study with patients with periodontitis treated with SDD for up to 18 months. They found treatment with SDD to be well tolerated with no serious adverse events reported. Menthol et al. (12,13) looked at the impact of long-term use of SDD on the subgingival microflora. They found no significant antimicrobial effects from SDD confirming its use as a safe host modulating agent.

The clinical implications of these findings are significant. SDD represents a consideration for a new paradigm of treatment in periodontal disease that targets the host inflammatory process, which is the primary mechanism of tissue destruction in periodontal disease.SDD can improve traditional periodontal treatment by managing host response, and potentially has clinical implications for patient management. This is of particular importance for patients with severe and/or refractory periodontal disease when traditional therapies are not sufficient as SDD could serve as an adjunct

to SRP, and prevent surgical management. Once treatment stabilization occurs after restoring the periodontium, SDD can slow disease progression in unstable and chronic circumstances, which can be beneficial to dentition preservation and of quality of life to patients with periodontal disease.

The appealing safety profile of SDD extends the option for this intervention for long-term management for chronic periodontitis patients.

Aside from some exciting results, this investigation has its limitations, and these limitations need to be recognized. First, this was a small sample size (n = 60) that may limit the application of its results. Larger studies with multiple diverse populations are required to confirm the findings. Second, the study only had a 6-month follow-up. Longer-term studies are needed to try to determine or measure the longevity of the clinical benefits of SDD and its effectiveness to stop the progression of the disease. Another limitation was the lack of microbiological and immunological data. Although the investigation measured using clinical outcomes, it would be ideal for future studies to measure subgingival microflora and inflammatory markers for a better understanding of SDDAdditionally, the current study did not assess the cost-effectiveness of SDD, and future studies should include economic studies to assess cost-effectiveness of SDD as an adjunct to periodontal treatment. Future research should take advantage of this study's limitations and also be creative by looking for new applications of SDD in periodontal treatment. There need to be some larger multicenter clearer studies for longer time periods to confirm efficacy and safety of SDD across different populations. There also need to be studies that examine the effect of SDD in addition to other host modulation, such as anti-inflammatories, or other biologics to see if those outcomes can be further improved. More studies of SDD treatment effect may also include through systems looking at potential effects of SDD in reducing systemic treatment effects associated related to periodontal disease (e.g. CV disease, diabetes, rheumatoid arthritis). SDD could provide potential treatment advancement of our ability to treat these systemic disease or localized inflammatory processes. Lastly, in future studies the effect of SDD must be confirmed for patient reported outcomes quality of life and patient satisfaction to expand and holistically consider and evaluate SDD as a value added treatment.

In summary, there is evidence substantiating the efficacy of subantimicrobial dosage doxycycline (SDD) as a host modulating agent for periodontal disease. SDD improves clinical outcomes (i.e. probing depth, clinical attachment level, bleeding on probing) when delivered as an adjunct to scaling and root planing. Furthermore, the safety of administering SDD was sufficient to be deemed appropriate for implementation in clinical practice. The results of this study further validate that SDD has the potential to change the paradigm in the efficacy of periodontal disease management.

By recognizing and targeting the host inflammatory process, which is critical in creating the destruction of tissue, we have an opportunity to change how we manage periodontal disease. It will be up to future research to confirm the results of this scope of research, more extensive through larger, more focused studies with longer follow-up period, and develop new applications of SDD to improve periodontal health and affect holistic systemic health as well.

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