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Efficacy of scaling and root planning with and without adjunct Nd:YAG laser therapy on clinical periodontal parameters and gingival crevicular fluid interleukin 1-beta and tumor necrosis factor-alpha levels among patients with periodontal disease: A prospective randomized split-mouth clinical study

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ABSTRACT

Background and aim: Limited evidence exists regarding the role of scaling and root planning (SRP) with adjunct neodymium yttrium aluminum garnet (Nd:YAG) laser therapy in reducing periodontal parameters (plaque index [PI], bleeding on probing [BOP] and probing pocket depth [PPD]) and levels of proinflammatory cytokines in the gingival crevicular fluid (GCF) among patients with periodontal disease (PD). The aim was to assess the effect of SRP with and without adjunct Nd:YAG laser therapy on clinical periodontal parameters and GCF interleukin 1-beta (IL-1β) and tumor necrosis factor-alpha (TNF-α) levels among patients with PD.

Methods: Demographic data was collected using a questionnaire. Mandibular right and left quadrants were randomly divided into test- (SRP + Nd:YAG laser) and control-sites (SRP alone). PI, BOP and PPD were assessed and GCF IL-1β and TNF-α levels were measured at baseline and at 3- and 6-month follow-up. Level of significance was set at $P < 0.05$.

Results: Twenty-eight male patients with PD were included. At 3- and 6-month follow-up, PI ($P < 0.01$), BOP ($P < 0.01$) and PPD ($P < 0.01$) were significantly higher in the control-sites than test-sites. In the test-sites, PI, BOP and PPD and GCF IL-1β and TNF-α levels were comparable at 3- and 6-month follow-up. At 6-month follow-up, IL-1β ($P < 0.05$) and TNF-α ($P < 0.05$) levels were significantly higher in control-sites than test-sites at 3- and 6-month follow-up.

Conclusion: At 3- and 6-month follow-up, SRP + Nd:YAG therapy was more effective in reducing periodontal inflammatory parameters and GCF IL-1β and TNF-α levels compared with SRP alone.

1. Introduction

The conventional treatment of periodontal disease (PD) involves mechanical debridement of teeth and root surfaces (scaling and root planning [SRP]) using hand instruments and/or ultrasonic scalers [1–3]; however, studies [4,5] have shown that treatment of PD using SRP alone is often insufficient in the complete removal of pathogenic microbes and their byproducts from inflamed periodontal pockets. Studies [4,6,7] have reported that SRP when performed with adjunct therapies such as laser therapy is more effective in reducing periodontal inflammation compared with SRP alone. The neodymiumyttrium-aluminum-garnet (Nd:YAG) laser ($\lambda = 1064$ nm), approved for treatment by the United States Food and Drug Administration is being used for periodontal curettage for nearly 40 years. This is primarily due to the fact that this wavelength gets absorbed only in soft tissues such as epithelial lining of the periodontal pocket and hard tissues, for example cementum and dentin are spared [8]. Result from a systematic review and metaanalysis showed that SRP with adjunct Nd:YAG laser therapy reduces periodontal inflammation to a significantly greater extent as compared to SRP alone [9]. However, controversial results have also been reported. According to Thomas and Shafer [10], there is inadequate evidence that pulsed Nd:YAG laser when used with SRP is superior to conventional SRP in the treatment of periodontal disease. Similar results were reported by Sgolastra et al. [11] and Slot et al. [12] This suggests that the efficacy of adjunct Nd:YAG laser therapy during SRP in the treatment of PD is debatable; and hence warrants further investigations.

The gingival crevicular fluid (GCF) is an inflammatory exudate present in the gingival sulcus. The volume of GCF increases under periodontal inflammatory conditions as a result of increased vascular

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permeability. GCF can be collected non-invasively and is a potential biochemical tool for the assessment of host responses among patients with periodontal disease. Studies [4,13,14] have reported that in patients with PD, proinflammatory cytokines (including interleukin [IL] 1-beta [β], IL-6, tumor necrosis factor-alpha [TNF-α] and matrix metalloproteinase [MMP] 8 and 9) leak into the gingival crevices as a result of increased capillary blood flow and permeability. Moreover, an increased expression of proinflammatory cytokines (such as IL-1β and TNF-α) in the GCF enhances periodontal inflammation by inducing a state of oxidative stress in the periodontal tissues due to an increased production of advanced glycation endproducts and reactive oxygen species (ROS) [15–17]. It is hypothesized that SRP with adjunct Nd:YAG laser therapy reduces (a) clinical periodontal inflammatory parameters (plaque index [PI], bleeding on probing [BOP] and probing pocket depth [PPD]); and (b) GCF levels of IL-1β and TNF-α to a significantly greater extent compared with SRP alone.

The aim of the present prospective split-mouth randomized clinical study was to assess the efficacy of SRP with and without adjunct Nd:YAG laser therapy on clinical periodontal parameters and GCF IL-1β and TNF-α levels among patients with PD.

2. Materials and Methods

2.1. Ethical Approval

The study was approved by the Research Ethics Review Committee of the College of Dentistry, King Saud University, Riyadh, Saudi Arabia. All volunteering individuals were requested to read and sign an informed consent form. Participants were also informed that participation is completely voluntary and that they could withdraw from the study at any stage of the investigation without penalty.

2.2. Inclusion and Exclusion Criteria

The inclusion criteria were as follows: (a) signing the informed consent form; (b) patients with PD (at least 30% sites with BOP and PPD ≥ 4 mm [18,19]). The exclusion criteria were as follows: (a) habitual tobacco smoking and/or smokeless tobacco consumption; (b) habitual alcohol consumption; (c) patients with systemic diseases including acquired immune deficiency syndrome, cardiovascular disorders, diabetes mellitus, hepatic disorders and renal disorders; (d) use of antibiotics, steroids and/or non-steroidal anti-inflammatory drugs within the past 3 months; (e) periodontal treatment within the past 6 months; and (f) lactating and/or pregnant females.

2.3. Recruitment of Participants

Patients with PD were recruited from the outpatient department of an academic institution in Riyadh, Saudi Arabia. All participants were examined at the Department of Dentistry of the same institution.

2.4. Interview Questionnaire

Using a questionnaire, a trained interviewer (FV) collected information regarding age, gender, family history of periodontal disease, and daily tooth brushing habits from all participants.

2.5. Treatment Protocols and Randomization

Maxillary and mandibular premolars and molars (excluding third molars) were randomly assigned as “test-sites” or “control-sites”. The teeth on test-sites received SRP and adjunct Nd:YAG laser therapy. The control-sites underwent SRP alone. Randomization was done by tossing a coin.

2.6. SRP and Nd:YAG Laser Irradiation

Under local anesthesia, SRP was performed using hand instruments (American Eagle Curette, Missoula, MT). Laser therapy was performed as described elsewhere [20]. In summary, laser therapy was performed by a trained and calibrated investigator (TA) (*kappa* 0.88). Laser was applied by inserting the fiber into the periodontal pocket almost parallel to the tooth and moving from mesial to distal directions continuously on the buccal and the lingual aspect of the tooth. The fiber was held in a constant motion in contact with the pocket epithelial lining almost parallel to the long axis of the root. An Nd:YAG laser system (Genius Dental, Tureby, Denmark), which emitted pulsed light at 1064 nm was used. To avoid thermal effects, the instrument was set at level 5 using the following parameters: average output: 4 W (W); energy per pulse: 80 mJ; pulse width: 350 μs, pulse-repetition rate: 50 Hz; pulse peak power: 240 W; average power density at the fiber end: 1430 watts per square centimeters (W/cm^2); and peak power density: 85,800 W/cm^2 [4]. The laser treatment was performed with air and water-cooling. Irradiation parameters were governed through the fiber diameter, treatment time, power of the laser at the tip of the fiber, and surface area of the irradiation site. The time spent on each tooth varied between 60 and 120 s, depending on accessibility. The laser energy per treated site was 240 to 480 J.

2.7. Collection of GCF Samples and Assessment of IL-1β and TNF-α Levels

GCF samples were collected at baseline and at 3 and 6-months' follow-up by a trained investigator (FV). Prior to GCF sampling, tooth surfaces were dried using a triple syringe and isolated with cotton rolls to avoid salivary contamination. Prefabricated paper strips (PerioPaper, Ora*flow*, Plainview, NY) were placed in the deepest pocket of teeth #19 and #30 for approximately 30 s in each patient. If any of these teeth were missing, then the GCF samples were collected from the adjacent posterior tooth. Samples that accidentally got contaminated with blood or saliva were discarded and another sample was taken from the same site after 24 h. All samples from the test- and control-sites were placed in sterile microtubes and frozen at −70 °C until analysis.

The GCF volume was determined using a calibrated machine (Oraflow Inc. Plainview, NY). To assess the GCF cytokine profile, the samples were placed at 4 °C for 60 min following which, 250 ml of phosphate buffered saline was added to each microtube. The samples were then centrifuged at 20,000 rpm for 10 min at 4 °C. All GCF samples from test and control-sites were analyzed for the concentrations of IL-1β (IL-1β ELISA Kit, USCN Life Science; Houston, TX) and TNF-α (TNF-α ELISA Kit, USCN Life Science; Houston, TX) using the sandwich enzyme linked immunosorbent assay (R&D systems, Minneapolis, MN, USA). Standard curves were made by plotting the concentrations of IL-1β and TNF-α within a standard range of 4 to 250 pg/ml and 23 to 1500 pg/ml, respectively.

2.8. Periodontal Parameters

One calibrated investigator (FV) blinded to the test- and control-sites performed the clinical periodontal examination (*kappa* 0.85). PI [21], BOP [21] and PPD in millimeters (mm) [21] were measured at six sites per tooth (mesiobuccal, midbuccal, distobuccal, distolingual/distopalatal, midlingual/midpalatal and mesiolingual/mesiopalatal) on all maxillary and mandibular teeth (excluding bilateral maxillary and mandibular third molars). PPD was measured to the nearest millimeter (mm) with a graded probe (Hu Friedy, IL., Chicago, USA) [21,22]. These measurements were performed at baseline and at 3 and 6-months follow-up periods. Fractured teeth with embedded root remnants were also excluded.

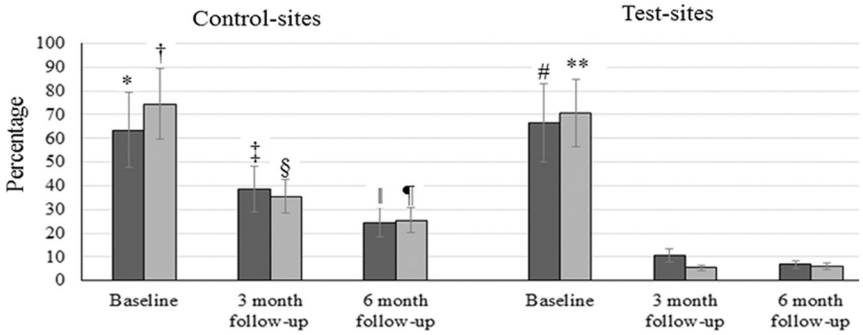

Fig. 1. Mean ± SD of plaque index (dark gray bars) and bleeding on probing (light gray bars) in the test- and control-sites at baseline and at 3- and 6-month follow-up. *Compared with PI at 3 and 6-month follow-up in the control sites (P < 0.001); †Compared with BOP at 3 and 6-month follow-up in the control sites (P < 0.001); ‡Compared with PI at 3- and 6-month follow-up in the test-sites (P < 0.01); §Compared with BOP at 3- and 6-month follow-up in the test-sites (P < 0.01); ‖Compared with PI at 3- and 6-month follow-up in the test-sites (P < 0.01); ¶Compared with BOP at 3- and 6-month follow-up in the test-sites (P < 0.01); #Compared with PI at 3 and 6-month follow-up in the test-sites (P < 0.001); **Compared with BOP at 3 and 6-month follow-up in the test-sites (P < 0.001).

2.9. Oral Hygiene Instructions

Oral hygiene instructions were given to all participants. The participants were encouraged to brush their teeth twice daily and were also encouraged to use dental floss daily.

2.9.1. Statistical Analysis

Statistical analysis was performed using a software program (SPSS Version 18, Chicago, IL). Inter- and intra-groups comparisons in terms of clinical periodontal parameters and GCF IL-1β and TNF-α levels among the test- and control-sites were performed using the Wilcoxon signed-rank test and Mann-Whitney *U* test. It was estimated that a minimum of 26 teeth in the test- and control-sites were needed to yield a power of 90% for the detection of a PPD difference of 1 mm between that received SRP + Nd:YAG laser therapy and SRP alone.

3. Results

3.1. General Characteristics of the Study Cohort

In total, 28 male participants (mean age 57.2 ± 8.5 years) with PD were included. In 9 patients, bilateral mandibular first molars were missing. In these patients GCF samples were collected from the deepest pocket of the bilateral mandibular second molars. Altogether, 56 sites were assessed (28 teeth in the test-sites and 28 in control-sites). On average, the total number of teeth present in these patients were 24.6 ± 1.7 teeth.

3.2. Periodontal Parameters

In the test- and control-sites, baseline scores of PI (P < 0.001) and BOP (P < 0.001) were statistically significantly higher compared with their respective values at 3- and 6-month follow-up. In the control-sites at 3-month follow-up, PI (P < 0.01) and BOP (P < 0.01) were statistically significantly higher compared with the test-sites at 3- and 6-month follow-up. In the control-sites at 6-month follow-up, PI (P < 0.01) and BOP (P < 0.01) were statistically significantly higher compared with the test-sites at 3- and 6-month follow-up. In the test-sites, there was no statistically significant difference in PI and BOP at 3- and 6-month follow-up (Fig. 1). The mean PPD in the test- and control-sites was statistically significantly higher at baseline as compared to the respective sites at 3- and 6-month follow-up. In the control-sites, PPD at 3- and 6-month follow-up was significantly higher than the PPD in the-test-site at 3 and 6-month follow-up. In the test-sites, there was no difference in PPD at 3- and 6-month follow-up (Fig. 2).

3.3. GCF IL-1β and TNF-α Levels in the Test- and Control-sites at Baseline and at 3- and 6-month Follow-Up

At baseline, IL-1β and TNF-α levels were comparable in the test-and control-sites. In the control-sites, IL-1β and TNF-α levels at baseline as compared to their concentrations at 3- (P < 0.001) and 6-month (P < 0.001) follow-up. In the control-sites, IL-1β (P < 0.05) and TNF-α (P < 0.05) levels were significantly higher at 3-month follow-up compared with 6-month follow-up. In the test-sites, IL-1β (P < 0.001) and TNF-α (P < 0.05) levels were significantly higher at baseline compared with their concentrations at 3- and 6-month follow-up. In the control-sites, IL-1β (P < 0.05) and TNF-α (P < 0.05) levels were significantly higher at 6-month follow-up as compared to 3- and 6-month follow-up in the test-sites. At 3 and 6-month follow-up, concentrations of IL-1β and TNF-α levels were comparable in the test-sites. Compared with the test-sites, GCF volume was significantly higher in the control-sites at 3- (P < 0.05) and 6-month (P < 0.05) follow-up (Table 1).

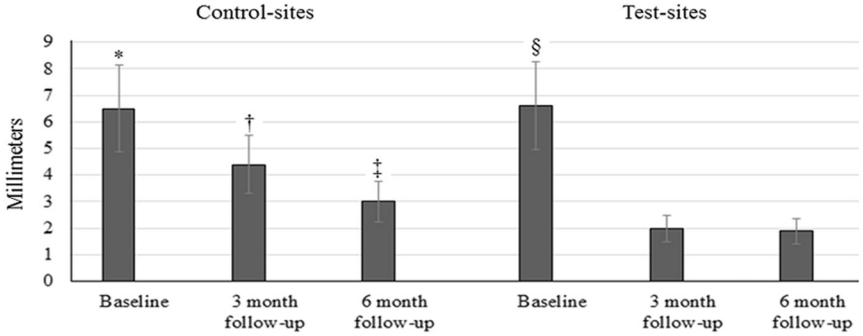

Fig. 2. Mean ± SD of probing pocket depth in the test- and control-sites at baseline and at 3- and 6-month follow-up. *Compared with PPD at 3- and 6-month follow-up in the control sites (P < 0.001); †Compared with PPD at 3- and 6-month follow-up in the test-sites (P < 0.001); ‡Compared with PPD at 3- and 6-month follow-up in the test-sites (P < 0.01); §Compared with PPD at 3- and 6-month follow-up in the test-sites (P < 0.01).

Table 1
Concentrations of GCF IL-1β and TNF-α at baseline and at 3- and 6-month follow-up in the control and test-sites. [*]Compared with 3- and 6-month follow-up in the control-sites ($P < 0.001$); [†]Compared with 6-month follow-up in the control-sites ($P < 0.05$); [‡]Compared with 3- and 6-month follow-up in the test-sites ($P < 0.001$); [§]Compared with 3- and 6-month follow-up in the test-sites ($P < 0.05$); [‖]Compared with 3- and 6-month follow-up in the test-sites ($P < 0.001$); [¶]Compared with 3- and 6-month follow-up in the control-sites ($P < 0.001$); [#]Compared with 6-month follow-up in the control-sites ($P < 0.05$); [**]Compared with 3- and 6-month follow-up in the test-sites ($P < 0.01$); [††]Compared with 3- and 6-month follow-up in the test-sites ($P < 0.05$); [‡‡]Compared with 3- and 6-month follow-up in the test-sites ($P < 0.05$); [§§]Compared with 3- and 6-month follow-up in the control-sites ($P < 0.05$); [‖‖]Compared with 3- and 6-month follow-up in the test-sites ($P < 0.05$). [¶¶]Compared with 3- and 6-month follow-up in the test-sites ($P < 0.05$); [##]Compared with 3- and 6-month follow-up in the test-sites.

Cytokine profile and GCF volume	Control-sites			Test-sites		
	Baseline	3-Month follow-up	6-Month follow-up	Baseline	3-Month follow-up	6-Month follow-up
IL-1β (in pg/ml)	405.4 ± 34.8[*]	101.5 ± 18.2[†‡]	62.5 ± 6.3[§]	447.5 ± 21.6[‖]	12.3 ± 3.4	8.7 ± 0.6
TNF-α (in pg/ml)	25.5 ± 4.6[¶]	11.5 ± 0.8[#,**]	6.2 ± 1.5[††]	27.2 ± 2.5[‡‡]	3.2 ± 0.5	2.3 ± 0.2
GCF Volume (μl)	1.6 ± 0.2[§§]	0.7 ± 0.3[‖‖]	0.4 ± 0.1[¶¶]	1.63 ± 0.4[##]	0.2 ± 0.08	0.1 ± 0.03

GCF: Gingival crevicular fluid. IL-1β: Interleukin 1 beta.
TNF-α: Tumor necrosis factor alpha.

4. Discussion

The present study was based on the hypotheses that (a) clinical periodontal parameters (PI, BOP and PPD) are significantly higher in the control-sites (sites that received SRP alone) than the test-sites (sites that received SRP + Nd:YAG laser); and (b) GCF levels of IL-1β and TNF-α are significantly higher in the control-sites compared with the test-sites. The present results are in accordance with these hypotheses since the test-sites showed a significant reduction in periodontal inflammation and GCF IL-1β and TNF-α at 3- and 6-month follow-up compared with the control-sites. One explanation in this regard is that the 1064 nm Nd:YAG laser is absorbed only by soft tissues such as the pocket epithelial lining and dental hard tissues, such as cementum and/or dentin remain unaffected [23]. Moreover, it has also been reported that Nd:YAG laser therapy increases the proliferation of gingival epithelial cells and fibroblasts and periodontal ligament cells [24–27]. The present results are contradictory to those reported in the study by Gómez et al. [28] in which, no statistically significant differences were found in clinical parameters (PI. BOP and PPD) among patients treated with either SRP + Nd:YAG laser therapy or SRP alone. This outcome could possibly be associated with the maximum follow-up duration in the study by Gómez et al. [28] (8 weeks) in contrast to the present study (24 weeks). It is therefore speculated that complete clinical healing may not have occurred due to the short-term follow-up duration (8 weeks) in the study by Gómez et al. [28]. However, the present results support the studies by Qadri et al. [4,7], in which 3-month follow-up results showed a statistically significant reduction in PI, PPD and gingival index among patients that underwent SRP + Nd:YAG laser therapy compared with those that received SRP alone. In the present study, oral hygiene instructions were given to the patients during which brushing and flossing techniques were explained to the patients. In the present study, oral hygiene instructions were given to all patients. Although the contribution of regular oral hygiene maintenance towards a better dental health status cannot be disregarded, the clinical periodontal parameters and GCF proinflammatory cytokine levels continued to be higher in the control-sites compared with the test-sites. These results indicate that despite oral hygiene instructions, adjunct therapies (such as Nd:YAG laser therapy) are more effective in reducing clinical and immunological inflammatory parameters compared with SRP alone.

Traditionally, clinical and radiographic investigations are performed to assess the outcomes of periodontal therapy [29,30]; however, laboratory-based investigations have also been shown to be useful in this context [31]. Studies [32–34] have reported that assessment of proinflammatory cytokines in the GCF are correlated with the progression of PD and treatment of periodontal therapy. In the present study, the 3- and 6-month follow-up results showed that the GCF volume as well as levels of IL-1β and TNF-α were significantly higher in the control-sites compared with the test-sites. In addition, the clinical periodontal parameters (PI, BOP and PPD) were also significantly higher in the control-sites compared with the test-sites at 3- and 6-month follow-up. This suggests that assessment of GCF cytokine profile is a non-invasive and valuable tool to assess the progression of PD in the community. Interestingly, there was no statistically significant difference in periodontal parameters and GCF IL-1β and TNF-α levels in the test-sites at 3- and 6-month follow-up. It is hypothesized that the anti-inflammatory effects of SRP with adjunct Nd:YAG laser therapy can last for a period of at least 6-months following which, a reassessment of the patient's periodontal status may be required.

A limitation of the present study is that tobacco-smokers and individuals with systemic diseases such as diabetes mellitus were excluded. It has been reported that outcomes of periodontal therapy are compromised in smokers compared to non-smokers [35,36]. According to Katz et al. [37], there is an increased expression of advanced glycation endproducts (AGEs) and their receptors (RAGE) in the gingival tissues of smokers compared with non-smokers, which impairs periodontal healing. Moreover, nornicotine (a metabolite of nicotine), has also been reported to increase the expression of RAGE in the periodontal tissues which in turn increases the secretion of proinflammatory cytokines that jeopardize the periodontal apparatus [37]. Similarly, an increased expression of AGEs and RAGE have also been reported in the periodontal tissues of patients with chronic hyperglycemia [38,39]. Moreover, among hyperglycemic individuals, wound healing is also impaired due to the loss of fibroblasts and osteoblasts through apoptosis [40]. It is therefore hypothesized that the outcomes of SRP with or without adjunct Nd:YAG laser therapy are compromised in patients with chronic hyperglycemia and smokers compared with systemically healthy individuals and non-smokers. Further studies are needed to test this hypothesis.

5. Conclusion

At 3- and 6-month follow-up, SRP + Nd:YAG therapy was more effective in reducing periodontal inflammatory parameters and GCF IL-1β and TNF-α levels compared with SRP alone.

Conflict of Interest Statement

None declared.

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