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The short-term effects of full-mouth or quadrant-wise applied subgingival instrumentation on immune response and oxidation process in saliva: a randomized clinical trial

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Abstract

Aim To evaluate oxidation and antioxidant activity in the saliva of periodontitis patients following non-surgical periodontal therapy applied either as full mouth subgingival instrumentation (FM) or quadrantwise (Q).

Methods Patients affected by periodontitis were randomly allocated to receive FM or Q and followed up at 1st and 3rd months. Saliva samples and periodontal variables were collected at baseline, 1st, and 3rd month. The primary outcomes were the total antioxidant status (TAS), total oxidant status (TOS). Secondary outcomes were clinical measurements, Tumour Necrosis Factor alpha (TNF alpha), and Oxidative Stress Index (OSI) parameters.

Results Forty-five subjects were included in the study. Both FM and Q resulted reductions in all periodontal variables, TNF alpha and TOS values, with an improvement in TAS values compared to baseline. Significant differences were observed in the reductions of probing pocket depth (PPD) and clinical attachment level (CAL) between the FM group and the Q group as periodontal variables ($p < 0.05$). The change in TNF alpha (ng/L) and TAS (mmol Trolox Eq/L) from baseline to post treatment significantly improved in FM group compared to Q.

Conclusion Both treatment protocols were efficient in the treatment of periodontitis but the FM therapy significantly reduced periodontal tissue inflammation, as evidenced by changes in both clinical and biochemical parameters in our study. However, it may be seen that FM therapy is more effective during short-term recovery, maybe the reason could be attributed to TAS and TNF alpha changes following FM therapy.

Trial registration This study was registered at Thai Clinical Trials Registry. (https://www.thaiclinicaltrials.org/show/TCTR20240416007, TCTR ID: TCTR20240416007; date of registration: 16 April 2024)—retrospectively registered).

Keywords Chronic periodontitis, Oxidative stress, Full-mouth debridement, Subgingival instrumentation, Total antioxidant status, Total oxidant status, TNF alpha

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Clinical relevance

Background: There is no strong evidence that full mouth periodontal therapy approaches provide additional clinical benefit compared to quadrant wise. It was noticed that there was no examination in terms of salivary oxidant/antioxidant capacity comparing two treatment modalities.

Added value of this study: Improvements in clinical, biochemical and immune response were observed in both treatment modalities compared to baseline. Only the difference values obtained in TNF alpha and TAS data compared to baseline showed a significant difference between the two groups.

Clinical implications: One stage full mouth treatment may be a preferable treatment option to support antioxidant capacity in patient groups with initially high oxidative stress.

Introduction

Periodontitis is recognised as a chronic multi-factorial inflammatory disease associated with dysbiotic dental plaque biofilm, affecting the tissues surrounding the teeth characterised by clinical attachment level (CAL), radiographically assessed alveolar bone loss, presence of periodontal pocketing and gingival bleeding [1, 2]. The goal of periodontal treatment is to eliminate subgingival biofilm and achieve homeostasis. This is primarily accomplished through non-surgical periodontal therapy, involving subgingival instrumentation, formerly known as scaling and root planing (SRP). It entails the mechanical removal of hard and soft residues from tooth surfaces. The traditional protocol for treating periodontitis is quadrant-wise scaling and root planing (Q), typically performed at weekly intervals. Considering the possible translocation of bacteria within the oral cavity, a recently instrumented deep pocket could be recolonized from untreated pockets or other intraoral niches before a less pathogenic ecosystem can be established [3–5]. Therefore, some studies have evaluated whether performing full-mouth subgingival instrumentation (FM) within a short period could prevent bacterial reload, leading to better clinical outcomes [6–8] . In a recent Cochrane systematic review, it was noted that there is no definitive evidence supporting the idea that full-mouth treatment modalities provide additional clinical benefits compared to conventional mechanical treatments for periodontitis. The conclusion drawn from the review suggests that the choice between these approaches should be based on patient and dentist preferences and convenience [9].

Oxidative stress is defined as an imbalance between the production of reactive oxygen species (ROS) and the antioxidant capacity of the organism. Like many other inflammatory diseases, periodontitis is associated with an increased local and systemic oxidative stress and compromised antioxidant capacity in its inflammatory response, contributing to the loss of supporting tooth tissue [10, 11]. Salivary biological markers of oxidative stress have been extensively studied as a potential periodontal diagnostic tool. Former studies demonstrated elevated salivary concentrations of lipid peroxidation products (such as malondialdehyde and 4-hydroxy-2-nonenal), protein oxidation markers (specifically advanced oxidation protein products), and a DNA damage marker (comprising 5-hydroxydeoxyuridine and 8-hydroxydeoxyguanosine) in individuals affected by periodontitis [12]. Total oxidative status (TOS) assay developed by Erel [13] provides a possibility to measure additive effects of oxidants. Previous studies showed that salivary TOS was elevated in individials with periodontitis and such elevation can be ameliorated through periodontal therapy [14, 15]. During an inflammatory response, oxidants either interact with target proteins or are neutralized by different antioxidant molecules. Thus, measuring salivary total antioxidant capacity (TAS) is a crucial part of periodontal screening. Furthermore, studies indicate that individuals with periodontitis might have lower salivary TAS levels [16, 17]. The balance relates to the ratio of TAS to TOS as determined by the oxidative stress index (OSI).

There is insufficient evidence to support the FM approach over the Q. There hasn't been an investigation assessing the impact of the FM approach on oxidative stress, even though the majority of studies have focused on the clinical and microbiological aspects of FM treatment, with only a small number examining the biochemical effects of this protocol, [18–20]. This is the first study to investigate the potential effects of both FM and Q treatment approaches on salivary antioxidant and oxidant status while also monitoring clinical outcomes for both strategies.

The aim of this study was to assess salivary oxidation and antioxidation activity in a group of individuals with periodontitis before and after receiving non-surgical periodontal therapy using either FM or Q.

Material and method

Trial design

This study was reported following the Consolidated Standards of Reporting Trials (CONSORT) 2010 guidelines [21]. The study was designed as a single center, randomized clinical trial with 2-arm parallel design, allocation ratio is 1:1, with a 3 month follow up. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved

by the Bezmialem University Ethics Committee for Clinical Research (Permission Reference No: 7/43) and it was registered at Thai Clinical Trials Registry (https://www.thaiclinicaltrials.org/show/TCTR20240416007, TCTR ID: TCTR20240416007; Registration Date16 April 2024). Registration was conducted retrospectively in April 2024 after completion of data assessment. Written consent forms were obtained from individuals who agreed to participate in the study. Beyond the stipulated inclusion and exclusion criteria, individuals with orthodontic appliances, crown and bridge prostheses, and grade III mobile teeth were excluded from the study.

Participants

Individuals referred to the Istanbul University, Faculty of Dentistry, Department of Periodontology clinics were screened for eligibility. Subjects were eligible to participate if they met the following inclusion criteria: I. aged 25 and above, II. systemically healthy and lifelong non smokers III. at least had 20 teeth IV. diagnosis of moderate-advanced periodontitis defined as ≥ 4 mm in ≥ 2 non-adjacent teeth [22], V. $>30\%$ alveolar bone loss VI. at least a tooth with probing depth (PD) ≥ 5 mm in each quadrant. Subjects were excluded if they were I. pregnant or lactating females, II. had a diagnosis of any systemic disease as diabates, III. had removable prosthesis, and IV. had undergone periodontal treatment or V. used antibiotics in the last 6 months.

According to the 2017 classification, the patients were retrospectively evaluated, revealing that the patient group, included based on these new criteria, met the definition of Stage II- III periodontitis [23]. All participants received a subject information sheet, and written informed consent was acquired. Preceding this, detailed medical and dental histories were documented, followed by a comprehensive oral examination.

Interventions

Oral hygiene instructions (OHI) and motivation sessions were given to each patient before treatment and were reinforced during follow-up visits. The treatment protocol was as follows; supragingival and subgingival mechanical instrumentation of the root surface was performed by a single periodontist (SB), using both hand (Gracey Periodontal Currettes (Hu-Friedy®)) and ultrasonic instrumentation with fine tips (Cavitron Dentsply); under local anaesthesia. FM was performed within a single session. Q was performed one quadrant per session, with an interval of 1 week between instrumentation sessions for a total of 3 weeks.

Outcomes

The primary outcome of the study involved analyzing the alterations in oxidation and antioxidation levels following treatment. The secondary outcomes encompassed evaluating the impact of these changes in biochemical parameters on clinical parameters and analyzing the alterations in clinical parameters.

Clinical measurement

At baseline, all participants received a full periodontal evaluation by a single examiner. Full-mouth clinical measurements of plaque index (PI Silness&Löe 1964), [24] bleeding on probing (BOP%), [25] probing pocket depth (PPD) and CAL were recorded using a manual periodontal probe (PCP-UNC 15, Hu-Friedy Manufacturing Co., Chicago, IL, USA) at six sites of each tooth (mesial, central and distal; buccally and orally). PPD was measured from the base of the pocket to the gingival margin. CAL is assessed as the distance from the base of the pocket to the cemento-enamel junction. Additionally, measurements did not encompass the third molar. All clinical measurements are designated as secondary outcomes within the study framework.

Saliva sampling

Saliva samples were collected prior to clinical measurements to mitigate the risk of potential contamination from blood and dental plaque. Unstimulated whole expectorated saliva (10 mL) was systematically collected from each individuals between 09:00 and 10:00 h. Patients were instructed to abstain from consuming any food prior to the sampling procedure. Subjects rinsed their mouths with water before sampling. Subsequently, they expectorated saliva into sterile tubes (Salivette, Sarstedt, Germany) designed for this specific sampling procedure, while seated in an upright position. Collected samples were immediately transported to the frozen at -80 °C until biochemical testing. The samples were collected at baseline, 1st and 3rd months during follow up.

Follow up

Figure 1 shows the study outline. All patients were re-examined at1st month and 3rd month. Within the FM group, the 1st-month follow-up corresponded to the month subsequent to the first session; conversely, in the Q group, it designated the month following the conclusion of the fourth treatment session. The 3rd-month follow-up scheme maintained a parallel definition with the

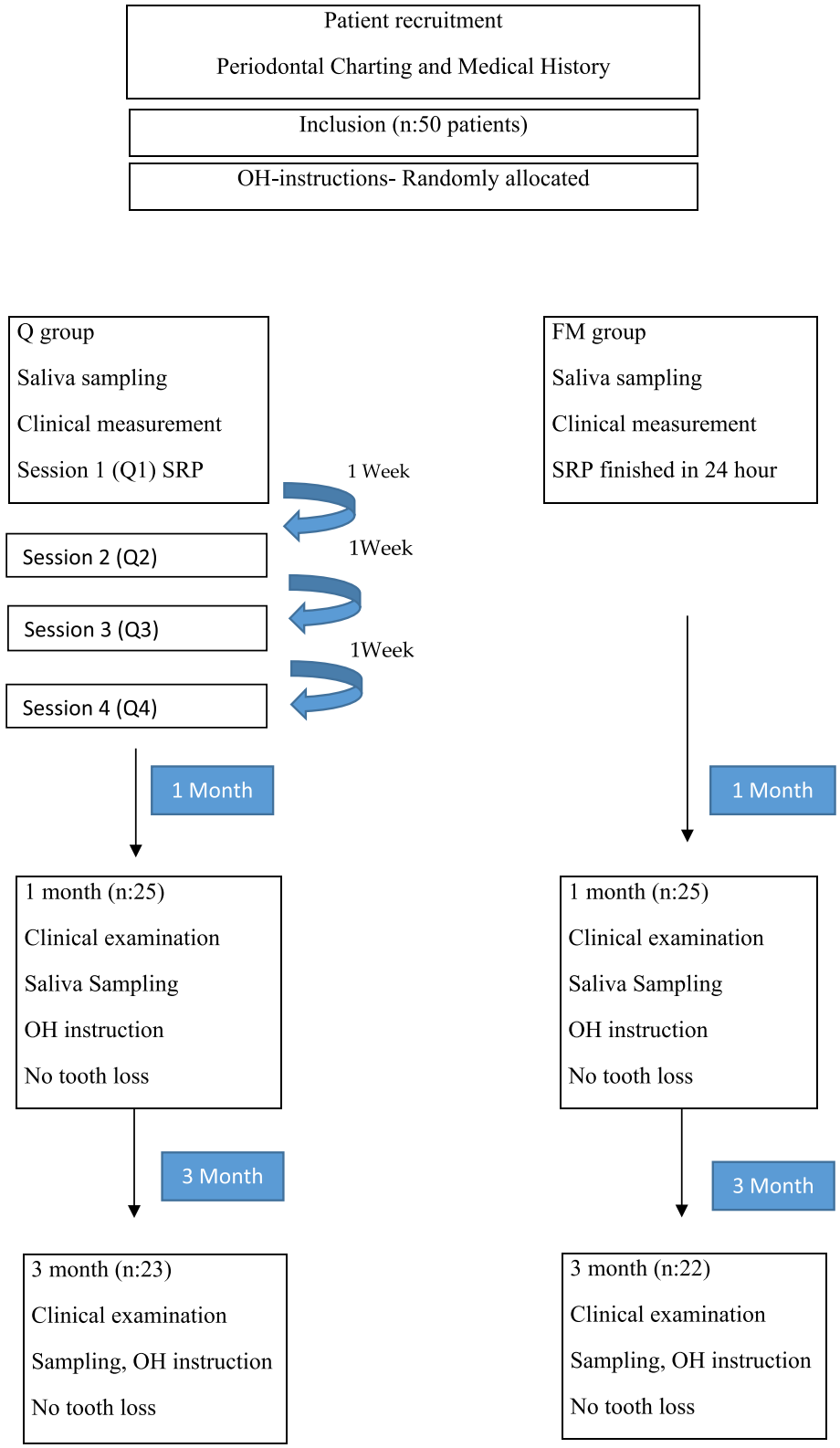

Fig. 1 Flow chart (Supplementary Figure)

1st month. The recorded variables at each time point are shown in Fig. 1. (Supplementary Figure).

Biochemical analyses

All biochemical analyses were conducted utilizing specific ELISA kits following the manufacturer's instructions and saliva samples were analyzed using an ELISA microplate reader (Thermo Scientific™ Varioskan™ Flash Multimode Reader) at a wavelength of 450 nm. Salivary TNF alpha levels were measured using an ELISA kit (Eastbiopharm—Human TNF-alpha Platinum ELISA, Cat No: CK-E10110). The outcomes were quantified and reported in nanograms per liter (ng/L). Salivary TAS levels were assessed using an ELISA kit (Eastbiopharm—Human Total Antioxidant Capacity (T-AOC) ELISA Kit, Cat.No: CK-E90253), and the results were quantified and expressed as mmol Trolox Equivalents/L. Salivary TOS levels were evaluated using an ELISA kit (Eastbiopharm—Human Total Oxidant Capacity (T-OC) ELISA Kit, Cat No: CK-E90252), and the results were quantified and expressed as micromoles of hydrogen peroxide equivalents per liter (μmol H2O2 Eqv./L).

Sample size

The sample size was calculated by taking type 1 error as 5%, type 2 error as 20%, and power of study as 80%. According to the sample size calculation, the minimum number of cases for each group was 18 [20]. To protect from possible dropouts, the sample size was increased to 25 participants per group.

Randomization and allocation concealment

Participants were randomly allocated in a 1:1 ratio to receive either FM or Q therapy by using coin toss randomization method. Allocation to treatment revealed to the therapist and patient on the day of the treatment.

Blinding

Blinding of intervention was not implemented in the methodology employed for our study as it is impossible to blind the therapist (SB) as she perform quadrant-wise or full-mouth instrumentation. All measurements were conducted by a single periodontist, who remained blinded to the assigned treatment groups throughout the process.

Statistical analyses

Statistical analysis was conducted utilizing the SPSS (Statistical Package for Social Sciences) 21 software program. A significance level of $p < 0.05$ was established to assess statistical significance. After verification of data distribution, intragroup comparisons were conducted. Variables indicating normality were assessed using the Paired Sample T-Test, while those without evidence of normal distribution were analyzed using the Wilcoxon test. Baseline and post-treatment differences for each variable were calculated and compared using the Paired Sample T-Test in independent groups when normal distribution was observed, and the Mann–Whitney U test for variables not conforming to normal distribution. Pearson correlation analysis was conducted to investigate the correlations among the clinical and biochemical parameters. A univariate linear regression model was built to evaluate the predictive ability of the relative total oxidation/antioxidation differences after periodontal treatment on change in clinical outcomes after treatment. The relationship between parameters was evaluated using univariate linear regression models.

Results

Patient recruitment was halted after reaching the targeted goal of 50 (FM25/Q25) eligible patients between May 2016 and November 2016. The study concluded in February 2017 due to completion of the 3-month follow-up process, which surpassed the initially aimed number of 36 (FM18/Q18). Forty-five patients (FM22/Q23) completed the study. Five participants were excluded from the study due to various reasons. Four subjects did not show up for their follow up appointments and one subject used antibiotic drug unrelated to periodontal therapy. Postoperative healing was uneventful in all cases, and no adverse events or complications were recorded during the study.

Participant characteristics

Forty five patients (21 male, 24 female) participated in the study. The average age of the FM group was 36.95 ± 5.32 years and the average age of the Q group was 35.39 ± 6.30 years that was not statistically significantly different from the FM group ($p > 0.05$). There was no statistically significant difference between the groups in terms of gender distribution and average age. Furthermore, no statistically significant differences were found between the groups in any of the clinical measurements or biochemical parameters examined at baseline ($p > 0.05$).

Clinical analyses

Treatment resulted in significant benefits in terms of periodontal parameters in both groups. Table 1 presents the mean values and mean differences in clinical parameters at baseline, first month, and third month, including the changes between baseline and first month, as well as baseline and third month for both treatment groups following therapy. At baseline there were no statistically significant differences between the two treatment

Table 1 Mean values and mean difference for all sites at different time points for the clinical measurement variables

Variable	Time point	Mean (SD)		*p*-Value between groups	MD (95% CI)
		Q	FM		
PPD	Baseline	3.70 + 0.62	4.01 + 0,54	0.08	-0.31 (-0.66; 0.03)
	1.month	2.84 + 0.43	2.60 + 0,51	0.095	0.24 (-0.04; 0.52)
	3.month	2.47 + 0.38	2.14 + 0,39	**0.007***	0.33 (0.10; 0.56)
	0–1 month	0.87 + 0.49	1.42 + 0,68	**0.003***	-0.55 (-0.91; -0.19)
	0–3 month	1.24 + 0.59	1.88 + 0,54	**0.00****	-0.64 (-0.98; -0.30)
	P value for intra group (baseline-1.month-3. month)	**< 0.001****	**< 0.001****		
CAL	Baseline	2.02 + 0.65	2.06 + 0.49	0.816	-0.04 (-0.39; 0.31)
	1.month	1.10 + 0.58	0.72 + 0.52	0.026	0.38 (0.05; 0.71)
	3.month	0.66 + 0.46	0.32 + 0.32	0.006	0.34 (0.10; 0.58)
	0–1 month	0.92 + 0.65	1.34 + 0.61	**0.032***	-0.42 (-0.80; -0.04)
	0–3 month	1.35 + 0.67	1.73 + 0.45	**0.031***	-0.38 (-0.73; -0.04)
	P value for intra group (baseline-1.month-3. month)	**< 0.001****	**< 0,001****		
BOP	Baseline	0.80 + 0.2	0.82 + 0.29	0.858	-0.01 (-0.17; 0.14)
	1.month	0.30 + 0.25	0.21 + 0.18	0.171	0.09 (-0.04; 0.22)
	3.month	0.20 + 0.25	0.06 + 0.12	**0.020***	0.14 (0.02; 0.26)
	0–1 month	0.5 + 0.26	0.61 + 0.33	0.256	-0.10 (-0.28; 0.07)
	0–3 month	0.60 + 0.30	0.76 + 0.30	0.084	-0.16 (-0.34; 0.02)
	P value for intra group (baseline-1.month-3. month)	**< 0.001****	**< 0.001****		
PI	Baseline	1.62 + 0.45	1.64 + 0.58	0.904	-0.02 (-0.33; 0.29)
	1.month	0.58 + 0.45	0.87 + 0.46	**0.041***	-0.29 (-0.56; -0.019
	3.month	0.76 + 0.43	0.67 + 0.63	0.587	0.09 (-0.24; 0.42)
	0–1 month	1.04 + 0.39	0.77 + 0.51	**0.034***	0.27 (-0.01; 0.54)
	0–3 month	0.86 + 0.53	0.97 + 0.58	0.356	-0.11 (-0.44; 0.23)
	P value for intra group (baseline-1.month-3. month)	**< 0.001****	**< 0.001****		

Bold values indicate statistical significance. *$p < 0.05$, **$p < 0.01$

Abbreviations: *CI* Confidence interval, *BOP* Bleeding on probing, *CAL* Clinical attachment level, *FM* Full mouth therapy, *MD* Mean difference, *PPD* Probing pocket depth, *PI* Plaque index, *Q* Quadrant wise therapy, *SD* Standard deviation

groups in all clinical parameters (Table 1). Intra-group differences were statistically significant for all periodontal parameters (Table 1). There was a significant difference between the FM and Q groups in the amount of change in PPD measures between baseline and the first month ($p = 0{,}003$) and between baseline and the third month ($p = 0{,}00$). PPD reduction was found to be relatively greater in the FM group. There was a significant difference between the FM and Q groups in the amount of change CAL measures between baseline and the first month ($p = 0{,}032$) and between baseline and the third month ($p = 0{,}031$). CAL gain was found to be relatively higher in the FM group. When comparing the change from baseline to the first and third months in terms of BOP and PI between the two groups, only the first-month change in PI measurement was found to be statistically significant between FM and Q ($p < 0.05$).

Biochemical analyses

Both groups experienced significant improvements in biochemical parameters as a result of treatment. Table 2 presents the mean values and mean differences in biochemical parameters at baseline, first month, and third month, including the changes between baseline and first month, as well as baseline and third month for both treatment groups following therapy. At baseline there were no statistically significant differences between the two treatment groups in all clinical parameters ($p > 0.05$). The amount of change in TNF-alpha and TAS levels between baseline and the first month and baseline and the third month was significantly different for the FM and Q groups ($p < 0.05$).

TOS and OSI levels were reduced compared with baseline values in both groups but there was no significant difference between groups in terms of change values

Table 2 Mean values and mean difference for all sites at different time points for the biochemical variables

Variable	Time point	Mean (SD)		*p*-Value between groups	MD (95% CI)
		Q	FM		
TNF alpha	Baseline	448.921 + 73.366	495.764 + 83.253	0.51	-46.84 (-93.96; 0.28)
	1.month	336.522 + 42.637	217.708 + 57.110	**< 0.001****	118.81 (88.31; 149.31)
	3.month	168.090 + 30.650	57.974 + 55.134	0.455	10.12 (-17.12; 37.35)
	0–1 month	112.40 + 91.27	278.06 + 79.62	**0.001****	-165.66 (-217.24; -114.07)
	0–3 month	280.831 + 81.86	337.79 + 74.39	**0.017***	-56.96 (-104.05; -9.87)
	P value for intra group (baseline-1.month-3. month)	**< 0.001****	**< 0.001****		
TAS	Baseline	0.56 + 0.11	0.52 + 0.13	0.247	0.04 (-0.03; 0.11)
	1.month	0.71 + 0.10	0.76 + 0.10	0.107	-0.05 (-0.11; 0.01)
	3.month	0.76 + 0.11	0.82 + 0.09	**0.035***	-0.06 (-0.12; -0.004)
	0–1 month	-0.14 + 0.09	-0.23 + 0.10	**0.003***	0.09 (0.03; 0.15)
	0–3 month	-0.19 + 0.10	-0.30 + 0.12	**0.003***	0.11 (0.04; 0.17)
	P value for intra group (baseline-1.month-3. month)	**< 0.001****	**< 0.001****		
TOS	Baseline	8.51 + 1.12	8.01 + 0.63	0.076	0.49 (-0.05; 1.04)
	1.month	6.54 + 0.88	5.91 + 0.77	**0.015***	0.62 (0.12; 1.12)
	3.month	5.53 + 0.88	5.27 + 0.60	0.256	0.26 (-0.20; 0.71)
	0–1 month	1.97 + 1.09	2.10 + 0.76	0.649	-0.13 (-0.70; 0.44)
	0–3 month	2.97 + 1.24	2.74 + 0.63	0.43	0.23 (-0.36; 0.83)
	P value for intra group (baseline-1.month-3. month)	**< 0.001****	**< 0.001****		
OSI	Baseline	15.15 + 4.82	15.00 + 6.25	0.926	0.16 (-3.19; 3.50)
	1.month	8.67 + 2.75	7.30 + 1.84	0.056	1.38 (-0.04; 2.79)
	3.month	7.42 + 1.43	6.47 + 0.90	**0.011***	0.94 (0.23; 1.66)
	0–1 month	6.48 + 4.54	7.70 + 6.16	0.414	-1.22 (-4.46; 2.02)
	0–3 month	7.74 + 4.27	8.52 + 6.07	0.364	-0.79 (-3.93; 2.36)
	P value for intra group (baseline-1.month-3. month)	**< 0.001****	**< 0.001****		

Bold values indicate statistical significance. *$p < 0.05$, **$p < 0.01$

Abbreviations: *CI* Confidence interval, *FM* Full mouth therapy, *MD* Mean difference, *OSI* Oxidative stress index, *Q* Quadrant wise therapy, *SD* Standard deviation, *TAS* Total antioxidant status, *TNF* Tumor necrosis factor, *TOS* Total oxidant status

between baseline-first month and baseline-third month ($p > 0.05$).

Correlations between clinical and biochemical markers

The analysis focused on changes within the Q group between the baseline and the 1st month. Subsequently, TAS values exhibited a moderate negative correlation with OSI, while CAL demonstrated moderate and strong positive correlations with BOP and PPD, respectively (Table 3). Examination of changes between the baseline and the 3rd month revealed a strong positive correlation solely between PPD and CAL values (Table 4). An analysis of changes within the FM group, from baseline to the first month, was conducted. TAS values exhibited moderate negative correlations with OSI, PPD, and CAL (Table 5). Additionally, a moderate positive correlation was observed between TOS and BOP, as well as between CAL and PPD. Notably, examination of changes between baseline and the 3rd month identified a strong negative correlation between TAS and OSI, and a strong positive correlation between CAL and PPD (Table 6). Linear regression analysis results are reported in Table 7. The impact of difference in PPD values on the change in CAL values ranged from 54.6% to 92.1%. Within the Q group, no notable influence of biochemical parameters on clinical values was discerned. Conversely, in the FM group, alterations in TAS during the baseline first month period exhibited an impact on both PPD and CAL values, accounting for 18.6% and 18.3%, respectively. Furthermore, TOS elucidated 18.9% of the alterations observed between baseline and the first month in BOP. The influence of TAS on OSI showed a variability between 31% and 64.9%.

Table 3 Correlations between salivary and clinical parameters in control group (difference's correlation values between initial and 1. month)

		TAS 0–1	TOS 0–1	TNF 0–1	OSI 0–1	PPD 0–1	CAL 0–1	BOP 0–1	PI 0–1
TAS 0–1	cc	1	0.264	0.313	-0.557	0.077	-0.090	-0.325	0.367
	p		0.224	0.145	**0.006****	0.726	0.684	0.131	0.085
	n	23	23	23	23	23	23	23	23
TOS 0–1	cc	0.264	1	-0.222	0.110	0.078	-0.037	0.174	0.366
	p	0.224		0.308	0.618	0.724	0.866	0.428	0.086
	n	23	23	23	23	23	23	23	23
TNF 0–1	cc	0.313	-0.222	1	-0.161	-0.154	-0.300	0.006	0.065
	p	0.145	0.308		0.464	0.484	0.164	0.979	0.768
	n	23	23	23	23	23	23	23	23
OSI 0–1	cc	-0.557	0.110	-0.161	1	-0.105	0.081	0.133	-0.229
	p	**0.006****	0.618	0.464		0.633	0.713	0.546	0.294
	n	23	23	23	23	23	23	23	23
PPD 0–1	cc	0.077	0.078	-0.154	-0.105	1	0.778	0.375	0.088
	p	0.726	0.724	0.484	0.633		**0.001****	0.078	0.691
	n	23	23	23	23	23	23	23	23
CAL 0–1	cc	-0.090	-0.037	-0.300	0.081	0.778	1	0.416	-0.015
	p	0.684	0.866	0.164	0.713	**0.001****		**0.048***	0.945
	n	23	23	23	23	23	23	23	23
BOP 0–1	cc	-0.325	0.174	0.006	0.133	0.375	0.416	1	0.014
	p	0.131	0.428	0.979	0.546	0.078	**0.048***		0.948
	n	23	23	23	23	23	23	23	23
PI 0–1	cc	0.367	0.366	0.065	-0.229	0.088	-0.015	0.014	1
	p	0.085	0.086	0.768	0.294	0.691	0.945	0.948	
	n	23	23	23	23	23	23	23	

Bold values indicate statistical significance. * Correlation is significant at the 0.05 level (2tailed) ** Correlation is significant at the 0.01 level (2 tailed)

Abbreviations: *BOP* Bleeding on probing, *CAL* Clinical attachment level, *cc* Correlation coefficient, *OSI* Oxidative stress index, *PPD* Probing pocket depth, *PI* Plaque index, *TAS* Total antioxidant status, *TNF* Tumor necrosis factor alpha, *TOS* Total oxidant status

Discussion

One-stage full-mouth subgingival instrumentation is associated with greater changes in TAS values from baseline to the 1st and 3rd months compared to quadrant-wise periodontal therapy in subjects affected by moderate to advanced periodontitis, indicating higher antioxidant capacity. Similar improvements were observed in the full-mouth subgingival instrumentation group regarding the change in TNF-alpha values over the same periods compared to quadrant-wise periodontal therapy. Additionally, it was observed that only in the full-mouth subgingival instrumentation group, the influence of biochemical markers on clinical parameters reached statistical significance.

In congruence with previous investigations, including our own, both treatment modalities yielded significant clinical amelioration across the follow up period [20, 26, 27]. However, our study delineated superior outcomes following FM therapy, characterized by more pronounced reductions in PPD and greater CAL gain from baseline to 1st and 3rd months compared to Q therapy. This enhanced clinical resolution may be ascribed to the comprehensive nature of FM therapy, which, by completing periodontal treatment in a single session, likely eradicated or mitigated bacterial reservoirs within the oral cavity, thus fostering optimal healing at treated sites. In contrast to earlier studies [20, 28, 29] comparing FM and Q, which revealed no differences in clinical parameters among receiving treatment, Ouirynen et al. reported significantly superior outcomes for patients undergoing full-mouth treatment compared to those receiving quadrant-wise periodontal therapy, evidenced by additional reductions in pocket depth and gains in clinical attachment after 1 and 2 months [7]. The disparity between the studies results may be attributed to differences in study protocols, such as differences in the intervals between quadrant-wise treatments, oral hygiene instructions, recall periods, and disease severity.

In this study, PPD was assessed by measuring the distance from the gingival margin to the pocket base. Gingival recession was not evaluated separately, and CAL measurements were taken directly. The study cohort

Table 4 Correlations between salivary and clinical parameters in control group(difference's correlation values between initial and 3. month)

		TAS 0–3	TOS 0–3	TNF 0–3	OSI 0–3	PPD 0–3	CAL 0–3	BOP 0–3	PI 0–3
TAS 0–3	cc	1	0.200	0.315	-0.349	0.224	0.061	-0.82	0.149
	p		0.361	0.143	0.102	0.304	0.780	0.711	0.497
	n	23	23	23	23	23	23	23	23
TOS 0–3	cc	0.200	1	-0.411	0.339	-0.120	-0.057	0.261	-0.075
	p	0.361		0.051	0.114	0.585	0.798	0.230	0.734
	n	23	23	23	23	23	23	23	23
TNF 0–3	cc	0.315	-0.411	1	-0.193	0.002	-0.184	-0.073	0.027
	p	0.143	0.051		0.379	0.992	0.401	0.742	0.901
	n	23	23	23	23	23	23	23	23
OSI 0–3	cc	-0.349	0.339	-0.193	1	-0.102	0.035	0.295	0.067
	p	0.102	0.114	0.379		0.644	0.874	0.172	0.761
	n	23	23	23	23	23	23	23	23
PPD 0–3	cc	0.224	-0.120	0.002	-0.102	1	0.739	0.165	0.280
	p	0.304	0.585	0.992	0.644		**0.001****	0.451	0.195
	n	23	23	23	23	23	23	23	23
CAL 0–3	cc	0.061	-0.057	-0.184	0.035	0.739	1	0.128	0.226
	p	0.780	0.798	0.401	0.874	**0.001****		0.561	0.299
	n	23	23	23	23	23	23	23	23
BOP 0–3	cc	-0.82	0.261	-0.073	0.295	0.165	0.128	1	0.237
	p	0.711	0.230	0.742	0.172	0.451	0.561		0.276
	n	23	23	23	23	23	23	23	23
PI 0–3	cc	0.149	-0.075	0.027	0.067	0.280	0.226	0.237	1
	p	0.497	0.734	0.901	0.761	0.195	0.299	0.276	
	n	23	23	23	23	23	23	23	23

Bold values indicate statistical significance. * Correlation is significant at the 0.05 level (2tailed) ** Correlation is significant at the 0.01 level (2 tailed)

Abbreviations: *BOP* Bleeding on probing, *CAL* Clinical attachment level, *cc* Correlation coefficient, *OSI* Oxidative stress index, *PPD* Probing pocket depth, *PI* Plaque index, *TAS* Total antioxidant status, *TNF* Tumor necrosis factor alpha, *TOS* Total oxidant status

predominantly exhibited edematous periodontal pockets. The average pocket depth and CAL values for the cases were calculated, and statistical analyses were conducted based on these mean measurements. The discrepancy where PPD exceeds CAL, as seen in Table 1, may be attributed to the presence of gingival inflammation and edema, which can temporarily increase PPD without a corresponding loss of attachment. In other words, the PPD reflects the depth of the inflamed pocket, while CAL measurements account for the actual loss of attachment to the tooth surface. Therefore, the discrepancy between PPD and CAL can be explained by the fact that the former includes the effects of soft tissue swelling, while CAL directly measures the true loss of periodontal attachment, which may not be as pronounced as the pocket depth would suggest.

In the present study, FM and Q therapy proceed significant reductions in saliva TNF-alpha levels compared with baseline values. However, the FM group exhibited a notably higher reduction in TNF-alpha levels compared to the Q group. This discrepancy can be elucidated by several factors: a more comprehensive reduction of microflora, a faster acute phase response, synchronized healing of all periodontal pockets, and a quicker resolution of inflammation in the short-term follow-up. Subgingival instrumentation leads to a shift from a predominantly Gram-negative anaerobic microbial community to a more Gram-positive one, with a reduction in putative periodontal pathogens, fostering the establishment of bacterial species that are more compatible with periodontal health. However, the re-emergence of periodontal pathogens 3 to 12 months post-debridement may suggest insufficient resolution of the periodontal lesion [30]. In the absence of appropriate home care, the pretreatment microbial profile can be re-established within a matter of weeks. Based on this, it is possible that the microflora may not become dysbiotic again until the third month. Although no further intervention is made beyond the first month, the observed reduction in TNF-alpha levels may reflect the persistent effects of the initial treatment. However, if recolonization occurs within the 3–12 month period, inflammatory markers such as

Table 5 Correlations between salivary and clinical parameters in FM group (difference's correlation values between initial and 1. month)

		TAS 0–1	TOS 0–1	TNF 0–1	OSI 0–1	PPD 0–1	CAL 0–1	BOP 0–1	PI 0–1
TAS 0–1	cc	1	-0.17	0.072	-0.647	-0.432	-0.427	0.075	0.108
	p		0.941	0.752	**0.001****	**0.045***	**0.047***	0.739	0.631
	n	22	22	22	22	22	22	22	22
TOS 0–1	cc	-0.17	1	0.174	-0.142	-0.046	0.037	0.435	-0.184
	p	0.941		0.439	0.529	0.838	0.869	**0.043***	0.414
	n	22	22	22	22	22	22	22	22
TNF 0–1	cc	0.072	0.174	1	0.131	0.288	0.249	-0.026	-0.237
	p	0.752	0.439		0.560	0.194	0.263	0.909	0.289
	n	22	22	22	22	22	22	22	22
OSI 0–1	cc	-0.647	-0.142	0.131	1	0.332	0.255	-0.151	-0.041
	p	**0.001****	0.529	0.560		0.131	0.252	0.502	0.855
	n	22	22	22	22	22	22	22	22
PPD 0–1	cc	-0.432	-0.046	0.288	0.332	1	0.960	0.282	0.303
	p	**0.045***	0.838	0.194	0.131		**0.001****	0.204	0.171
	n	22	22	22	22	22	22	22	22
CAL 0–1	cc	-0.427	0.037	0.249	0.255	0.960	1	0.411	0.274
	p	**0.047***	0.869	0.263	0.252	**0.001****		0.057	0.216
	n	22	22	22	22	22	22	22	22
BOP 0–1	cc	0.075	0.435	-0.026	-0.151	0.282	0.411	1	0.380
	p	0.739	**0.043***	0.909	0.502	0.204	0.057		0.081
	n	22	22	22	22	22	22	22	22
PI 0–1	cc	0.108	-0.184	-0.237	-0.041	0.303	0.274	0.380	1
	p	0.631	0.414	0.289	0.855	0.171	0.216	0.081	
	n	22	22	22	22	22	22	22	22

Bold values indicate statistical significance. * Correlation is significant at the 0.05 level (2tailed) ** Correlation is significant at the 0.01 level (2 tailed)

Abbreviations: *BOP* Bleeding on probing, *CAL* Clinical attachment level, *cc* Correlation coefficient, *OSI* Oxidative stress index, *PPD* Probing pocket depth, *PI* Plaque index, *TAS* Total antioxidant status, *TNF* Tumor necrosis factor alpha, *TOS* Total oxidant status

TNF-alpha may return to baseline levels. A comparative study of full-mouth and quadrant-wise SRP treatment was carried out by Graziani et al. to investigate acute-phase (24-h) and medium-term (3 months) inflammation. Their results revealed no discernible difference in plasma levels of TNF-alpha between the two treatment modalities [18]. It is evident that smokers were part of the participant pool in this study. The evidence suggests that smokers produce fewer proinflammatory biomarkers [31]. As a consequence, our study exclusively focused on non-smoking patients. This discrepancy in participant selection may contribute to the variance observed in our study findings compared to those of Graziani et al. [18]. Additionally, prior research has indicated that saliva exhibits comparable levels of various cytokines and notably higher concentrations of TNF-alpha in comparison to plasma or urine [32]. Therefore, based on these findings, we elected to utilize saliva as the medium for assessing cytokine concentrations and antioxidant activity.

This study demonstrates that subgingival instrumentation enhanced all evaluated levels of salivary antioxidants and oxidants. Both treatments resulted in significant increases in saliva TAS while decreasing saliva TOS within groups. However, only the TAS increase in the FM group differed significantly from the Q group. The reduction of oxidative stress and increase in antioxidant capacity following non-surgical periodontal therapy have been reported in the literature [10, 15]. Brock et al. reported that nonsurgical periodontal therapy can enhance antioxidant defense in patients with periodontitis, along with improvements in clinical parameters, [33] Kim et al. found that the TAS in saliva decreased immediately after SRP [34]. Over time, there was a slight increase in TAS, which remained relatively unchanged compared to the baseline until the 3-month. Guentsch et al. reported that salivary glutathione peroxidase levels decreased and that periodontal therapy influenced lipid peroxidation [35]. In response to non-surgical periodontal therapy, Chapple et al. showed stable TAS in plasma but a considerable increase in TAS in gingival crevicular fluid, which is consistent with our findings in saliva [10].

Table 6 Correlations between salivary and clinical parameters in FM group (difference's correlation values between initial and 3. month)

		TAS 0–3	TOS 0–3	TNF 0–3	OSI 0–3	PPD 0–3	CAL 0–3	BOP 0–3	PI 0–3
TAS 0–3	cc	1	-0.056	-0.051	-0.806	-0.201	-0.302	0.014	0.327
	p		0.805	0.822	**0.001****	0.369	0.172	0.950	0.138
	n	22	22	22	22	22	22	22	22
TOS 0–3	cc	-0.056	1	-0.163	0.066	-0.309	-0.347	0.401	-0.255
	p	0.805		0.470	0.772	0.162	0.114	0.065	0.252
	n	22	22	22	22	22	22	22	22
TNF 0–3	cc	-0.051	-0.163	1	0.028	0.197	0.240	-0.185	0.129
	p	0.822	0.470		0.902	0.380	0.283	0.409	0.567
	n	22	22	22	22	22	22	22	22
OSI 0–3	cc	-0.806	0.066	0.028	1	0.130	0.298	-0.114	-0.324
	p	**0.001****	0.772	0.902		0.563	0.178	0.612	0.141
	n	22	22	22	22	22	22	22	22
PPD 0–3	cc	-0.201	-0.309	0.197	0.130	1	0.839	0.179	0.093
	p	0.369	0.162	0.380	0.563		**0.001****	0.426	0.681
	n	22	22	22	22	22	22	22	22
CAL 0–3	cc	-0.302	-0.347	0.240	0.298	0.839	1	0.220	0.142
	p	0.172	0.114	0.283	0.178	**0.001****		0.326	0.530
	n	22	22	22	22	22	22	22	22
BOP 0–3	cc	0.014	0.401	-0.185	-0.114	0.179	0.220	1	0.211
	p	0.950	0.065	0.409	0.612	0.426	0.326		0.347
	n	22	22	22	22	22	22	22	22
PI 0–3	cc	0.327	-0.255	0.129	-0.324	0.093	0.142	0,211	1
	p	0.138	0.252	0.567	0.141	0.681	0.530	0.347	
	n	22	22	22	22	22	22	22	22

Bold values indicate statistical significance. * Correlation is significant at the 0.05 level (2tailed) ** Correlation is significant at the 0.01 level (2 tailed)

Abbreviations: *BOP* Bleeding on probing, *CAL* Clinical attachment level, *cc* Correlation coefficient, *OSI* oxidative stress index, *PPD* Probing pocket depth, *PI* Plaque index, *TAS* Total antioxidant status, *TNF* Tumor necrosis factor alpha, *TOS* Total oxidant status

Table 7 Linear univariate regression analysis evaluating the impact of biochemical parameters on clinical variables

Dependent variables	Independent Variables Predictors	R^2	(df) = F	β-coefficient	SE	t	p	(95% CI, lower and upper bound)
OSI 0–1	TAS 0–1	0.310	(1,21) = 9.441	-0.557	9.163	-3.073	0,006	-47.209; -9.099
CAL 0–1	PPD 0–1	0.605	(1,21) = 32.154	0.778	0.180	5.670	< 0.001	0.645; 1.392
CAL 0–1	BOP 0–1	0.173	(1,21) = 4.396	0.416	0.492	2,097	0.048	0.008; 2.056
CAL 0–3	PPD 0–3	0.546	(1,21) = 25.228	0.739	0.169	5.023	< 0.001	0.497; 1.200
OSI 0–1	TAS 0–1	0.419	(1,20) = 14.422	- 0.647	9.874	-3.798	0.001	-58.094;-16.901
PPD 0–1	TAS 0–1	0.186	(1,20) = 4.580	- 0.432	1.285	-2.140	0.045	-5.431; -0.070
CAL 0–1	TAS 0–1	0.183	(1,20) = 4.468	- 0.427	1.168	-2.114	0.047	-4.905; -0.033
BOP 0–1	TOS 0–1	0.189	(1,20) = 4.658	0.435	0.086	2.158	0.043	0.006; 0.367
CAL 0–1	PPD 0–1	0.921	(1,20) = 233.954	0.960	0.057	15.296	< 0.001	0.752; 0.989
OSI 0–3	TAS 0–3	0.649	(1,20) = 37.000	- 0.806	6.401	-6.083	< 0.001	-52.290; -25.585
CAL 0–3	PPD 0–3	0.704	(1,20) = 47.498	0.839	0.101	6.892	< 0.001	0.487; 0.911

Abbreviations: *CI* Confidence interval, *df* Degrees of freedom, *F* F test, *R2* R-squared, *SE* standard error, *t* t test, *BOP* Bleeding on probing, *CAL* Clinical attachment level, *OSI* Oxidative stress index, *PPD* Probing pocket depth, *PI* plaque index, *TAS* Total antioxidant status, *TOS* Total oxidant status

Oxidative stress is a crucial component of the inflammatory process, and it is reasonable to hypothesize that it influences both the severity of disease and the healing process. Maintaining reduced levels of ROS is imperative for sustaining essential biological functions, including the elimination of pathogenic microorganisms and the stimulation of fibroblast and epithelial cell proliferation. Conversely, elevated ROS levels can induce significant cell damage and contribute to the destruction of periodontal tissues. An excess of ROS and the depletion of antioxidant levels in gingival crevicular fluid contribute to the persistent local activation of periodontal inflammation and subsequent tissue destruction [36]. Gingival BOP serves as an indicator of an inflammatory lesion in both the epithelium and the connective tissue, distinguishing it from healthy gingiva [37]. While gingival BOP may not be an optimal diagnostic indicator for clinical attachment loss, absence of bleeding is the best indicator that there will be no attachment loss in the long term [38]. In cases of moderate or advanced periodontitis, the presence of BOP is considered indicative of active tissue destruction. In the regression analysis presented in our research findings, it was observed that the TOS value had a 19% impact on the BOP value. Consequently, the TOS value can be regarded as a secondary inflammation marker and a risk factor for periodontal tissues. Another indicator of local inflammation, distinct from bleeding on probing, is an elevated temperature. Since our study did not analyze the increase in body temperature post-periodontal therapy, as noted in the Cochrane review, it serves as a limitation to our investigation. To address this limitation, it is recommended to assess body temperature, gingival temperature, and C-reactive protein – an inflammation marker – in both groups. This evaluation should be conducted within 24 h after treatment to comprehensively evaluate signs of inflammation. The observation that the TOS parameter only correlated with BOP values and did not impact clinical parameters suggests that a reduction in oxidative stress load alone is insufficient for attachment gain. This underscores the importance of antioxidative capacity as a contributing factor. The negative correlation between TAS and CAL as well as PPD in the FM group further supports this hypothesis.

Conclusion

The FM therapy led to a significant reduction in periodontal tissue inflammation, as demonstrated by changes in both clinical and biochemical parameters in our study. This outcome may be attributed to the further increase in TAS levels following FM therapy. However, there are some limitations to our study. Although the same periodontist conducted all periodontal measurement, the consistency of these measurements within the cohort was not assessed prior to the study. A larger sample size would strengthen the findings. Additionally, gingival crevicular fluid samples would likely provide a more accurate reflection of periodontal inflammation and tissue damage than saliva samples. Further research is required to clarify the underlying mechanisms of this effect.

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Not applicable.

Data availability statement
The data that support the findings of this study are openly available in Thai Clinical Trials Registry website at https://www.thaiclinicaltrials.org/show/TCTR20240416007 and reference number is TCTR20240416007.
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request. However, for privacy reasons, no individual data allowing identification of participants can be provided.

Study characteristics
Study design: RCT with 2-arm parallel design.
Recruitment period: May 2016 to February 2017.
Setting: Department of Periodontology, Faculty of Dentistry, Istanbul University.
Number of centres: 1

Funding source
Individuals (SB).

Participants
Inclusion criteria: diagnosis of chronic periodontitis with PD ≥ 5 mm AL ≥ 4 mm.
Exclusion criteria: systemic disease or on antibiotics from 6 months before or during study.
Age: 26–48 years.
Sex: 24 F and 21 M.
Smokers: none.
Number randomised: 45 (22 FM group, 23 Q group).

Interventions
Comparison: FM vs Q.
FM group: (FM-SRP) 1 sessions same day.
Control group: (Q-SRP) 4 sessions at 1-weekly intervals.
OHI before study start: SB.
Instruments used: Hand and US instruments.
Maintenance: at baseline, 1 months and 3 months from baseline (both groups).
Retreatment: none.
Duration of study: 3 months.

Outcomes
Primary outcome: TAS, and TOS.
Secondary outcomes: CAL, PPD, BOP, PI, TNF alpha, OSI.
Teeth: whole-mouth recordings with manual probe.
Outcome time reported: 3-month data used.

Authors' contributions
Ş.B., K.N., A.Ç., Ü.B., and G.I. developed the concept and methodology Ş.B. carried out investigations Ş.B. and S.K. wrote the main manuscript S.K. prepared Fig. 1 and Table 1–7 A.Ç, Ü.B, and G.I. performed supervision G.I. performed project administration Ş.B., S.K., K.N., A.Ç., Ü.B., and G.I. performed the review and editing.

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Data availability
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request. However, for privacy reasons, no individual data allowing identification of participants can be provided.

Declarations

Ethics approval and consent to participate
The study has ethics committee approval. The study was approved by the Bezmialem University Ethics Committee for Clinical Research (Permission Reference No: 7/43). The authors declare that our study has the approval of the ethics committee and the subjects participated in the study by signing the voluntary consent documents. Informed consent forms were obtained from individuals who agreed to participate in the study. The study protocol was conducted in accordance with the ethical principles for medical research (involving human participants, including research using identifiable human material or data) of World Medical Association (WMA) Declaration of Helsinki.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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