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Effect of quadrantwise versus full-mouth subgingival instrumentation on clinical and microbiological parameters in periodontitis patients: A randomized clinical trial

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Abstract

Aim: This study evaluated the efficacy of quadrantwise subgingival instrumentation (Q-SI) versus one-stage full-mouth subgingival instrumentation (FM-SI) on probing depth and periodontal pathogen reduction over a 6-month follow-up period, as well as whether baseline periodontal pathogens influenced the impact of periodontal treatment protocols on outcomes.

Methods: Patients with periodontitis were randomized to receive Q-SI ($n = 43$) or FM-SI ($n = 45$). Patients were instructed and motivated to maintain optimal oral hygiene during the treatment sessions. Clinical (probing pocket depth [PPD], clinical attachment loss [CAL], and bleeding on probing [BOP]) and periodontal pathogens were assessed at baseline and after 30, 90, and 180 days. Total bacterial load and periodontal pathogens were analysed via real-time PCR.

Results: At the 6-month follow-up, the median PPD decreased from 4.8 mm (interquartile range [IQR]: 4.3–5.2) to 2.6 mm (IQR: 2.3–2.9) in FM-SI patients and from 4.7 mm (IQR: 4.1–5.2) to 3.2 mm (IQR: 2.4–3.5) in Q-SI patients ($p < .001$). At 6 months, FM-SI was more effective at reducing the median proportions of *Porphyromonas gingivalis* (*Pg*), *Aggregatibacter actinocomyctemcomitans*, and *Tannerella forsythia* (*Tf*) ($p < .001$ for each value). Multilevel linear regression analysis demonstrated that high baseline PPD ($p = .029$), *Pg* ($p = .014$), and *Tf* ($p < .001$) levels and the FM-SI protocol ($p < .001$) were statistically significant predictors of PPD reduction at 6 months. Furthermore, PPD reduction was significantly greater in the FM-SI group when lower baseline *Pg* levels were detected.

Conclusion: The FM-SI was more effective than the Q-SI in reducing the mean PPD and number of periodontal pathogens in periodontitis patients over a 6-month follow-up period. Higher baseline PPD and *Pg* levels had a negative impact on PPD reduction at 6 months after FM-SI.

KEYWORDS
biofilm, clinical trial, dental prophylaxis, periodontal instrumentation, periodontal therapy, periodontitis

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1 | INTRODUCTION

Periodontitis is a chronic inflammatory disease caused by an imbalance between the periodontal microbiome and host defence mechanisms that, if not properly managed, results in an immune-inflammatory response that destroys tooth-supporting tissues and can lead to tooth loss.[1–3] The success of periodontal therapy primarily depends on both the effective removal of the supra- and subgingival biofilms that are present and on patient self-care.[4] Patient motivation and instruction in oral hygiene, accompanied by nonsurgical periodontal treatment (NSPT), results in a reduction in bleeding on probing (BOP), probing pocket depth (PPD), and clinical attachment loss (CAL).[5] In this regard, the recently published guidelines of the European Federation of Periodontology (EFP) state that step 2 of NSPT, which is traditionally performed with quadrantwise subgingival instrumentation (Q-SI) completed at appointments scheduled 1–4 weeks apart[6] or via a one-stage full-mouth subgingival instrumentation (FM-SI) approach, are equally recommended for the treatment of stage I–III periodontitis.[5,7]

Recent studies comparing the efficacy of NSPT approaches[8,9] have shown that both Q-SI and FM-SI have equally favourable clinical outcomes; however, the FM-SI approach, in which therapy is delivered over 24–48 h (either performed alone or with the additional use of chlorhexidine),[10] has been reported in some studies to be more effective than conventional Q-SI in reducing periodontal pathogens, especially in deep pockets.[11,12] These favourable outcomes may be due to "shock therapy" to all niches and periodontal sites within a short period of time.[10,13,14]

Over the past few decades, some evidence has suggested that the elimination or reduction of periodontal pathogens such as *Aggregatibacter actinomycetemcomitans* (*Aa*) and *Porphyromonas gingivalis* (*Pg*) is a key element in achieving long-term periodontal outcomes.[15–17] Interestingly, the detection of specific levels of periodontal pathogens has been shown to be a valuable predictor for the persistence of sites with PPD >4 mm and BOP at 12 months posttreatment.[18] Therefore, it seems reasonable to investigate the differential clinical outcomes of NSPT approaches based on specific microbial profiles.

Furthermore, recent studies have highlighted the idea that the limited long-term efficacy of NSPT, whether performed with both the Q-SI or FM-SI approach, is related to the presence or absence of specific bacteria at baseline, such as *Aa* and *Pg*.[19–22] However, it is still unclear at present whether periodontitis patients harbouring specific pretreatment pathogens may benefit more from a particular NSPT protocol.[20,23]

When considering the abovementioned evidence, the aims of the present randomized clinical trial (RCT) were to evaluate the clinical efficacy of NSPT delivered by Q-SI or FM-SI in periodontitis patients at a 6-month follow-up and to investigate the possible interaction between the presence of specific periodontal pathogens at baseline and the efficacy of NSPT protocols. The null hypotheses to be rejected were that there was no difference between the two treatment protocols at the 6-month follow-up and that the concentration of periodontal pathogens at baseline did not affect the efficacy of NSPT.

2 | METHODS

2.1 | Study design

For this RCT, 325 patients were initially screened between January 2020 and December 2022. The study was conducted according to the guidelines of the Helsinki Declaration for medical research, as revised in 2013. Patients were informed about the characteristics and risks of the study and signed a consent form before enrolment. Ethical approval was obtained from the local review board of the University of Catania, Catania, Italy (n. 215/PO), and the study protocol was registered on clinicaltrials.gov. The manuscript was reported according to the CONSORT (Consolidated Standards Of Reporting Trials) and TIDieR (Template for Intervention Description and Replication) guidelines (Tables S1 and S2).[24]

The RCT included patients with a diagnosis of periodontitis[1] aged 35–70 years. Patients had to meet the following inclusion criteria: (1) at least 16 teeth; (2) PPD ≥4 mm and clinical attachment level (CAL) ≥2 mm in at least 40% of the periodontal sites[25]; (3) at least ≥40% of all periodontal sites with bleeding on probing (BOP); and (4) at least two sites with a distance ≥3 mm from the cementoenamel junction (CEJ) to the alveolar crest (AC) as assessed by periapical X-rays. The exclusion criteria were (1) use of contraceptives 6 months prior to the study; (2) use of anti-inflammatory, immunosuppressive or antibiotic drugs during the 6 months prior to the study; (3) pregnancy or lactation; (4) any alcohol consumption; (5) allergy or intolerance to drugs; (6) any periodontal treatment 6 months prior to the study; and (7) any type of systemic disease that could influence the study results.

2.2 | Clinical assessment and study outcomes

At the baseline, demographic parameters such as age, sex, race, level of education (primary, high school, and university), the body mass index (BMI), the presence of any chronic disease, medication, smoking history (current smoker, former smoker – cessation ≥5 years, and nonsmoker) and dental history were recorded. At the first visit, BMI (kg/m^2) was measured by a clinician who divided the patient's weight by the square of their height. PPD, BOP, gingival recession (REC) and plaque score (PI)[26] were recorded at six sites per tooth for all teeth that were present (excluding wisdom teeth) with a periodontal probe (UNC-15, Hu-Friedy, Milan, Italy). Clinical attachment loss (CAL) was calculated as the sum of the PPD value and gingival recession. The CEJ was used as a reference for recession, which was recorded as a positive value if the free gingival margin was apical to the CEJ and a negative value if it was coronal to the CEJ. To record PI, all of the bacterial plaques were stained with a disclosing agent (recorded as present or absent).

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The primary outcome was the median PPD after NSPT performed either by Q-SI or FM-SI in periodontitis patients at the 6-month follow-up. The secondary outcomes included the percentage of sites with a PPD ≥6 mm and with a PPD 4–5 mm, which were BOP positive at the 6-month follow-up after NSPT.

2.3 | Reliability evaluation

For each patient, a calibrated examiner (SS) recorded all of the periodontal indices at baseline and at each follow-up session by using a periodontal probe (UNC-15, Hu-Friedy, Milan, Italy). Calibration was performed on a total of 20 nonstudy patients with periodontitis. Probing consistency was considered sufficient if the percentage of agreement within ±2 mm between repeated measurements was at least 95%; in this case, the agreement within 1 mm was 95.8%.

The intraexaminer reliability for the PPD (percentage of agreement within ±2 mm between repeated measurements) was randomly determined for 20 selected patients, and good examiner reliability was indicated (ICC = 0.835).

2.4 | Power and the sample size

Using statistical software (G POWER; Universität Düsseldorf, Düsseldorf, Germany), the sample size was calculated based on the primary outcome (mean difference in the PPD between the Q-SI and FM-SI at 6 months after NSPT). Assuming a mean PPD difference between groups of 0.3 mm and a standard deviation (SD) of 0.5 mm, as well as 80%, power, a 2-sided significance level of 5%, and a 1:1 allocation ratio, the sample size calculation suggested a minimum of 36 patients per group. To account for a potential 20% drop-out rate, a minimum of 43 patients per group were enrolled to achieve a good power sample.

2.5 | Randomization

Patients were randomized to treatment groups by using sealed and numbered envelopes; details of the sequence were concealed from all of the clinicians who were involved in the RCT. An operator who was not involved in the clinical trial generated a 1:1 random allocation sequence by using a computer generator, prepared the sealed envelopes and handed them to clinicians who performed the instructional, motivation, and treatment procedures. The calibrated examiner and the statistician were unaware of the allocation of the patients to the treatment groups.

2.6 | Microbiological analysis

Microbial samples were collected from the same eight deepest sites at each session by a blinded examiner before treatment and at 30, 90, and 180 days after treatment. Two sterile paper points (ISO no. 45) were inserted simultaneously into the periodontal pockets for 40 s, after which they were removed and immediately transferred to a sterile tube. Microbiological bacterial concentrations were quantified by using real-time PCR (Applied Biosystems, Foster City, CA, USA),[27] and the detection level was set at 10^3 bacteria. For each patient, all of the samples were analysed individually to detect *Aa*, *Pg*, *Tannerella forsythia* (*Tf*), *Treponema denticola* (*Td*), *Prevotella intermedia* (*Pi*), *Peptostreptococcus micros* (*Pm*), *Fusobacterium nucleatum* (*Fn*), *Campylobacter rectus* (*Cr*), and *Eikenella corrodens* (*Ei*), as well as the total bacterial load. In addition, the log counts of *Pg*, *Tf*, and *Td* were calculated and grouped as "*red complex*" according to Socransky's classification.[28]

2.7 | Treatment

All of the patients underwent an initial supragingival instrumentation session. They also received detailed information about the aetiology of periodontitis and individualized oral hygiene instructions, which included interdental plaque control with interproximal brushes (tailored to each patient) and toothbrushing using a modified Bass technique. All of the participants were provided with the same type of toothbrush, toothpaste (Meridol, CP-GABA, Hamburg, Germany) and interdental brushes (Tepe, Malmo, Sweden).

The NSPT was performed by two periodontists (AP and GI) using curettes (1/2, 5/6, 7/8, 11/12, and 13/14) and an ultrasonic device with inserts (No. #1, 2#, and #1S) according to the operator preference (Hu Friedy, Milan, Italy). The ultrasonic device was used with constant water irrigation and a frequency of 20 kHz at a power setting of 60 μm. The endpoint of the NSPT was checked with an explorer. Patients in the Q-SI group received quadrant SI in four different sessions with an interval of 1 week between each quadrant treatment session. For each patient, the first session was initiated in the upper right maxillary quadrant. Patients in the FM-SI group first received a full-mouth session of SI on one side of the mouth, followed within 24 h by a second session on the other side of the mouth. Specifically, two right quadrants were instrumented in the morning session, and the other quadrant was instrumented in the afternoon. Treatments were performed under local anaesthesia only when necessary and were recorded in minutes. No mouthwashes, antibiotics or other medications were prescribed after treatment. At the end of each treatment session, patients were reinstructed and motivated to perform personal oral hygiene with both toothbrushes and interdental toothbrushes. Oral hygiene procedures were reinforced at 3 and 6 months after treatment.

2.8 | Statistical analyses

Clinical and microbial data are expressed as medians and interquartile ranges (IQRs), whereas categorical variables are expressed as numbers and percentages. A nonparametric approach was used because

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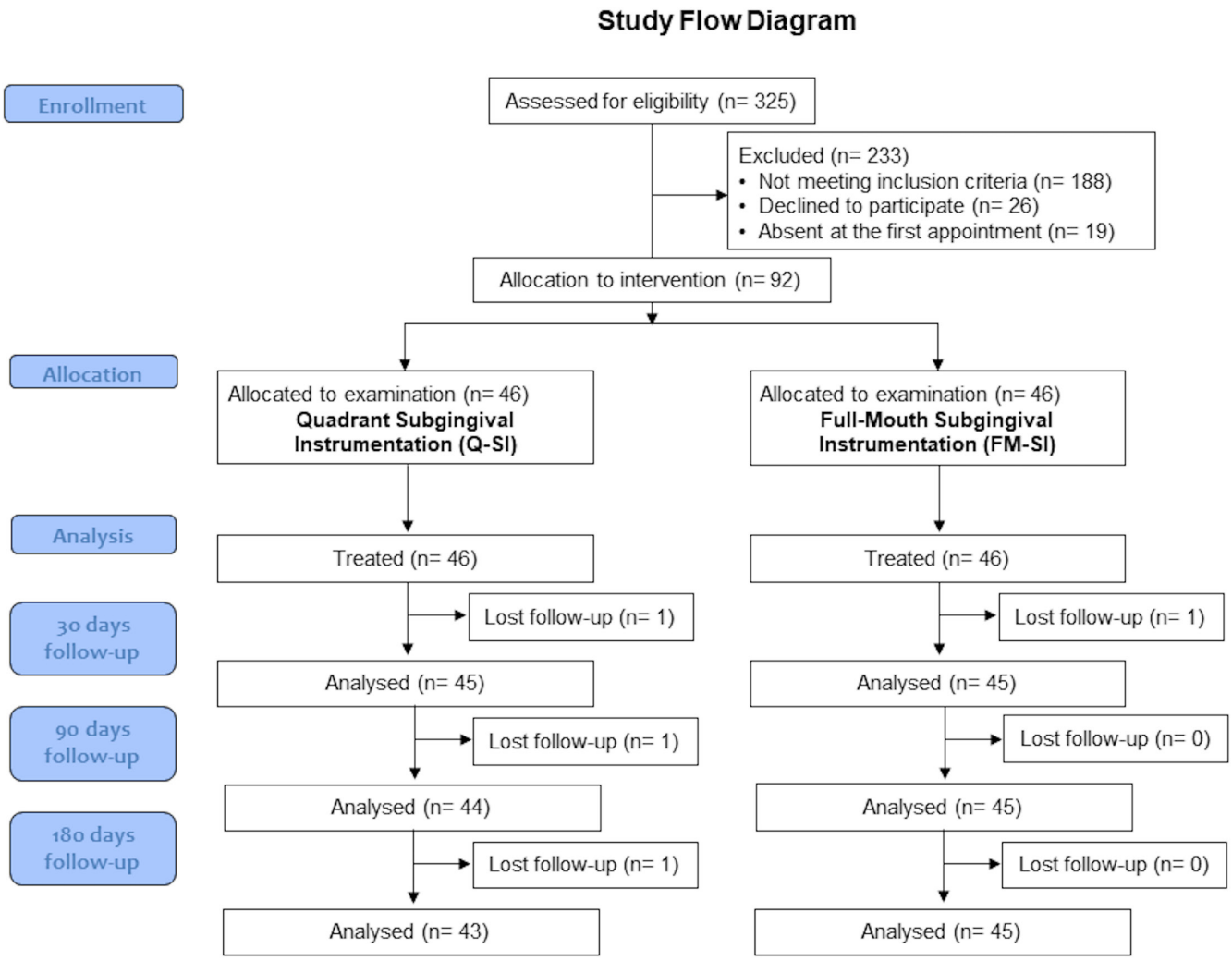

FIGURE 1 Study flowchart.

most of the variables were not normally distributed, as verified via the Kolmogorov–Smirnov test. Comparisons between groups were made by using the Mann–Whitney test for numerical variables and the chi-square test for categorical variables. The chosen unit of analysis was the patient. For both groups, the Friedman test was used to perform within-group comparisons. In particular, the numerical variables (PPD, CAL, BOP, and bacterial concentrations) were compared at four time points (baseline and at 30, 90, and 180 days); in addition, two-by-two comparisons between dependent groups were performed by using the Wilcoxon test. Bonferroni correction was applied for multiple comparisons. Analyses were performed per the protocol.

To analyse the effect of the treatment protocol and of selected species (as continuous variables) on study outcomes, multilevel generalized linear regression models (with the periodontal site as the first level and patient as the second level, adjusted for sex, age, smoking status, education, BMI, baseline PPD, and PI) were performed with robust standard errors for the main outcome, which involved mean PPD reduction (as the difference between baseline and 180 days) after treatment. The basic "site" level was nested in the upper "patient" level, and patient effects on the outcomes were

TABLE 1 Characteristics of the study sample at the baseline.

Characteristics	Q-SI (*n* = 43)	FM-SI (*n* = 45)
Male/female, no.	22/21	23/22
Age, median (IQR)	57 (55–58.5)	56 (54–58.1)
Caucasians, *n* (%)	43 (100)	45 (100)
Education level		
Primary School, *n* (%)	21 (48.8)	23 (51.2)
High School, *n* (%)	12 (27.8)	11 (24.4)
University, *n* (%)	10 (23.4)	11 (24.4)
BMI (kg/m^2), median (IQR)	20.1 (18.9–21.1)	20.4 (18.7–20.8)
Smoking		
Current smokers, *n* (%)	2 (4.7)	3 (6.7)
Former smokers, *n* (%)	1 (2.3)	3 (6.7)
Non-smokers, *n* (%)	40 (93)	39 (86.6)
Teeth at baseline median (IQR)	21 (19.1–22.3)	22 (21.4–22.9)

Note: The results are presented as frequency, median and IQR, and IQR (1st; 3rd).

Abbreviations: BMI, body mass index; FM-SI, one-step full-mouth subgingival instrumentation (SI); IQR, interquartile range; Q-SI, quadrantwise subgingival instrumentation (SI).

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TABLE 2 Periodontal characteristics of the analysed sample at the baseline and at each follow-up session and comparisons between groups.

Variable	Q-SI ($n=43$)	FM-SI ($n=45$)	p-Value
Median PPD (mm)			
Baseline	4.7 (4.1–5.2)	4.8 (4.3–5.2)	
30 days	4.4 (3.9–4.7)[a]	3.8 (3.1–4.5)[a]	<.001
90 days	3.7 (3.4–3.9)[b]	3.2 (2.7–3.6)[b,d]	.002
180 days	3.2 (2.4–3.5)[c]	2.6 (2.3–2.9)[c,f]	<.001
%sites with PPD ≤3 mm			
Baseline	40.3 (35.8–48.3)	41.1 (34.9–49.5)	
30 days	48.4 (41.9–59.2)	59.6 (51.9–66.3)[a]	.041
90 days	61.2 (51.4–68.9)[b]	74.6 (62.3–80.7)[b,d]	.011
180 days	71.8 (62.4–83.5)[c]	80.7 (70.6–91.5)[c,f]	.002
% sites with PPD 4–5 mm			
Baseline	44.6 (41.6–59.5)	45 (34.5–52.3)	
30 days	39.5 (29.5–48.5)[a]	31.3 (24.1–35.2)[a]	.066
90 days	29.5 (21.2–34.9)[b]	21.3 (17.5–24.2)[b]	.041
180 days	21.8 (11.6–19.5)[c]	15.2 (9.5–18.2)[c,f]	.044
% sites with PPD ≥6 mm			
Baseline	15.1 (8.6–18.5)	13.9 (8.5–16.8)	
30 days	12.1 (8.9–15.6)	9.1 (7.3–11.6)[a]	.074
90 days	9.5 (6.6–11.2)[b]	3.9 (3–5.9)[b]	.003
180 days	6.4 (4.2–7.9)[c]	4.1 (3.2–4.9)[c,f]	.051
% sites PPD 4–5 mm BOP+			
Baseline	35.6 (30.6–37.4)	38.2 (25.6–41.5)	
30 days	31.1 (24.5–34.6)[a]	21.2 (16.5–29.4)[a]	.019
90 days	22.8 (18.6–25.6)[b]	18.9 (14.5–21.1)[b]	.108
180 days	15.5 (7.6–18.4)[c]	9.6 (6.5–11.3)[c,f]	.042
Median CAL (mm)			
Baseline	5.1 (4.2–5.7)	4.8 (4.2–5.5)	
30 days	4.4 (3.3–6.1)[a]	3.9 (3.3–4.7)[a]	.014
90 days	4 (3.3–5.5)[b]	3.6 (2.8–4.7)[b,d]	.028
180 days	3 (2.4–4.1)[c]	3.2 (2.4–3.2)[c,f]	.104
% sites with CAL ≤3 mm			
Baseline	38.5 (31.6–45.8)	40.5 (34.6–51.1)	
30 days	51.4 (44.5–61.5)	53.2 (45.8–64.5)[a]	.055
90 days	64.4 (55.1–75.9)[b,d]	66.2 (60.6–71.7)[b,d]	.048
180 days	70.5 (63.3–79.5)[c,f]	75.5 (65.5–81.5)[c,f]	.045
% sites with CAL 4–5 mm			
Baseline	46.7 (34.1–52.8)	44.4 (38.5–49.8)	
30 days	42.5 (36.2–48.9)[a]	42.9 (36.1–47.6)[a]	.114
90 days	31.8 (25.4–36.8)[b]	31.5 (18.5–37.1)[b]	.339
180 days	24.1 (18.5–28.5)[c,f]	21.1 (15.4–26.6)[c,f]	.025
% sites with CAL ≥6 mm			
Baseline	14.8 (11.2–17.6)	14.9 (11.5–17.9)	
30 days	6.1 (5.2–9.8)[a]	3.9 (2.8–5.5)[a]	.033
90 days	4.2 (3.1–7.5)	2.3 (1.7–4.2)[b]	.032
180 days	5.4 (2.9–6.6)[c]	3.4 (2.1–5.5)[c]	.021
% BOP			
Baseline	45.2 (32.2–59.6)	47.1 (38.9–55.1)	
30 days	32.5 (21.6–43.9)[a]	23.8 (17.7–33.9)[a]	<.001
90 days	25.9 (19.6–31.4)[b,d]	21.1 (13.5–29.6)[b,d]	.011
180 days	21.3 (15.9–27.9)[c,e]	17.9 (14.4–22.6)[c]	.054
No. patients with sites BOP <10%			
Baseline	0 (100)	0 (100)	.334
30 days	16 (37.2)[a]	26 (57.8)[a]	.003
90 days	29 (67.4)[b]	30 (66.7)[b]	.479
180 days	33 (76.7)[c]	37 (82.2)[c,f]	.062
% PI (%)			
Baseline	35.8 (28.1–45.9)	36.2 (26.5–43.9)	
30 days	28.3 (22.4–37.6)[a]	24.2 (17.5–27.8)[a]	.027
90 days	24.1 (19.3–26.5)[b,d]	21.1 (16.1–35.8)[b,d]	.035
180 days	18.1 (14.4–22.8)[c,f]	15.3 (11.3–19.5)[c,f]	.046

Note: The values are presented as means ± standard deviations (SDs). p-Value significant <.008 (Bonferroni corrections) indicated statistical significance.

Abbreviations: BOP, bleeding on probing; CAL, clinical attachment loss; FM-SI, one step full-mouth subgingival instrumentation (SI); PI, plaque index; PPD, probing pocket depth; Q-SI, quadrant-wise subgingival instrumentation (SI).

[a]Significance between baseline and 30 days.

[b]Significance between baseline and 90 days.

[c]Significance between the baseline and 180 days.

[d]Significance between 30 and 90 days.

[e]Significance between 30 and 180 days.

[f]Significance between 90 and 180 days.

assumed to be random. Similar models were used for the secondary outcome BOP changes.

Based on the quartile distribution of the median baseline *Pg* load, the median PPD for each session was stratified according to the treatment protocol. Whether PPD was significantly changed across *Pg* quartiles was assessed. The Jonckheere–Terpstra (J-T) test was used to estimate the p-trend for the ordered *Pg* quartiles. In addition, the median PPDs of the first and fourth *Pg* quartiles for each session within each treatment protocol were compared by using the Mann–Whitney *U*-test. Statistical analyses were performed by using statistical software (Satelec, Acteon, Varese, Italy). A p value <.05 was considered to be statistically significant for all of the 2-sided tests (SPSS 22.0; IBM, Bologna, Italy).

3 | RESULTS

After screening, 233 patients were excluded because they did not meet the inclusion criteria ($n=188$), refused to participate in the study ($n=26$) or were absent at the first evaluation visit ($n=19$)

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TABLE 3 Comparisons between the mean proportion of periodontal bacteria at the baseline and at each follow-up session stratified by the Q-SI and FM-SI.

Variable	Q-SI ($n=43$)	FM-SI ($n=45$)	p-Value
Total bacterial load			
Baseline	9.1 (8.7–9.5)	9.3 (9.1–9.5)	
30 days	5.6 (5.3–5.8)[a]	4.5 (4.2–4.7)[a]	.025
90 days	3.4 (3.5–4.2)[b]	4.1 (3.7–4.4)[b,d]	.178
180 days	4.5 (3.9–4.4)[c]	4.2 (4–4.5)[c,e]	.113
Red complex bacteria			
Baseline	12.5 (10.2–14.2)	13.2 (11.3–15.6)	
30 days	11.3 (8.5–13.2)	9.4 (7.2–10.6)[a]	.038
90 days	9.2 (6.7–11.3)[b]	8.2 (5.4–9.3)[d]	.044
180 days	8.1 (5.3–10.9)[c]	7.6 (4.3–8.6)[c,e]	.047
A. actinomycetemcomitans			
Baseline	0.6 (0.5–0.8)	0.5 (0.3–0.6)	
330 days	0.6 (0.4–0.8)[a]	0.4 (0.3–0.6)[a]	.019
90 days	0.5 (0.3–0.6)[b]	0.4 (0.2–0.6)[b,d]	.001
180 days	0.6 (0.5–0.7)[c]	0.4 (0.3–0.6)[a,e]	<.001
P. gingivalis			
Baseline	3.4 (3–3.6)	3.6 (3.5–3.7)	
30 days	2 (1.7–2.4)[a]	1.9 (1.8–2.4)[a]	.005
90 days	1.7 (1.4–1.9)[b]	1.4 (1.2–1.8)[b,d]	<.001
180 days	1.5 (1.1–1.6)[e,f]	1.3 (1–1.5)[c,e,f]	<.001
T. forsythia			
Baseline	3.6 (3.4–3.8)	3.6 (3.6–3.7)	
30 days	3.1 (2.9–3.4)[a]	2.9 (2.8–3.2)[a]	<.001
90 days	3.2 (3.1–3.4)[b]	2.8 (2.5–2.8)[b,d]	<.001
180 days	2.6 (2.4–2.9)[c]	2.3 (2.2–2.4)[c,e,f]	<.001
T. denticola			
Baseline	2.9 (2.7–3)	3 (2.6–3.4)	
30 days	2.2 (1.8–2.3)[a]	1.7 (1.6–1.8)[a]	.003
90 days	1.1 (0.9–1.3)[b]	0.8 (0.6–1.1)[b,d]	.031
180 days	1.1 (0.9–1.4)[c]	0.9 (0.5–1.1)[e,f]	.044
P. intermedia			
Baseline	2.5 (2.4–2.8)	2.7 (2.5–2.8)	
30 days	2.5 (2.4–2.7)	2 (1.8–2.1)[a]	<.001
90 days	2.3 (2–2.4)[b]	1.9 (1.7–2.2)[b]	.012
180 days	1.9 (1.7–2.1)[c]	1.7 (1.5–1.9)[c,f]	.367
P. micros			
Baseline	4 (3.8–4.2)	3.9 (3.7–4.1)	
30 days	3.5 (3.3–3.8)	3.4 (3.1–3.5)	.276
90 days	3.2 (3.1–3.4)[b,d]	3.1 (2.7–3.3)[b]	.133
180 days	2.6 (2.3–3.1)[c,f]	2.3 (2.1–2.7)[c,e]	.015
F. nucleatum			
Baseline	4.1 (3.6–4.3)	4.3 (4.1–4.4)	
30 days	4.2 (4–4.4)	4.1 (3.8–4.2)[a]	.621
90 days	3.9 (3.8–4.1)[b]	3.8 (3.5–4.1)[b]	.371
180 days	3.1 (3–3.3)[c,f]	2.8 (2.4–3.1)[c]	.004
C. rectus			
Baseline	2.8 (2.6–2.9)	2.8 (2.6–3.2)	
30 days	2.6 (2.4–2.7)[a]	2.4 (2.1–2.6)[b]	.072
90 days	2.1 (1.9–2.5)[b]	2.2 (2–2.5)[b]	.128
180 days	1.9 (1.8–2.2)[c,e,f]	2 (1.8–2.3)[c,e,f]	.205
E. corrodens			
Baseline	3 (2.7–3.3)	3.1 (2.9–3.4)	
30 days	2.6 (2.5–2.9)[a]	2.5 (2.1–2.7)[a]	.046
90 days	2.6 (2.4–2.8)[b]	2.5 (2.2–2.9)[b,d]	.081
180 days	2.3 (2.1–2.5)[c,e,f]	2.4 (2.2–2.8)[c,e]	.304

Note: The results are expressed as the mean and standard deviation (SD). Red complex bacteria (*P. gingivalis*, *T. forsythia*, *T. denticola*). p Value <.008 (Bonferroni correction) indicated statistical significance.

Abbreviations: FM-SI, one-step full-mouth subgingival instrumentation (SI); Q-SI, quadrantwise subgingival instrumentation (SI).

[a]Significant difference between the baseline and 30 days.

[b]Significant difference between baseline and 90 days.

[c]Significant difference between the baseline and 180 days.

[d]Significant difference between 30 and 90 days.

[e]Significant difference between 30 and 180 days.

[f]Significant difference between 90 and 180 days.

(Figure 1). Ninety-two patients were ultimately enrolled in the present RCT; three patients were lost to follow-up in the Q-SI group, and one patient was lost to follow-up in the FM-SI group. In the final per-protocol analysis, 43 patients were included in the Q-SI group, and 45 were included in the FM-SI group.

There were no differences between treatment groups with respect to age, sex, race, BMI, number of smokers (Table 1), or treatment time (39.6 ± 3.4 min in the FM-SI group; 40.1 ± 3.4 min in the Q-SI group per quadrant). Compared to baseline, both protocols significantly reduced the median PPD, CAL, BOP, and PI at 180 days of treatment ($p<.001$) (Table 2). After 180 days of NSPT, FM-SI was more effective than Q-SI in reducing the median PPD (FM-SI/Q-SI: 2.6 [IQR: 2.3–2.9] mm vs. 3.2 [IQR: 2.4–3.5] mm), the median percentage of sites with PPD ≤3 mm (FM-SI/Q-SI: 71.8% [IQR: 62.4–83.5] vs. 80.7% [IQR: 70.6–91.5] $p=.002$), PPD 4–5 mm (FM-SI/Q-SI: 21.8 [IQR: 11.6–19.5] vs. 15.2 [IQR: 9.5–18.2] $p=.044$), CAL ≤3 mm (FM-SI/Q-SI:70.5 [IQR: 63.3–79.59] vs. 75.5 [IQR: 65.5–81.5] $p=.045$), and CAL 4–5 mm (FM-SI/Q-SI: 24.1 [IQR: 18.5–28.5] vs. 21.6 [IQR: 15.4–26]). Furthermore, at 6 months, in comparison with Q-SI, FM-SI significantly reduced the percentage of sites with PPD 4–5 mm BOP+ (Q-SI, 15.5% vs. FM-SI, 9.6%, $p=.042$) (Table 2).

The results of the microbiological data at baseline and at 30, 90, and 180 days after NSPT are shown in Table 3. Both NSPT protocols significantly reduced the total bacterial load at 180 days ($p<.008$); however, compared with the Q-SI group, the FM-SI group presented a significantly lower load of *Aa* (Q-SI, 0.6 [IQR: 0.5–0.7]; FM-SI, 0.4 [IQR: 0.3–0.6], $p>.001$), *Pg* (Q-SI, 1.5 [IQR: 1.1–1.6]; FM-SI, 1.3 [IQR: 1–1.5], $p<.001$), *Tf* (Q-SI, 2.6 [IQR: 2.4–2.9]; FM-SI, 2.3 [2.2–2.4], $p<.001$), *Td* (Q-SI, 1.1 [IQR: 0.9–1.4]; FM-SI, 0.9 [IQR: 0.5–1.1],

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$p = .044$), *Pm* (Q-SI, 2.6 [IQR: 2.4–3.1]; FM-SI, 2.3 [IQR: 2.1–2.7], $p = .015$), and *Fn* (Q-SI, 3.1 [3–3.3]; FM-SI, 2.8 [2.4–3.1], $p = .004$).

The multilevel regression analysis demonstrated that reduced median PPD levels at 180 days after therapy were significantly influenced by baseline median PPD levels (coeff. = 0.243, $p = .029$), age (coeff. = 0.031, $p < .001$), baseline *Pg* (coeff. = 0.332, $p = .014$), *Tf* (coeff. = 0.042, $p < .001$) and FM-SI (coeff. = −0.658, $p < .001$). The BOP reduction at 180 days was significantly influenced by baseline BOP levels (coeff. = 0.558, $p < .001$), as well as by baseline levels of *Pg* (coeff. = 0.031, $p = .034$), *Td* (coeff. = 0.035, $p = .042$), *Pm* (coeff. = 0.081, $p = .035$), *Fn* (coeff. = 0.047, $p = .023$), and FM-SI (coeff. = −0.147, $p < .001$) (Table 4).

Furthermore, in the FM-SI group, the median PPDs between the first and fourth quartiles of *Pg* load were significantly different at 30 ($p = .047$), 90 ($p = .028$) and 180 days ($p = .002$), whereas they were not significantly different in the Q-SI group (Table 5). The J-T test showed that, at the baseline and in the FM-SI group, there was no ordering of the median PPD values; however, at 30 ($p = .045$), 90 ($p = .035$) and 180 days ($p < .001$), the median PPD values increased significantly with a relative increase in the baseline *Pg* load. Specifically, there was a greater, significant reduction in PPD at 6 months in the FM-SI group with lower baseline *Pg* load levels. In contrast, in the Q-SI group, no significant difference was found between the median PPD and *Pg* load at any of the follow-up visits (Table 5).

TABLE 4 Multilevel linear regression analysis for mean PPD (primary outcome) and BOP (secondary outcome).

	Coeff.	95% CI	*p*-Value
Variable PD			
Main independent variable			
Treatment reference Q-SI	−0.658	−0.866;−0.442	<.001
Covariates			
Age (in years)	0.031	0.008;0.055	<.001
Sex (male reference)	0.042	−0.213;0.296	.744
Smoking	0.105	0.041;0.155	.159
Education	0.223	0.204;0.331	.336
BMI	0.189	0.047;0.287	.547
Baseline PI	0.241	0.043;0.189	.122
Baseline PD	0.243	0.038;0.442	.029
Total bacterial load	−0.023	−0.115;0.306	.741
P. gingivalis (red complex)	0.332	−0.112;0.457	.014
T. forsythia (red complex)	0.042	−0.866;0.456	<.001
T. denticola (red complex)	−0.227	−0.401;0.057	.205
P. micros	−0.041	−0.441;0.402	.457
P. intermedia	0.337	−0.049;0.621	.103
F. nucleatum	0.059	−0.147;0.233	.678
C. rectus	0.035	−0.266;0.389	.855
E. corrodens	0.204	−0.123;0.587	.287
A. actinomycetemcomitans	0.233	−0.214;0.678	.431
Variable BOP			
Main independent variable			
Treatment reference Q-SI	−0.147	−0.178;−0.157	<.001
Covariates			
Age (in years)	0.001	−0.002;0.005	.453
Sex	0.027	−0.008;0.061	.128
Smoking	0.147	0.081;0.348	.254
Education	0.189	0.102;0.196	.268
BMI	0.206	0.101;0.325	.442
Baseline PI	0.086	−0.144;0.289	.664
Baseline BOP	0.558	0.302;0.727	<.001
Total bacterial load	0.007	−0.032;0.045	.456
P. gingivalis (red complex)	0.031	0.007;0.099	.034
T. forsythia (red complex)	0.023	−0.011;0.048	.454
T. denticola (red complex)	0.035	0.013;0.066	.042
P. micros	0.081	0.028;0.185	.035
P. intermedia	−0.019	−0.055;0.043	.429
F. nucleatum	0.047	0.009;0.079	.023
C. rectus	−0.017	−0.060;0.039	.349
E. corrodens	0.027	−0.028;0.075	.223
A. actinomycetemcomitans	−0.066	−0.112;0.013	.106

Note: All parameters of the represented variables are at the baseline. With regard to gender, males served as a reference. For FM-SI, Q-SI served as a reference. For smoking, no smoking served as a reference. The variable education was dichotomized as primary school/high school (set as a reference) vs. university.

Abbreviation: PI, plaque index.

4 | DISCUSSION

Effective oral hygiene is the first and second step of therapy for patients with stage III periodontitis, according to the EFP S3 clinical practice guidelines,[5] and NSPT has been shown to determine a marked clinical reduction in PPD and BOP, as well as a gain of CAL.[29,30] Over the last two decades, a wide range of NSPTs have been investigated. In particular, the rationale for the FM-SI protocol is to prevent reinfection of treated sites from the remaining untreated pockets and other intraoral niches.[12,29,30] In the current study, both NSPT protocols were effective in reducing clinical periodontal parameters in the enrolled patients. However, in the present study, the FM-SI approach achieved a significantly greater median 0.6 mm PPD reduction than did the Q-SI approach at 180 days posttreatment. These rather favourable results for FM-SI treatment are consistent with some studies,[10,12,31,32] but they are in contrast to others that reported greater beneficial effects of Q-SI on PPD reduction,[33,34] PPD ≤4 mm reduction and pocket closure.[35]

It can be argued that the significant difference in PPD reduction of approximately 0.6 mm and in the number of sites with PPD 4–5 mm (6.6%) and PPD ≥6 mm (2.3%) in favour of FM-SI that were demonstrated in the present study may not be clinically significant. However, a PPD difference of approximately 0.6 mm with NSPT is similar to that of other periodontal treatment options. In this regard, a recent systematic review (SR)[36] of adjunctive

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TABLE 5 Mean (±SD) or IQR (1st; 3rd) of PPD across *Porphyromonas gingivalis* (*Pg*) quartiles and follow-up sessions for each treatment.

	Median *P. gingivalis* across quartiles distribution				Median PD across quartiles distribution of *P. gingivalis*			
Quartiles	Baseline	30 days	90 days	180 days	Baseline	30 days	90 days	180 days
FM-SI								
I	3.3 (3.3–3.5)	1.8 (1.6–1.9)	1.5 (1.3–1.7)	1.2 (1–1.4)	4.8 (4.6–5.1)	3.4 (3.1–3.5)	3.1 (3–3.6)	2.8 (2.6–2.9)
II	3.4 (3.1–3.5)	2.2 (1.8–2.4)	1.7 (1.6–1.9)	1.3 (1.3–1.5)	5.1 (4.9–5.3)	3.6 (3.5–4.5)	3.3 (3.1–3.5)	2.8 (2.3–3.5)
III	3.5 (3.5–3.6)	2.3 (2.2–2.5)	1.9 (1.8–2)	1.4 (1.1–1.6)	5.2 (4.9–5.5)	4.1 (3.7–4.3)	3.3 (3–4.1)	2.9 (2.5–3.3)
IV	3.6 (3.5–3.8)	2.5 (2.3–2.7)	2 (1.8–2.1)	1.6 (1.4–1.8)	5.3 (4.9–5.6)	4.2 (3.5–4.4)	3.5 (3.2–3.8)	3.1 (2.8–3.4)
J-T test					0.502	0.045	0.035	<0.001
I vs IV *P. gingivalis* quartiles					0.668	0.047	0.028	0.002
Q-SI								
I	3.3 (3.1–3.5)	1.7 (1.5–1.9)	1.5 (1.3–1.8)	1.2 (1–1.3)	4.9 (4.5–5.2)	4.1 (3.5–4.3)	3.7 (3.4–4.5)	3.1 (2.7–3.4)
II	3.5 (3.2–3.6)	1.8 (1.6–2.1)	1.7 (1.4–1.9)	1.3 (1.2–1.5)	5.1 (4.7–5.4)	4.2 (3.8–4.5)	3.9 (3.5–4.2)	3.2 (2.5–3.7)
III	3.6 (3.3–3.8)	1.9 (1.7–2.2)	1.8 (1.4–2)	1.4 (1.2–1.7)	5.2 (4.8–5.3)	4.3 (3.7–4.6)	4 (3.8–4.3)	3.4 (3.2–3.8)
IV	3.7 (3.5–4)	2.1 (1.7–2.2)	1.9 (1.5–2.1)	1.5 (1.1–1.6)	5.3 (4.5–5.4)	4.4 (4.1–4.6)	4.2 (3.7–4.5)	3.5 (3.2–3.9)
J-T test					0.344	0.398	0.685	0.554
I vs. IV *P. gingivalis* quartiles					0.771	0.344	0.834	0.898

systemic antimicrobials to NSPT reported an additive mean PPD reduction of 0.485 mm at 6 months compared to NSPT plus placebo.[37] Arguably, the periodontal community considers percent pocket closure as a more important clinical parameter than mean PPD reduction, as shallow pockets (≤4 mm) with <30% BOP are more likely to exhibit long-term periodontal stability.[36] Our results regarding the difference of 4.9% of patients without PPD sites 4–5 mm BOP+, as well as 5.3% of patients without PPD sites ≥6 mm at 180 days of treatment between Q-SI and M-SI (which were in agreement with what was reported by the SR of Teughels et al.[37]), elicit the question of whether one-stage FM-SI has actual clinical efficacy in patients with periodontitis. In favour of FM-SI, the additional organizational effort of FM-SI compared to that of Q-SI is small but results in modestly superior clinical outcomes. If a clinician prefers the FM-SI protocol, he or she should also consider the patient's systemic health status, as a stronger systemic inflammatory response has been observed in periodontitis patients after FM-SI than after Q-SI.[13,38] Conversely, two SRs comparing different NSPT approaches, such as Q-SI, FM-SI, and full-mouth disinfection (FMD),[39–41] showed significantly better mean PPD reduction with FMD or FM-SI than with the Q-SI approach, with slight superiority for FMD/FM-SI in both aggressive and chronic periodontitis patients. However, more recent SRs reporting studies without aggressive forms of periodontitis showed no benefit of FMD over Q-SI in terms of changes in PPD, CAL or BOP.[8,39] One reason as to why our RCT may have achieved more favourable statistically significant results than the included studies in these meta-analyses may involve the larger number of included patients. The studies that were analysed in the meta-analyses[7,8] included trials with a sample usually ranging from 16 to 40 patients, which sometimes indicated a general lack of statistical power,[7] whereas the present study included 88 patients with periodontitis. Furthermore, in the SR by Suvan et al.,[7] which included patients with a broad spectrum of periodontitis, the analysed studies were sometimes so different that direct comparisons between them were questionable, such as in the study of Wennstrom et al.,[42] in which there were also significant differences between the mean treatment time (FM-SI: 55 min versus Q-SI: 168 min).

The second objective of the current study was to investigate whether FM-SI has a differential effect based on the presence of specific periodontal pathogens. Our results confirm the landmark studies of the Socransky group,[43,44] which showed that periodontal therapy was able to reduce the total bacterial load by shifting the subgingival microbiota from a disease-associated state with a healthy composition and by reducing the proportion of periodontal pathogens, with a concomitant improvement in PPD levels. This shift led to clinical improvements in PPD and BOP, which were unaltered for up to 2 years after treatment.[43,45] In the present study, immediately after treatment, the total bacterial load in both groups was substantially reduced by approximately 50% up to 180 days, whereas the median number of periodontal pathogens decreased between 20% (*Aa*) and approximately 60% (*Pg*) in the FM-SI group, and PD and CAL generally decreased in both NSPT groups. This time sequence between mechanical treatment, microbial shift, and ensuring clinical healing events has been described many times beforehand.[44,45] However, more importantly, the data of the current study supported the hypothesis reported by the Leuven group,[46] which also showed how the treatment modality affects the clinical and microbial outcomes in periodontitis patients.

Finally, multilevel regression analysis demonstrated that high baseline levels of *Pg* significantly influenced the efficacy of NSPT by reducing PPD over 6 months of treatment. In this regard, Flemmig et al.[47] reported that periodontitis patients with high pretreatment *Aa* and *Pg* loads had greater clinical benefits from adjunctive antimicrobial therapy in terms of PPD reduction.

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Specifically, Flemmig et al.[47] found that the presence of high levels of certain periodontal pathogens prior to therapy not only negatively affected the overall biofilm composition (thus leading to increased virulence of the commensal oral flora and less CAL gain after NSPT) but also required the adjunctive use of systemic metronidazole plus amoxicillin and supragingival irrigation with chlorhexidine digluconate to achieve stable periodontal outcomes for successful treatment.

However, the current RCT had several limitations, such as its monocentric study design and short follow-up period. It would have been desirable to have a longer follow-up period to better validate the beneficial periodontal outcomes.

In addition, both NSPT approaches were not able to completely eradicate deep PPD pockets ≥6 mm (6.4%, Q-SI; 4.1%, and FM-SI) and the number of sites with PPD 4–5 mm BOP+ (15.5%, Q-SI; 9.6%, and FM-SI) at 6-months follow up.

5 | CONCLUSIONS

The results of the current RCT confirmed that NSPT approaches performed with either Q-SI or FM-SI were both effective in reducing microbial and clinical periodontal parameters, although one-stage FM-SI achieved more favourable results than the Q-SI approach. The presence of pretreatment baseline *Pg* concentrations influenced the efficacy of NSPT in periodontitis patients.

AUTHOR CONTRIBUTIONS

Gaetano Isola conceived the research, planned, and performed the experimental procedures and wrote the manuscript. Alessandro Polizzi and Simona Santonocito performed the procedures. Angela Alibrandi performed the statistical analysis and concealment, and Paolo Pesce performed the procedures and validated the experimental results. Thomas Kocher wrote the manuscript. All of the authors gave their final approval and agreed to be accountable for all aspects of the work.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest in the present study.

DATA AVAILABILITY STATEMENT

Derived data supporting the findings of this study are available from the corresponding author upon reasonable request.

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Additional supporting information can be found online in the Supporting Information section at the end of this article.

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