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The systemic inflammatory response following hand instrumentation versus ultrasonic instrumentation—A randomized controlled trial

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Abstract

Objective: This study sought to investigate whether the immediate systemic inflammatory response following full-mouth debridement differs following use of hand compared with ultrasonic instruments.

Methods: Thirty-nine periodontitis patients were randomized to treatment with full-mouth debridement using either hand or ultrasonic instrumentation completed within 24 hr. Serum and periodontal clinical parameters were collected at baseline, day 1, day 7 and day 90 post-treatment. Differences in systemic inflammatory markers were assessed using general linear models at each timepoint, corrected for age, gender, smoking status, body mass index and baseline levels of each marker.

Results: Across all patients, serum C-reactive protein increased at day 1, with no differences between hand and ultrasonic groups (p(adjusted) = .22). There was no difference between groups in interleukin-6 (p(adjusted) = .29) or tumour necrosis factor α (p(adjusted) = .53) at day 1. Inflammatory markers returned to baseline levels by day 7. Treatment resulted in equal and marked improvements in clinical parameters in both groups; however, total treatment time was on average shorter for ultrasonic instruments (p(adjusted) = .002).

Conclusions: Ultrasonic instrumentation resulted in shorter treatment time with comparable clinical outcomes. Levels of serum C-reactive protein at day 1 were similar following debridement with hand or ultrasonic instruments.

KEYWORDS

hand instruments, periodontal treatment, randomized controlled trial, systemic inflammation, ultrasonic instruments

William Johnston and Michael Paterson have equal contributions.

1 | INTRODUCTION

Periodontitis (PD) affects 20%–50% of the total global population, with severe disease occurring in 9.8% of individuals (Albandar & Rams, 2002; Bernabe et al., 2020). For the majority of patients, non-surgical periodontal treatment (NSPT) represents the first line of treatment and involves the physical debridement of subgingival plaque biofilms. There is significant evidence of clinical improvements in PD patients following NSPT, including gains in clinical attachment level, reductions in gingival inflammation and reduced periodontal pocket depths (Graziani et al., 2010; Heitz-Mayfield, Trombelli, Heitz, Needleman, & Moles, 2003; Suvan et al., 2019).

Non-surgical periodontal treatment may be carried out with hand instruments, ultrasonic instruments or a "blended approach" using both. Similarly, treatment may be staged over several visits with a "quadrant" approach, or with a "full-mouth debridement" approach, also referred to as an "intensive treatment" approach, that delivers complete debridement within 24 hr. Although the clinical outcomes for quadrant and full-mouth treatment appear similar, there is a measurable difference in the inflammatory response following full-mouth compared with quadrant debridement (Graziani et al., 2015). Intensive/full-mouth NSPT has been consistently shown to trigger a larger systemic inflammatory response, demonstrated by significant increases in serum levels of C-reactive protein (CRP), interleukin-6 (IL-6) and tumour necrosis factor alpha (TNFα) 24 hr following treatment (Graziani et al., 2015; Morozumi et al., 2018; Tonetti et al., 2007). Whilst this increase in systemic inflammation is short lived and typically resolves within 7 days (Graziani et al., 2015; Graziani et al., 2010; Tonetti et al., 2007), a recent joint consensus statement advised against full-mouth debridement for some medically compromised patients (Sanz et al., 2020).

Studies investigating the systemic inflammatory response generally report use of both hand and ultrasonic instruments in combination. When used individually, both types of instrument have been shown to significantly improve the clinical status of patients with equal efficacy (Ioannou et al., 2009; Suvan et al., 2019). Although the clinical outcomes are similar, several studies report lower treatment times using ultrasonic instruments in comparison with hand instruments (Copulos, Low, Walker, Trebilcock, & Hefti, 1993; Dragoo, 1992; Tunkel, Heinecke, & Flemmig, 2002; Yukna, Scott, Aichelmann-Reidy, LeBlanc, & Mayer, 1997). Interestingly, a positive correlation between treatment time and CRP levels 24 hr after treatment has been reported (Graziani et al., 2015).

Given this previous link between treatment time and the subsequent systemic inflammatory response, and the different features of each instrumentation technique including delivery of water irrigation and the reduction in cementum removal with ultrasonics (Bozbay et al., 2018; Ruhling, Bernhardt, & Kocher, 2005), we hypothesized that hand and ultrasonic instruments may differ in the extent of systemic inflammation they induce. Thus, the aim of this study was to investigate changes in systemic markers of inflammation 24 hr following full-mouth debridement, comparing hand instrumentation (HI) and ultrasonic instrumentation (UI). Secondary outcomes included comparing clinical parameters and treatment time between each group.

Clinical Relevance

Scientific rationale for the study: Intensive full-mouth debridement has been consistently demonstrated to induce a systemic inflammatory response 24 hr after treatment, which has previously been linked to duration of treatment. In medically compromised patients, this inflammatory response is hypothesized to potentially aggravate pre-existing conditions.

Principle findings: We have demonstrated that this systemic inflammatory response is comparable following full-mouth debridement with hand or ultrasonic instruments, with faster treatment time with ultrasonic instruments. Improvements in clinical outcomes were comparable between groups.

Practical implications: The choice of hand or ultrasonic instruments does not appear to impact the systemic inflammatory response 1 day following full-mouth debridement.

2 | METHODS

2.1 | Study design and patient selection

This was a single-centre randomized controlled trial with two intervention arms, with patients returning at day 1, day 7 and day 90 post-treatment. The study received approval from the Research Ethics Committee (18/NI/0059) and was registered with ClinicalTrials.gov (ID: NCT03501316). The principles in the Declaration of Helsinki were adhered to throughout the trial.

Patients were referred by their General Dental Practitioner (GDP) to Unit of Periodontics at Glasgow Dental Hospital for specialist management of periodontal disease. The specialist service is provided by the National Health Service, and prior to referral patients attend their GDP for assessment and initial periodontal treatment including oral hygiene instruction. Patients were approached during new patient assessment clinics in the Unit of Periodontics. All participants gave informed, written consent. The inclusion criteria were as follows: male or female patients aged 18–70 years inclusive with probing depths ≥5 mm on two or more teeth at non-adjacent sites with cumulative probing depths of ≥40 mm. Cumulative probing depth was calculated by examining six sites on each tooth. The deepest site on each tooth was recorded and if the value was >4 mm, this contributed to the cumulative total, with each tooth being only counted once towards the total to ensure extent of disease. The use of cumulative probing pocket depth ensured a minimum level of periodontal disease (≥2 sites with probing depths with ≥5 mm) (Page & Eke, 2007; Tonetti & Claffey, 2005) and has recently been adopted as a means of including patients

with a disease burden that is potentially relevant to systemic inflammation (Lopez-Oliva Santa Cruz 2018; Serban et al., 2019). Exclusion criteria included the following: known or suspected high risk for tuberculosis, hepatitis B or HIV infections; required interpreter/non-English language written material to understand and provide written, informed consent or any other reason for being unable to provide written, informed consent; history of bleeding diathesis; pregnant or lactating females; self-reported diagnosis of any systemic illnesses including cardiovascular, renal and liver diseases, and/or regular use of medication to control systemic illness; any pharmacological treatment within 1 month before the beginning of the study, including routine use of any over the counter medications and specialist periodontal treatment in the previous 6 months.

All visits were carried out within the clinical research facility of the Glasgow Dental Hospital. Baseline data were gathered including height, weight, blood pressure (using an automatic oscillometric unit) and smoking status was recorded as "never," "current" or "previous." Samples taken at baseline included serum, whole blood, saliva, subgingival plaque and gingival crevicular fluid.

2.2 | Study procedures

At the baseline visit, patients were provided with detailed oral hygiene instruction, dental health education and a full-mouth supragingival scale (using a Cavitron® Powerline® 1000 30K insert). All interventions and clinical data collection were carried out by an experienced dental hygienist (DM) and specialist trainee in restorative dentistry (MP). For calibration, both examiners completed pocket charts on the first twelve patients entering the study. Charts were assessed for agreement and a kappa score was calculated (0.66). Following collection of blood samples at day 1 post-treatment, patients were provided with an electric toothbrush (Oral-B Pro 2000) to standardize self-performed plaque control prior to day 90 follow-up.

At baseline and day 90, clinical parameters (full-mouth plaque, bleeding scores and detailed 6-point periodontal pocket charting) were assessed using a PCP-12 periodontal probe at six sites per tooth, excluding third molars (unless other molar units missing), with measurements rounded to the nearest millimetre. Following collection of clinical data, the periodontal inflamed surface area (PISA) was calculated as previously described (Nesse et al., 2008).

Patients were randomized to one of two treatments (HI or UI) (Figure 1). Randomization was performed using a computerized random number generator (using permuted blocks of 4 and 6). Patients were stratified according to smoking status prior to randomization.

For allocation concealment and blinding, patients were allocated to each arm of the study by a member of the research team not involved with the clinical delivery of the experimental interventions. Upon attending their treatment appointment, an opaque sequentially numbered envelope contained the allocated intervention arm for the patient. This was opened immediately before treatment was commenced.

Patients and clinicians both remained blinded to the intervention until the intervention visit. Statistical and laboratory personnel remained blinded to specific patient allocation throughout the entire process via patient barcodes. The key linking barcodes to patients was available only to the chief investigator. Intervention codes were only available once all analyses took place.

Full-mouth debridement was carried out within a 24-hr period. All but one patient completed treatment within the same day; a single patient completed debridement on consecutive days, within 24 hr, due to patient availability. Debridement was completed using Gracey and Universal curettes (Gracey 1/2, Gracey 7/8, Gracey 9/10, Gracey 11/12, Gracey 13/14, Columbia 4L-4R) and hoes (Hoe Scaler-lateral, Hoe Scaler-posterior, LM Dental) for the hand instrumentation (HI) group; or Cavitron Ultrasonic inserts (Cavitron® Thinsert® 30K, Cavitron® Slimline® 10S 30K, Cavitron® Slimline® 10L 30K, Cavitron® Slimline® 10R 30K, Cavitron® Slimline® 1000 30K, Cavitron® Powerline® 1000 30K; Dentsply Sirona) for the ultrasonic instrumentation (UI) group. Treatment was provided using local anaesthetic and timed by digital stopwatch from the point of first contact between instrument and tooth surface. Debridement was carried out until no supra or subgingival plaque or calculus deposits were detectable by visual examination with magnification or by tactile examination. Patients were recalled following periodontal treatment at day 1, day 7 and day 90. Samples were collected as per baseline visit (serum, whole blood, saliva, subgingival plaque, GCF) at each timepoint, with clinical parameters measured at day 90 only. Following day 90 review, any further treatment need was evaluated by a Specialist in Periodontology.

2.3 | Systemic inflammatory markers

Systemic inflammatory markers CRP (primary outcome), IL-6 and TNFα (secondary outcomes) were measured at all timepoints (baseline, day 1, day 7 and day 90). Levels of serum CRP were determined by high-sensitivity immunoturbidometry using the Cobas C311 analyser (Cobas; Roche Diagnostic). Serum IL-6 and TNFα were determined using high-sensitivity ProQuantum qPCR immunoassays (Thermo Fisher) measured on a StepOnePlus real-time PCR system. The limit of detection (LOD) for IL-6 and TNFα was 0.12 and 0.01 pg/ml, respectively. CRP and IL-6 were detected in all samples; TNFα was below LOD in seven samples which were assigned as LOD/2 for statistical analysis. All laboratory assays were conducted following study completion by laboratory staff masked to treatment groups. Analysis of serum CRP was performed at the British Heart Foundation Glasgow Cardiovascular Research Centre, with IL-6 and TNFα measurements performed at Glasgow Dental School. Intra- and inter-assay coefficients of variations were <5%.

2.4 | Sample size calculation

The primary outcome for this study was serum CRP levels at day 1 post-treatment. Secondary outcomes were CRP at day 7 and day

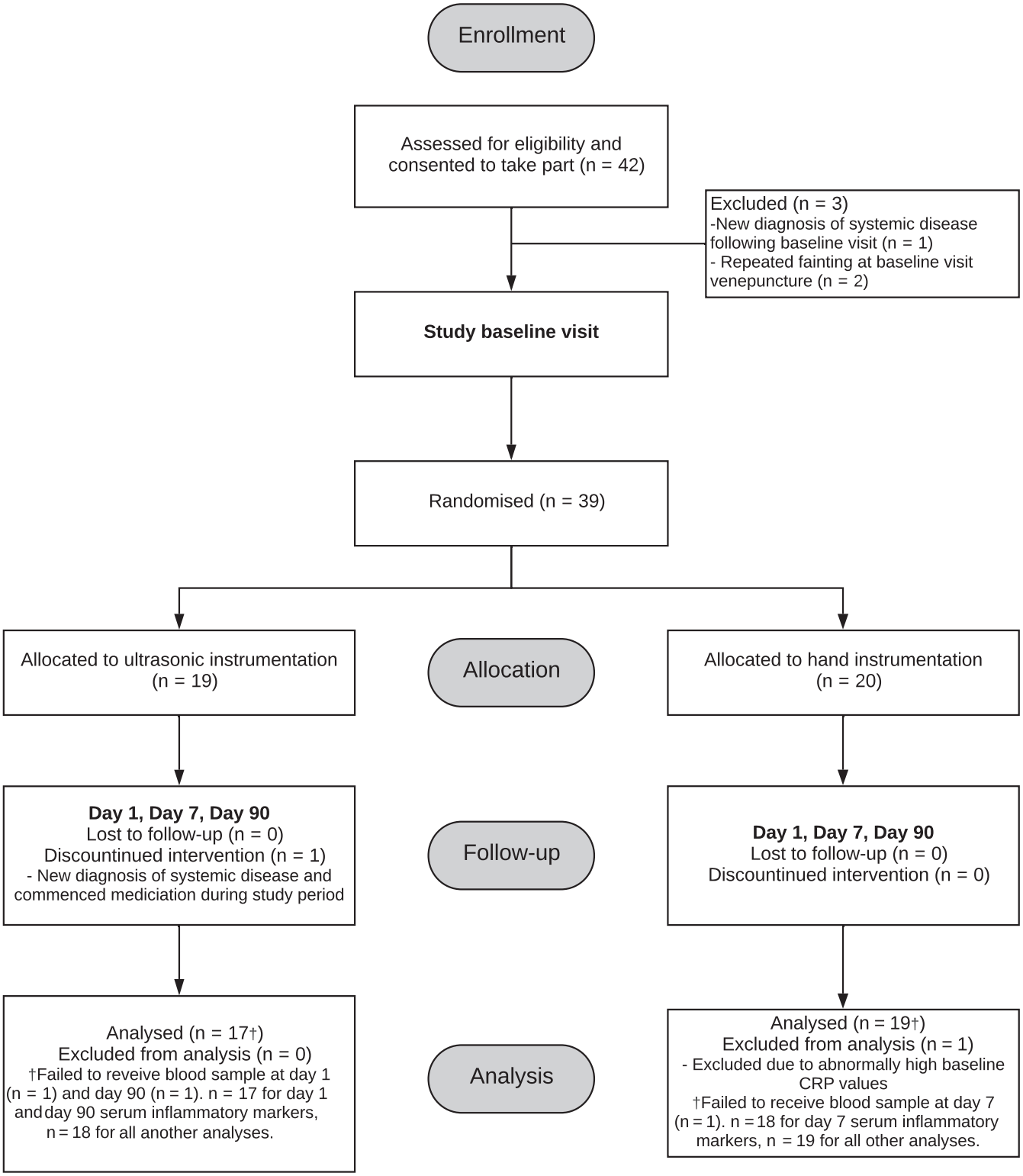

FIGURE 1 CONSORT flow diagram for study. Blood samples were not obtained from one patient at day 1 (UI group), one patient at day 7 (HI group) and one patient at day 90 (UI group). Therefore, for analysis of serum inflammatory markers; at day 1 (UI; $n = 17$, HI; $n = 19$), day 7 (UI; $n = 18$, HI; $n = 18$) and day 90 (UI; $n = 17$, HI; $n = 19$). For analysis of clinical parameters and treatment time (UI; $n = 18$, HI; $n = 19$)

90, other systemic inflammatory markers (IL-6, TNFα) at day 1, day 7 and day 90, clinical parameters at day 90 and treatment time. The sample size calculation was based on data from a previous study that measured changes in CRP following periodontal treatment (Graziani et al., 2015). From this study, a difference of 3.5 mg/L (SD = 3 mg/L) in CRP was detected between the two groups receiving different schedules of periodontal treatment (quadrant versus full-mouth debridement) at primary endpoint, and this has been considered

clinically relevant in recent guidelines (Sanz et al., 2020); therefore, this was considered a reasonable estimate of the minimum clinically relevant difference. At 80% power and a 5% significance level, a sample size of $n = 34$ (17 in each group) was required to detect a minimum difference of at least 1 standard deviation between CRP levels at primary endpoint (day 1) between the two groups (HI versus UI). To account for potential drop-out of 20%, 42 eligible patients were recruited.

2.5 | Statistical analysis

Study data were entered into SPSS (v26; IBM) using anonymous patient codes and then analysed using Stata (v21; Statacorp). Graphics were produced using PRISM (v8; GraphPad). All outcome data are summarized using median (Q1, Q3). Changes in clinical parameters and serum inflammatory markers between baseline and the various follow-ups were assessed using Wilcoxon signed rank tests. For between-group comparisons, general linear models (GLMs) were produced. Serum CRP, IL-6 and TNFα were skewed on visual inspection of histograms; therefore these were ln-transformed and shown to follow a ln-normal (symmetrical) distribution. GLMs were produced to test differences in systemic inflammatory markers (CRP, IL-6 and TNFα all ln-transformed) between the two groups (HI; US), unadjusted (model 1), after adjusting for baseline levels (model 2), and after adjusting for baseline levels, gender, age, smoking status and BMI (model 3). Differences in clinical parameters between groups at day 90 were assessed using GLMs adjusting for baseline levels, number of teeth, age, gender and smoking status. For skewed variables (FMPS, FMBS, Pockets ≥5 mm and PISA), ln-transformation resulted in normal distribution and these values were used. Differences in treatment time were assessed by a GLM controlling for disease severity (PISA mm^2) and number of teeth at baseline. Correlations between treatment time and disease severity (PISA mm^2) and change in inflammatory markers (day 1 minus baseline values) were conducted using Spearman's Rho. The correlations were ancillary post hoc analyses and were not pre-specified in the trial protocol.

3 | RESULTS

3.1 | Study population and clinical parameters

In total, 42 patients were recruited to the study. Throughout the course of the study, four subjects were excluded. One patient was withdrawn due to developing new medical diagnoses following baseline visit and two patients were withdrawn due to unexplained repeated fainting during venepuncture. One patient completed all interventions but was excluded from analysis due to an unexplained pathologically high baseline serum CRP level (11.97 mg/L), as shown in Figure 1.

TABLE 1 Baseline demographics and periodontal clinical parameters

Variable	Ultrasonic instruments ($n = 18$)	Hand instruments ($n = 19$)
Age, years	46.00 (36.75, 54.50)	41.00 (39.00, 49.00)
Gender, female (%)†	10 (56)	9 (47)
Smoking, current (%)†	5 (28)	6 (32)
BMI, kg/m^2	27.80 (22.68, 30.15)	29.70 (23.30, 34.40)
Systolic BP, mm Hg	124.00 (114.50, 139.50)	123.00 (117.00, 134.00)
Diastolic BP, mm Hg	79.50 (75.50, 89.00)	81.00 (73.00, 84.00)
CRP, mg/L	1.60 (0.62, 2.49)	1.21 (0.44, 2.03)
IL-6, pg/ml	2.61 (1.13, 3.54)	2.29 (1.52, 4.41)
TNFα, pg/ml	0.22 (0.11, 1.09)	0.13 (0.09, 0.36)
Number of teeth	27.50 (24.50, 30.00)	29.00 (27.00, 31.00)
FMPS (%)	45.92 (26.10, 63.33)	60.48 (25.00, 67.74)
FMBS (%)	38.11 (21.45, 61.49)	45.00 (21.26, 69.44)
PPD (mm)	3.70 (3.35, 4.12)	3.98 (3.11, 4.78)
CAL (mm)	4.14 (3.66, 4.44)	4.36 (3.29, 5.02)
Pockets ≥5 mm (%)	26.73 (22.08, 36.71)	28.85 (18.33, 51.39)
PISA (mm^2)	957.93 (385.55, 1,759.57)	1,010.02 (561.99, 2,190.01)

Note: Variables are presented as median (Q1, Q3), unless followed by "†" which are presented as *n* (%).

Abbreviations: BMI, body mass index; BP, blood pressure; CAL, clinical attachment loss; CRP, C-reactive protein; FMBS, full-mouth bleeding score; FMPS, full-mouth plaque score; IL-6, interleukin-6; PISA, periodontal inflamed surface area; PPD, probing pocket depth; TNFα, tumour necrosis factor alpha.

Baseline characteristics were comparable between treatment groups, including demographic, clinical and biological variables (Table 1). According to the 2017 Classification, 45% of the patients presented with Generalized Stage 4 Grade C periodontitis, 42% with Generalized Stage 3 Grade B periodontitis and 13% Generalized Stage 3 Grade C periodontitis (Papapanou et al., 2018).

There were significant improvements in clinical parameters across all patients following treatment ($p < .01$ for all clinical parameters comparing baseline and day 90 values, irrespective of treatment group). This included reductions in the percentage of pockets ≥5 mm (HI: 28.85%–11.67%, UI: 26.73%–10.88%) and PISA (HI: 1010.02–192.59 mm^2, UI: 957.93–134.85 mm^2). The improvement in clinical parameters was comparable between treatment groups ($p > .05$ for all; Table 2).

TABLE 2 Comparison of clinical parameters between groups at baseline (BL) and day 90 (D90)

Variable	Timepoint	Ultrasonic instruments $n = 18$	Hand instruments $n = 19$	Between group p-value[b]
FMPS (%)	Baseline	45.92 (26.10, 63.33)	60.48 (25.00, 67.74)	
	Day 90	7.80 (3.50, 13.25)	8.33 (4.17, 14.06)	
	Within group p-value[a]	<.001	<.001	.55
FMBS (%)	Baseline	38.11 (21.45, 61.49)	45.00 (21.26, 69.44)	
	Day 90	8.10 (4.12, 12.08)	8.33 (2.98, 13.10)	
	Within group p-value[a]	<.001	<.001	.94
Pockets ≥5 mm (%)	Baseline	26.73 (22.08, 36.71)	28.85 (18.33, 51.39)	
	Day 90	10.88 (3.87, 16.88)	11.67 (3.89, 30.95)	
	Within group p-value[a]	<.001	<.001	.23
PISA (mm^2)	Baseline	957.93 (385.55, 1,759.57)	1,010.02 (561.99, 2,190.01)	
	Day 90	134.85 (62.31, 219.72)	192.59 (59.78, 380.49)	
	Within group p-value[a]	<.001	<.001	.68
PPD (mm)	Baseline	3.70 (3.35, 4.12)	3.98 (3.11, 4.78)	
	Day 90	2.68 (2.39, 3.09)	3.02 (2.52, 3.73)	
	Within group p-value[a]	<.001	<.001	.08
CAL (mm)	Baseline	4.14 (3.66, 4.44)	4.36 (3.29, 5.02)	
	Day 90	3.64 (3.10, 4.12)	4.01 (3.03, 4.68)	
	Within group p-value[a]	<.001	.005	.14

Note: Values are presented as median (Q1, Q3).

[a]Differences between baseline and day 90 within groups tested using Wilcoxon signed rank test.

[b]GLMs were used to test differences in clinical parameters between the groups at day 90 having adjusted for baseline levels, number of teeth, age, gender and smoking status. For skewed variables (FMPS, FMBS, Pockets ≥5 mm and PISA) ln-transformed values were used.

3.2 | Systemic inflammation

When combining all patients, there were significant increases in the levels of serum CRP at day 1 ($p = .002$ day 1 versus baseline) which returned to baseline levels at day 7 ($p = .215$ day 7 versus baseline) and day 90 ($p = .255$ day 90 versus baseline; Figure 2a). Similarly, levels of serum IL-6 in all patients increased at day 1 ($p = .019$ day 1 versus baseline) and returned to baseline levels at day 7 ($p = .765$ day 7 versus baseline) and day 90 ($p = .671$ day 90 versus baseline; Figure 2b). There were low levels of serum TNFα in the majority of patients, with seven samples below the assay detection limit. Serum TNFα was significantly reduced at day 1 ($p = .002$ versus baseline). Interestingly, TNFα returned to baseline levels at day 7 ($p = .765$ versus baseline) but reduced again at day 90 ($p = .013$ versus baseline; Figure 2c).

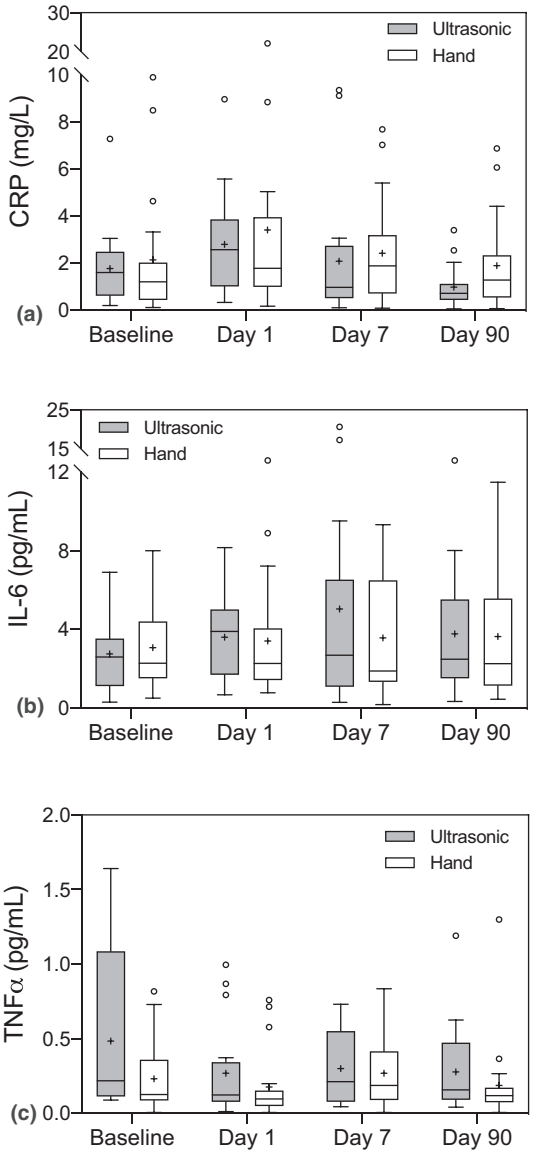

FIGURE 2 Levels of serum inflammatory markers in patients treated with ultrasonic (grey boxes) and hand instruments (clear boxes) at baseline, day 1, day 7 and day 90 follow-up. (a) CRP (b) IL-6 and (c) TNFα. Data are displayed as a Tukey boxplot, where the median is represented by the central horizontal line and mean displayed as "+". As described previously, day 1: UI; $n = 17$ HI; $n = 19$, day 7: UI; $n = 18$ HI; $n = 18$, day 90: UI; $n = 17$ HI; $n = 19$. For statistical analysis, see Table 3

The differences between treatment groups for serum inflammatory markers at day 1 (primary outcome), day 7 and day 90 were then investigated using a GLM controlling for baseline levels of each marker, smoking status, age, gender and BMI (Table 3). Despite significant increases in serum CRP at day 1, there were no statistically significant differences between treatment groups (p(adjusted) = .22). This remained consistent for CRP levels at day 7 (p(adjusted) = .53) and day 90 (p(adjusted) = .28). Similarly, there was no difference in levels of serum IL-6 and TNFα between treatment groups at day 1, day 7 and day 90 ($p > .05$ for both cytokines at all timepoints).

3.3 | Treatment time

We next sought to assess differences in treatment time between HI and UI groups. For total treatment time, the mean (SD) for UI was 75.39 (17.83) min, compared with 96.90 (23.54) min for HI (Figure 3a). The difference in treatment time between instruments (UI-HI) was assessed using a GLM controlling for disease severity (PISA mm^2) and number of teeth at baseline (β: −22.12, 95% CI: −35.19 to −9.06, $p = .002$). Following post hoc analysis, there was no correlation between treatment time and disease severity at baseline (PISA mm^2) for UI (Spearman $r = .152$, $p = .547$; Figure 3b), whilst there was a positive correlation for HI (Spearman $r = .598$, $p = .007$; Figure 3c). We found no significant positive or negative correlation between the change in serum inflammatory markers (day 1 minus baseline values) and the time of treatment (Figure 3d,f).

4 | DISCUSSION

To the authors' knowledge, this is the first randomized controlled trial to investigate the impact of different periodontal instrumentation techniques on systemic inflammation following full-mouth debridement. As expected, a significant increase in CRP was observed one day following treatment across all patients; however, the level of CRP at day 1 did not differ following hand or ultrasonic instrumentation.

The observed short-term CRP increase is consistent with previous studies conducted with similar inclusion and exclusion criteria (D'Aiuto, Nibali, Mohamed-Ali, Vallance, & Tonetti, 2004; Graziani et al., 2015; Graziani et al., 2010; Morozumi et al., 2018; Tonetti et al., 2007). However, the average magnitude of the increase in immediate post-treatment CRP was 1.67-fold in this study; somewhat less than that reported in previous studies (Graziani et al., 2015; Tonetti et al., 2007), which showed an approximately 3-fold and 8-fold increase in CRP 24-hr post-treatment respectively. An explanation for this may lie in the differential in mean treatment times between studies (Graziani et al., 2015; Tonetti et al., 2007). Mean treatment time for all patients in this study was 86.8 ± 23.5 min, which was less than Graziani *et al.* where the reported mean treatment time was 123 ± 18 min for their full-mouth debridement group. Similarly, the mean baseline plaque score for this study was 44.68 ± 25.68% (UI group) whereas Graziani et al. reported 70 ± 26% in their full-mouth debridement group. This difference may be due to patients in this study having received basic oral hygiene instruction prior to referral to the department. Furthermore, study patients received a full-mouth supragingival scale prior to treatment (Lang & Lindhe, 2015; Scottish Dental Clinical Effectiveness Programme 2014; Suvan et al., 2019) (following baseline plaque scoring), which will likely have reduced plaque scores even further prior to full-mouth debridement. These factors may help explain relative differences in mean treatment time or CRP response between studies.

A recently released joint consensus statement between the European Federation of Periodontology and American Academy

TABLE 3 Parameter estimates with 95% confidence intervals for ultrasonic instrumentation compared with hand instrumentation for ln-transformed serum CRP, IL-6 and TNFα levels at day 1, day 7 and day 90

	Day 1			Day 7			Day 90		
	β	95% CI	*p*-Value	β	95% CI	*p*-Value	β	95% CI	*p*-Value
C-reactive protein									
Model 1[a]	0.143	−0.582 to 0.867	.69	−0.271	−1.094 to 0.553	.51	−0.518	−1.239 to 0.202	.15
Model 2[b]	0.130	−0.369 to 0.628	.60	−0.311	−0.950 to 0.329	.33	−0.482	−1.038 to 0.073	.09
Model 3[c]	0.318	−0.196 to 0.832	.22	−0.231	−0.972 to 0.510	.53	−0.304	−0.867 to 0.259	.28
Interleukin-6									
Model 1[a]	0.133	−0.378 to 0.643	.60	0.176	−0.620 to 0.972	.66	−0.011	−0.671 to 0.650	.97
Model 2[b]	0.261	−0.093 to 0.614	.14	0.233	−0.524 to 0.991	.54	0.053	−0.546 to 0.653	.86
Model 3[c]	0.193	−0.173 to 0.559	.29	0.182	−0.634 to 0.999	.65	−0.005	−0.645 to 0.636	.99
Tumour necrosis factor α									
Model 1[a]	0.607	−0.307 to 1.521	.19	0.189	−0.568 to 0.946	.62	0.49	−0.192 to 1.171	.15
Model 2[b]	0.00003	−0.677 to 0.678	.99	−0.087	−0.843 to 0.669	.82	0.021	−0.512 to 0.555	.94
Model 3[c]	−0.215	−0.902 to 0.472	.53	−0.167	−1.022 to 0.688	.69	−0.121	−0.687 to 0.445	.67

Note: Parameter estimates (β-values) are based on ln-transformed data.

As described in Figure 1, day 1: UI; $n = 17$ HI; $n = 19$, day 7: UI; $n = 18$ HI; $n = 18$, day 90: UI; $n = 17$ HI; $n = 19$.

[a]Model 1: Unadjusted.

[b]Model 2: Adjusted for baseline levels of each serum marker.

[c]Model 3: Adjusted for baseline levels of serum marker, gender, age, smoking status and BMI at baseline.

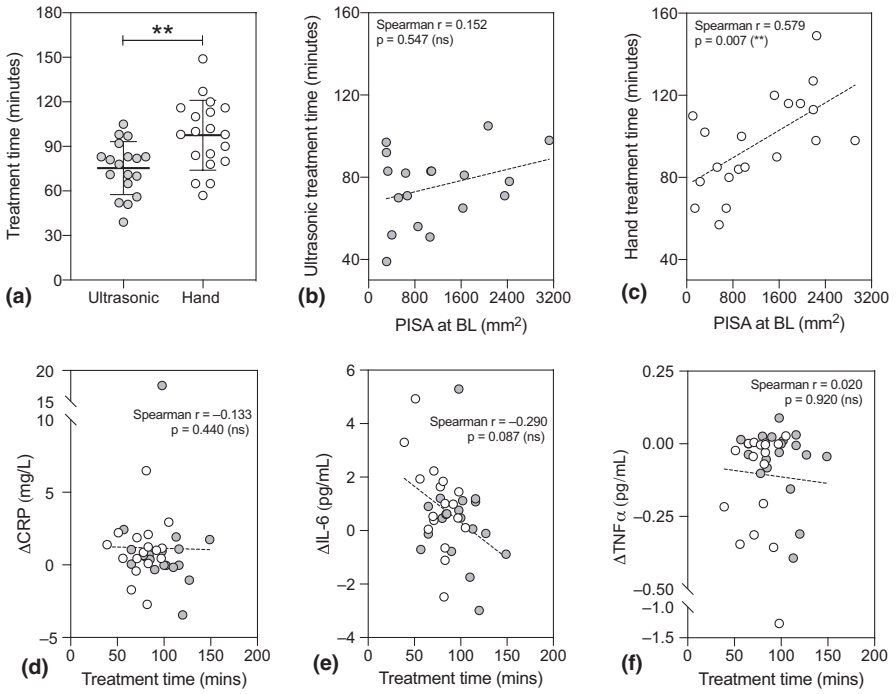

FIGURE 3 Treatment time comparison between ultrasonic ($n = 18$) and hand ($n = 19$) instrumentation. (a) Total treatment time controlled for number of teeth and disease severity (PISA mm^2) at baseline, $^{**}p < .01$, GLM. Correlation between total treatment time with (b) ultrasonic instruments and (c) hand instruments versus disease severity. Correlations between the change (Δ) in serum CRP (d), IL-6 (e) and TNFα (f) and treatment time. Grey circles represent patients in ultrasonic treatment group, white represent hand treatment group. All correlations are Spearman-rho, $^{**}p < .01$, ns indicates no significant difference. UI; $n = 18$, HI; $n = 19$

of Periodontology advised against the use of full-mouth debridement in patients with any level of cardiovascular disease (Sanz et al., 2020). In this study, an increase in serum CRP was observed across all patients (average increase of 1.07 mg/L), although we observed heterogeneity in the extent of this response. The absolute change in serum CRP from baseline to day 1 ranged from a 3.45 mg/L decrease to a 17.56 mg/L increase, suggesting large inter-patient variation, which did not relate to instrumentation choice. Therefore, establishing whether demographic, clinical or biological factors at baseline influence or predict this response is important in order to establish which patients may be more at risk of a significant CRP spike. As noted, there are differences in plaque indexes between

our study and those conducted previously. Thus, assessing whether supragingival debridement, prior to full-mouth debridement, may help reduce this spike would be an important addition to future research.

In this study, with respect to long-term changes in CRP, at day 90 follow-up serum CRP was similar to baseline levels. There were no changes in serum IL-6, although a reduction was found in TNFα at day 90 compared with baseline. However, the significance of this is questionable given that only very low levels of TNFα were detected at all time points. In relation to CRP and IL-6, 90-days following treatment may be too early to detect a net reduction in these circulating inflammatory markers. Moreover, the current study was not powered to detect this long-term difference. Some studies report a significant decrease in serum CRP (and IL-6) following intensive periodontal therapy at a follow-up of 2 months (D'Aiuto, Nibali, Parkar, Suvan, & Tonetti, 2005), whilst others report no change after 6 weeks (Ide et al., 2003). One explanation for these contrasting results may be patient comorbidities. A previous systematic review concluded that patients with comorbidities demonstrate significantly greater reductions in CRP following NSPT compared with systemically healthy patients (Teeuw et al., 2014). As the patients in the current study were systemically healthy and did not display elevated CRP levels (43% patients <1 mg/L, 41% patients 1–3 mg/L, 16% patients >3 mg/L at baseline), it is perhaps unsurprising that there was no notable reduction in serum CRP following treatment.

There were no discernible differences in clinical outcome, comparing instrumentation techniques, albeit this finding should be viewed as a secondary outcome measure that the study was not powered to investigate. Encouragingly, all patients' clinical parameters showed marked improvement following therapy. A pocket closure rate (defined as conversion of a periodontal site measuring ≥5 mm to a site measuring ≤4 mm) of 58.54%, mean periodontal probing depth reduction of 0.98 mm and mean PISA reduction of 985.92 mm^2 (80.83% reduction) was recorded on average across all patients at day 90. These findings are similar to a recent rigorous systematic review that identified pocket closure rates of 57% and mean periodontal probing depth reductions of 1.0 mm at 3/4 month follow-up (Suvan et al., 2019).

The reduced treatment time for use of ultrasonic compared with hand instruments is commensurate with previous studies (Badersten, Nilveus, & Egelberg, 1981; Breininger, O'Leary, & Blumenshine, 1987; Dragoo, 1992; Laurell, 1990; Tunkel et al., 2002; Yukna et al., 1997). Interestingly, treatment time for hand instrumentation correlated with disease severity, whist ultrasonic showed no such relationship; it could be speculated that ultrasonics may offer greater time saving for the treatment of severe PD. However, it should be noted that this is an incidental finding of this study and confirmation would require more rigorous investigation.

The current study was designed from the outset to investigate CRP levels at day 1 following two methods of periodontal instrumentation. Robust randomization, concealed allocation and appropriate blinding were implemented. Inevitably, potential for bias and limitations remain in certain aspects of this clinical trial. For example, there may be uneven distribution of unidentified confounding variables between interventional arms. Inclusion of factors such as BMI and baseline CRP in stratification techniques could be considered for future studies. In addition, patients with good motivation and compliance with dental care may self-select for inclusion within trials and this has implications for external validity as patients within the larger population may not adhere to oral hygiene instruction to the same extent—thus influencing their periodontal disease outcome. In this study, it was impossible to blind operators to treatment modality which may potentially result in observation bias. The current study found equivalence between the groups in terms of the primary outcome measure of change in CRP post-treatment. The findings from the current study can be considered robust; however, the study was designed to detect a meaningful difference, and not designed to detect equivalence, thus the data should be interpreted with due consideration to this caveat.

In conclusion, the data presented show that systemic inflammation, as measured by serum CRP, showed a significant increase 1-day following full-mouth debridement. There was no difference in CRP at day 1 between hand instrumentation and ultrasonic instrumentation techniques. Treatment efficacy was similar in both groups; however, treatment was significantly quicker with ultrasonic instruments regardless of disease severity.

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CONFLICT OF INTEREST

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