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ORIGINAL ARTICLE

Clinical and microbiological effects of a single application of sodium hypochlorite gel during subgingival re-instrumentation: a triple-blind randomized placebo-controlled clinical trial

Viorelia Radulescu[1] · Marius Ion Boariu[2] · Darian Rusu[1] · Alexandra Roman[3] · Petra Surlin[4] · Adrian Voicu[5] · Andreea Cristiana Didilescu[6] · Holger Jentsch[7] · Vincenzo Iorio Siciliano[8] · Luca Ramaglia[8] · Octavia Vela[1] · Giorgios Kardaras[1] · Anton Sculean[9] · Stefan-Ioan Stratul[1]

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Abstract

Objectives The aim of this study is to assess the clinical and microbiological effects of a single subgingival administration of sodium hypochlorite gel (NaOCl) and compare it with 1% chlorhexidine (CHX) gel and a placebo gel following mechanical re-instrumentation during supportive periodontal therapy (SPT).

Materials and methods Sixty-two patients who had been treated for stage III–IV periodontitis and enrolled in SPT were included in the study based on following criteria: (1) active periodontal therapy completed at least 6 months before enrollment in the study, (2) presence of at least 4 non-adjacent sites with probing pocket depths (PPDs) ≥ 4 mm with bleeding on probing (BOP), or presence of 5–8 mm PPDs with or without BOP. All sites presenting PPD ≥ 4 mm and BOP at baseline and 3-, 6-, and 9-month follow-up timepoints were subgingivally re-instrumented with ultrasounds. Selected patients were randomly assigned into three groups and treated additionally with a single subgingival administration of NaOCl gel (group A); 1% CHX gel (group B); and placebo gel (group C). Main outcome variable was pocket closure at 12 months. Secondary outcome variables were changes in mean PPD, BOP, and clinical attachment level (CAL) along with changes in the numbers of the following five keystone bacterial pathogens: *Aggregatibacter actinomycetemcomitans* (*A.a.*), *Porphyromonas gingivalis* (*P.g.*), *Prevotella intermedia* (*P.i.*), *Tannerella forsythia* (*T.f.*), and *Treponema denticola* (*T.d.*).

Results At 12 months, pocket closure was obtained in 77.5% in the NaOCl treated sites. The reduction in PPD was higher with CHX than with NaOCl, although a statistically significant adjunctive effect for NaOCl ($P = 0.028$) was only observed in comparison with placebo only. Mean CAL improved in all groups and at all timepoints, compared to the baseline ($P < 0.05$). However, after 6 months, CAL gain was statistically significantly higher in the NaOCl treated group than following application of CHX ($P = 0.0026$).

Conclusion In SPT patients, a single adjunctive use of a NaOCl gel may provide benefits in controlling inflammation and residual pockets.

Trial registration ISRCTN Registry of Clinical Trials (ISRCTN11387188).

Clinical relevance A baseline single application of NaOCl gel in conjunction with mechanical debridement may achieve substantial pocket closure in patients enrolled in SPT; treatment time, cost, and applicability considerations should be taken into account when selecting this therapy.

Keywords Periodontal maintenance · Subgingival re-instrumentaion · Sodium hypochlorite · Probing pocket debridement

Introduction

Substantial evidence has shown that periodontitis is triggered and maintained by dysbiosis of the periodontal pathogenic biofilm and subsequent destructive inflammatory response. Consequently, treatment of periodontitis

✉ Marius Ion Boariu
boarium@yahoo.com

Extended author information available on the last page of the article

always focuses in all phases on the mechanical removal or destruction of the supra- and subgingival biofilm [1–5].

Subgingival re-instrumentation during supportive periodontal therapy (SPT) has been shown to result in additional clinical improvements in only about 50% of affected sites, as evidenced by a reduction in probing pocket depths and bleeding on probing, while the rest of affected sites may show further disease progression [6–8].

The goals of SPT are to minimize or prevent recurrence of the disease and/or arrest its progression to maintain long-term periodontal health and chewing comfort [9–11]. Substantial evidence indicates that SPT plays a key role in arresting periodontal disease prognosis and increases tooth survival [12–16]. It is recommended that SPT starts once the endpoint of active periodontal therapy (APT) is reached (i.e., PPD ≤ 4 mm, absence of BOP of 4 mm sites) [17–20].

Mechanical disruption of the biofilm is an effective approach and is still considered as the "gold standard"; it is sometimes limited by the inadequate access and visibility to the operative sites [21, 22]. Air polishing devices have been proposed as a more effective alternative for biofilm removal at sites difficult to access with hand curettes or machined driven instruments, since the stream of abrasive particles can remove biofilm residues which may remain after conventional instrumentation [23]. Recent data provide evidence suggesting that air polishing devices may represent a valuable modality for biofilm removal during SPT [24]. However, the rationale of performing repeated subgingival scaling at 3-month intervals for patients with persistent disease has been questioned [25], thus pointing to the need, in specific clinical scenarios, of using adjunctive antimicrobials having as main rationale the antimicrobial effect at sites that are inaccessible to mechanical therapy thus increasing the possibility of reaching and destroying remaining pathogens [26]. Local delivery systems containing antibiotic or antiseptic drugs allow therapeutic agents to target diseased sites with minimal systemic effects [27]. Compared to use of SRP only, the combined use of several local anti-infective agents and scaling and root planning (SRP) seems to provide additional benefits in PPD reduction and clinical attachment level (CAL) gain [28]. Within the last decade, topical slow-release antimicrobials, such as chlorhexidine, doxycycline, minocycline, and metronidazole, have been used subgingivally in conjunction with mechanical instrumentation during SPT [29–33]. Substantial evidence indicates that adding a chemotherapeutic agent to conventional SPT has an adjunctive effect in interrupting further periodontal disease progression, as observed in persistent or recurrent periodontitis after local use of doxycycline [6, 31, 34]. The adjunctive application of an antimicrobial agent may be also useful for patients with contraindications of surgery and patients with extreme sensitivity after active periodontal treatment [32].

A recent study [35] has evaluated the potential benefit of an enamel matrix derivative (EMD) as an adjunct to re-instrumentation of residual pockets during the step 3 of periodontal therapy [20]. The frequency of pocket closure in the test group was statistically significantly higher than in the control group at 6 months and was maintained up to 12 months.

Very recently, the use of sodium hypochlorite (NaOCl) has been also suggested as a possible alternative to improve the outcomes of subgingival SRP. This is mainly due to its broad antimicrobial activity, fast bactericidal action, and non-toxicity at application concentration [36, 37]. Histologically, subgingival application of (NaOCl) provides chemolysis of the soft tissue wall of the periodontal pocket with minimal effect on the adjacent tissues. Hence, its use in the maintenance phase of periodontal therapy has been recommended [38].

Antimicrobials which are currently use adjunctively in subgingival re-instrumentation during SPT (i.e., mainly antibiotics and CHX) have been associated with potential risks of antimicrobial resistance [37, 39]. For instance, the oral cavity has been highlighted as potential reservoir for antimicrobial resistance genes in numerous publications from recent years [40, 41]. NaOCl could be an interesting alternative because its mechanism of action is rather non-selective (oxidative burst) as opposed to antibiotics or CHX [42]. Thus, development of resistances toward NaOCl seems less likely as toward antibiotics or CHX.

Recently, a novel formulation of NaOCl gel (Perisolv, RLS Global AB, Gothenburg, Sweden) buffered with leucine, lysine, and glutamic acid was used as an adjunct to subgingival instrumentation [43] and re-instrumentation [44] for the treatment of peri-implant mucositis [45] and peri-implantitis [46]. The active ingredients in the gel create chloramines, which have a strong antimicrobial effect and can penetrate the biofilm [44], thus making an alternative approach to improve the outcomes of ultrasonic re-instrumentation (USI) procedures [47, 48]. An in vitro study indicated that the NaOCl gel had antimicrobial activity against Gram-negative species associated with periodontitis, although it failed to eliminate a multi-species biofilm [40].

The phase of therapy at which other topical slow-release antimicrobials are most beneficial remains unclear. However, these formulations appear to be most beneficial when used during SPT at non-responding or recurrent chronic inflammation sites [49].

Accordingly, to the best of our knowledge, at present, only one study has addressed the issue of topical NaOCl gel in re-instrumentation of persistent pockets during SPT [44]. However, in that study, the treatment consisted of repeated topical applications of the novel hypochlorite gel in conjunction with short-time ultrasonic debridement. As other studies have indicated, the existing data on the potential clinical relevance of local application of NaOCl gel used in conjunction with subgingival mechanical instrumentation remains limited [43].

Therefore, the aim of this triple-blinded randomized placebo-controlled clinical study was to compare the clinical and microbiological effects between the adjunctive subgingival administration of NaOCl gel and chlorhexidine and a placebo gel with subgingival re-instrumentation and air polishing during the first 12 months of SPT.

Material and methods

Study design

This study was conducted as a triple-blinded randomized placebo-controlled clinical trial of 12 months with a parallel design of three independent groups by a 1:1:1 allocation ratio. The study was approved by the Research Ethics Committee of the Victor Babes University of Medicine and Pharmacy Timisoara (approval no.1/21.01.2018). The study was conducted according to the principles outlined in the Declaration of Helsinki on human medical experimentation. All participants provided written informed consent, giving permission for the dental procedures and sampling of biological material. The study was conducted between January 2018 and September 2019. The study was registered in the ISRCTN Registry of Clinical Trials (ISRCTN11387188) and followed the guidelines described in the CONSORT 2010 statement on clinical trials.

Study population

Out of 85 randomly selected and screened patients, 62 patients agreed to participate in the study. The participants were randomly assigned to one of the three study groups: groups A, B, and C. Not more than 50% of the patients were smokers. With respect to smoking, the patients were distributed in three groups: smokers (> 10 cigarettes/day regularly), former smokers, and non-smokers [50].

Patients that were included in the study had completed APT and received SPT for a minimum of 6 months of documented SPT, until the desired number of participants was attained. APT was performed in a private practice in Timisoara, Romania, whereas SPT was performed in a private practice and in the Department of Periodontology, Victor Babes University of Medicine and Pharmacy, Timisoara, Romania. A flowchart of the study according to CONSORT is provided in Fig. 1.

The inclusion criteria were as follows:

(a) Patients aged 20–80 years
(b) Patients enrolled in SPT after at least 6 months following APT for periodontitis stages III–IV
(c) **A**t least four non-adjacent sites with PPDs ≥ 4 mm with BOP or PPDs > 5 mm, but not deeper than 8 mm, with or without BOP, needing retreatment ("reference sites") [6]
(d) Neither furcation involvement, nor third molars or severely malpositioned teeth
(e) Vital teeth or teeth with "lege-artis" root canal treatment
(f) Full mouth bleeding score (FMBS) ≤ 20%
(g) Full mouth plaque score (FMPS) ≤ 20%
(h) Mobility degree ≤ 2 [53]
(i) Patients treated (no surgical/surgical if indicated) in the same private practice where the study was conducted.
(j) Patients willing to provide written informed consent and willing to complete the 12-month study follow-up.

Exclusion criteria:

(a) Known allergies or adverse reactions to hypochlorite
(b) Clinically relevant psychological disorders
(c) Alcohol abuse
(d) HIV infection
(e) Self-reported diabetes mellitus
(f) Use of local or systemic administration of antibiotics during the last 3 months
(g) Pregnancy and breast feeding
(h) Heavy smokers. If progression of periodontal destruction was observed or if adverse reactions to the test product were reported, the participant was excluded from the study. Progression of periodontal destruction was defined as attachment loss > 2 mm or an increase in PPD > 2 mm between subsequent evaluations [6, 26].

Clinical examination

The clinical examination team included an examiner (specialist in periodontology), a randomizer, and an operator (specialist in periodontology) with at least 4 years of clinical experience. The intra-examiner calibration for reliability testing resulted in $\kappa = 0.92$ for repeated measurements of PPD and CAL in two quadrants of five patients, other than the patients recruited for the study. Periodontal diagnosis was made according to the new classification system for periodontal and peri-implant diseases and conditions (2018) [51]. Each patient's medical history was updated.

All clinical measurements (i.e., at baseline, at 3-, 6-, 9-, and 12-months) were performed by the same investigator (SS). Additionally, FMPS and FMBS were calculated [52]. PPD, gingival recessions (REC), and clinical attachment levels (CAL) were measured at six sites per tooth using a manual periodontal probe (PCP-UNC15, Hu-Friedy, Chicago, IL, USA). Measurements were recorded to the nearest millimeter. Mobility was recorded according to the Miller classification [53]. Periodontal parameters were recorded in the periodontal chart (http://www.periodontalchart-online.com/uk/), saved in "pdf" format, printed, and included the observation file of each patient.

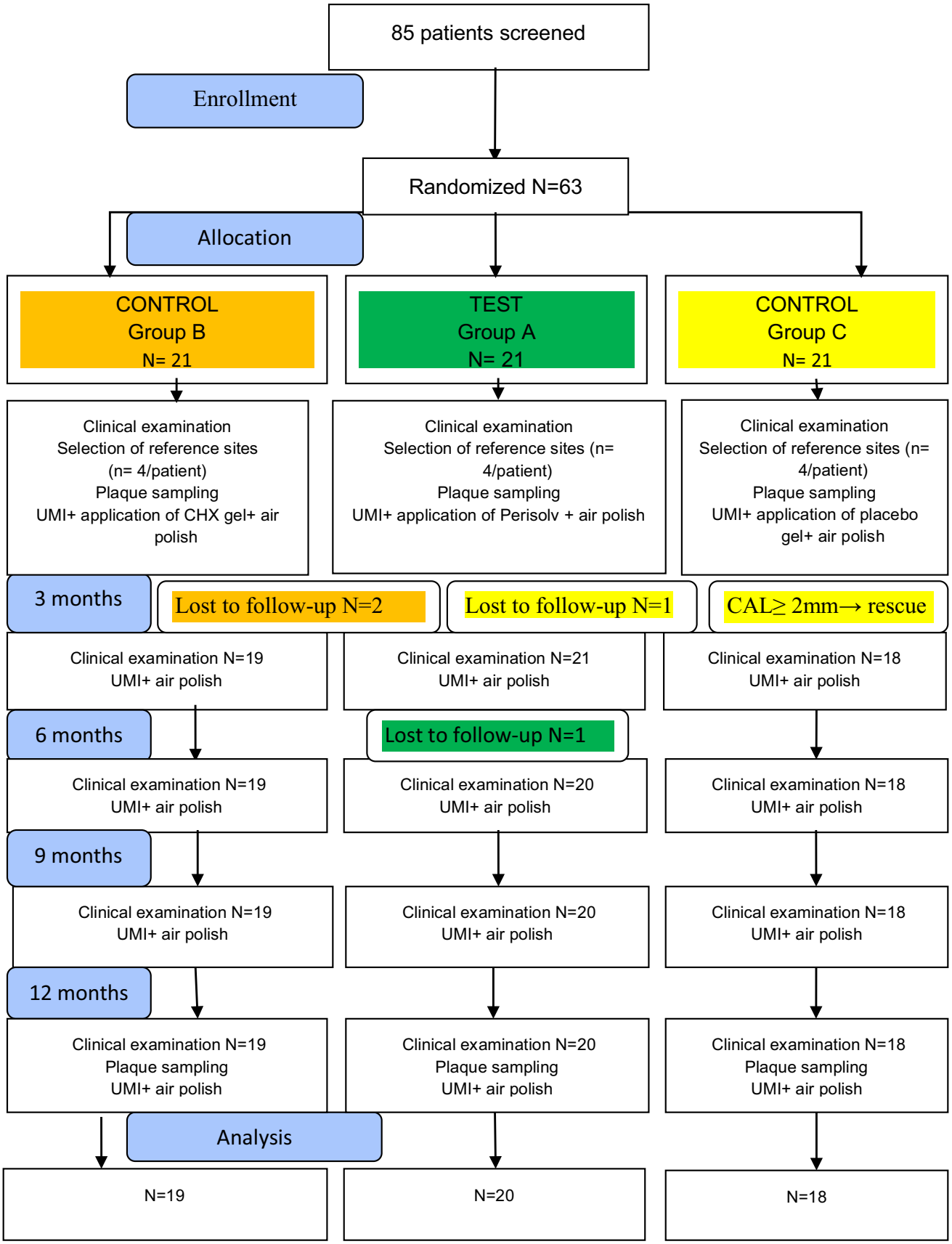

Fig. 1 CONSORT flow chart of patient enrolment and follow-up examination

Microbiological examination

To detect the selected bacteria, *Aggregatibacter actinomycetemcomitans* (*A.a.*), *Porphyromonas gingivalis* (*P.g.*), *Prevotella intermedia* (*P.i.*), *Tannerella forsythia* (*T.f.*), and *Treponema denticola* (*T.d.*), a molecular genetic analysis was performed. The semi-quantitative analysis of bacteria was assessed using the commercial kit, micro-IDent® plus (Hain Lifescience GmbH, Nehren, Germany), which is based on DNA STRIP technology. The microbiological samples were collected by the treating clinician (VR) from the teeth with the deepest PPD recorded at the initial evaluation. The microbiological samples at the 12-month re-evaluation time point were harvested exactly from the same sites. Subgingival plaque was collected for microbiological examination as follows. First, the site was isolated with cotton rolls. After removing the supragingival plaque and the debris with a sterile cotton gauze, the gingival surface was dried. The plaque samples were collected by inserting one sterile paper point ISO #30 in each one of the four reference sites and allowing them 30 s in situ for saturation [54]. The paper points were pooled immediately into sterile-sealed Eppendorf tubes and sent for polymerase chain reaction (PCR). The PCR testing was conducted in the laboratories of the Department of Biochemistry, Victor Babeş University of Medicine and Pharmacy. The cones were removed after 15 min of vortex mixing at room temperature, and the eluates were clarified by centrifugation for 5 min at 3000 × g at 23 °C. The samples were stored for one day at – 20 °C, and then at – 80 °C until the microbiological analysis was performed (not more than 30 days later).

Randomization and therapy assignment

Randomization was achieved using a number generator (www.randomizer.org) by a randomizer who was independent of the operator or evaluator. The randomizer ensured blinding by using a placebo gel similar in aspect and consistency to the test gel. Moreover, neither the patients, operator, nor clinical examiner knew the groups the patients were assigned. The computerized randomization assigned the patients to one of the three groups by an allocation ratio of 1:1:1. The randomizer performed the assignment to interventions, while a dental assistant performed the documentation. An allocation table containing the names of the patients was created and used to assign patient treatment numbers, as indicated by the randomization process. Each patient was given a sealed opaque envelope containing the treatment number.

SPT procedures

The operator (VA) performed the supragingival debridement (EMS Piezon® Master, EMS, Nyon, Switzerland) and air polishing (standard air-flow nozzle, AIRFLOW® PLUS powder (EMS, Nyon, Switzerland) at all sites. The reference sites and all sites presenting PPD ≥ 4 mm at baseline and 3-, 6-, and 9-month follow-up timepoints were re-instrumented with USI using fine subgingival inserts (PS (Perio Slim) EMS, Nyon, Switzerland) in the context of regular SPT. The NaOCl gel, chlorhexidine gel, or placebo gel was not reapplied at the 3-, 6-, and 9-month timepoints.

The investigated antimicrobial product (Perisolv®, Regedent AG, Zürich, Switzerland) consisted of two components contained in two separate interconnectable syringes: 0.95% sodium hypochlorite solution and transparent gel (the activating vehicle), containing amino acids (glutamic acid, leucine, lysine), carboxymethylcellulose, and ultrapure water. The two components were mixed before use to generate chloramines [44]. The chlorhexidine product (Clorhexamed® 1% gel, GSK, Germany) and placebo treatment consisted of gels with similar aspect and consistency as the test product, packaged in transparent syringes and identical with the syringe for the test product.

In group A, the reference sites were additionally treated as follows. According to the manufacturer's instructions, Perisolv® was applied by interconnecting the two syringes and mixing the liquids by alternately pushing the plungers. It was mixed until the liquid became homogeneous (10–15 cycles) and was then pushed into the transparent syringe. A blunt applicator was applied to this syringe and was inserted into the pocket mesially, lingually, distally, and buccally to cover the full circumference of the teeth and reach the bottom of the pocket. Perisolv® gel was left in situ for 30 s after application, followed by USI. After 15 min, Perisolv® was applied again, and teeth were re-instrumented subgingivally after 30 s using USI. Air polishing was used on all teeth to destroy the biofilm. In groups B and C, the reference sites were additionally treated with the chlorhexidine gel and placebo gel. The gels were applied in the same manner as in group A. For USI, no time limitations were set, and instrumentation was performed without local anesthesia until the treating clinician felt comfortable with the debrided root surfaces.

During the first periodontal re-evaluation, the investigator asked patients if any allergy or adverse reactions occurred after the treatment procedure, or if they had used medication that might interfere with the inclusion criteria. If necessary, the individual's oral hygiene was reinforced.

The participants were instructed to avoid using any other local or systemic antimicrobials. Oral hygiene instructions that were given to all participants during the initial periodontal therapy (i.e., use of rotary toothbrushing, dental floss, interdental brushes, pulsated water jet) were repeated and reinforced during each visit of the SPT. The timeline of the study is presented in Fig. 2.

Data analysis

The statistical analyses were performed using the software R version 4.0.0 (R Development Core Team, R Foundation

for Statistical Computing, Vienna, Austria) [55]. Statistical analysis was conducted intra- and inter-groups. The main outcome variable was pocket closure at the 12-month timepoint. Mean PPD changes, BOP, mean CAL changes, and the changes in the frequency detection scores of the five selected bacterial species were regarded as secondary outcomes. The sample size calculation was based on earlier reports on periodontal re-instrumentation [35, 56]. A minimal required sample size of 16 patients per group was required to achieve 80% power for detecting a statistically significant mean difference of 1 mm in the reduction of PPD between groups, assuming a common standard deviation of 0.8 mm and given significance level, $\alpha = 0.05$. The Pitman asymptotic relative efficiency correction was applied in the sample size computation to account for the use of nonparametric comparison tests. At least 18 patients were enrolled in each of the 3 groups to account for possible attrition. For each of the quantitative variable, PPD, REC, and CAL, a patient mean value was computed per timepoint, which was further used in the statistical analyses. For quantitative data, intergroup comparisons were made using the Kruskal–Wallis tests with Mann–Whitney post-hoc tests. Differences within each group from baseline to later timepoints (3, 6, 9, and 12 months) were analyzed using Wilcoxon signed-rank tests. Chi-squared tests or Fisher's exact tests, as appropriate, were used for comparisons between groups in the case of qualitative data. Statistical significance was set at $P < 0.05$.

Regarding the microbiological status, changes in the detection frequency scores of major keystone bacteria were assessed. Results were recorded and classified into one of the following categories: 0 = nondetectable, 1 = detectable $< 10^4$ (10^3 for *A.a*), 2 = 10^4–10^5 (10^3–10^4 for *A.a*), 3 = 10^5–10^6 (10^4–10^5 for *A.a*), and 4 ≥ 10^7 (10^6 for *A.a*) [54]. Intra-group comparisons of detection scores of pathogen species between the baseline and 12-month re-evaluation timepoints were performed using Wilcoxon signed rank test. The Kruskal–Wallis test was used for inter-group comparisons of detection scores for each timepoint.

Results

No side or adverse effects related to any of the treatment procedures occurred in any of the patients. Table 1 presents the characteristics of the patients at baseline. Test and control groups showed no statistically significant differences regarding sex, smoking, age, FMPS, FMBS, and PPD at baseline. The intragroup distribution was well pondered. The PPD of the sites ranged from 4 to 7 mm at baseline. The mean PPD at baseline was 4.56 ± 0.46 mm for the Perisolv® group, 4.48 ± 0.36 mm for the chlorhexidine group, and 4.57 ± 0.46 mm for the placebo group (Table 2). Additionally, 83.75% of Perisolv® treated sites, 94.74% of chlorhexidine treated sites, and 95.83% of placebo sites were identified as BOP-positive after probing at baseline (Table 3).

Out of 85 individuals that were screened, 63 patients met the inclusion criteria, gave written informed consent to participate, and were included in the study. Due to attrition, 57 patients were available for examination after 12 months. During the study, two participants showed disease progression; therefore, they were excluded from the study to undergo standard therapy. Figure 1 presents the study flow chart according to the CONSORT guidelines.

Tooth types (incisors/canines/premolars/molars) of reference teeth were distributed among groups as follows: 15/9/26/30 for Perisolv®, 7/11/27/31 for Chlorhexidine, and 20/15/18/19 for placebo. A total of 228 reference sites

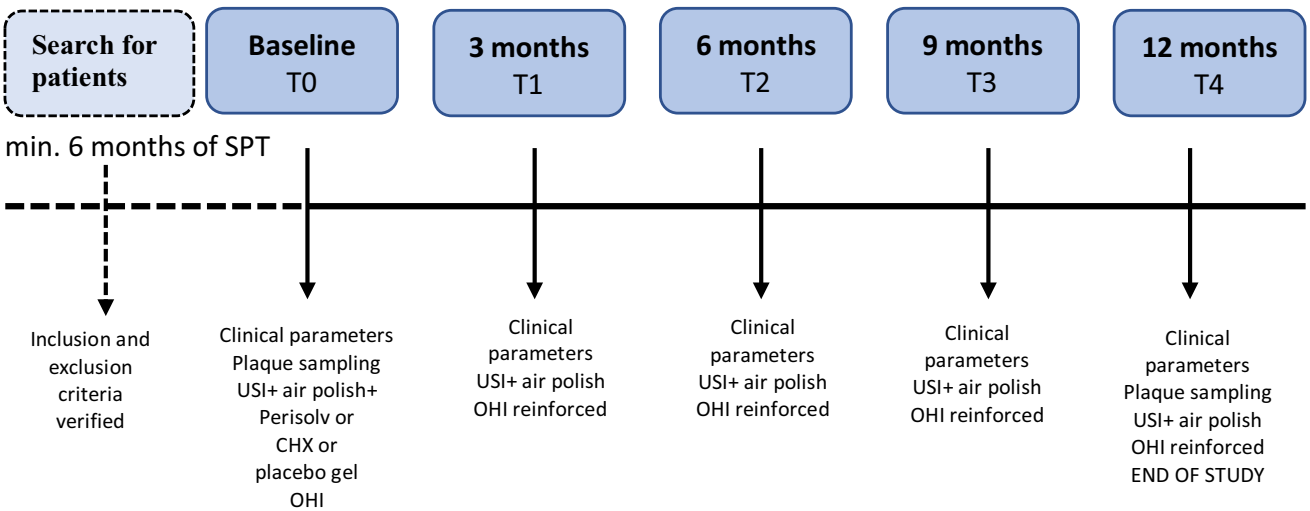

Fig. 2 Timeline of the study

Table 1 Characteristics of study participants at baseline

Parameter	Perisolv ($n=20$)	CHX ($n=19$)	Placebo ($n=18$)	p value
Age (years, mean ± SD)	44.60 ± 9.86	48.68 ± 11.63	50.61 ± 9.31	0.155[a]
Sex = female (n, %)	10 (50%)	8 (42.11%)	12 (66.67%)	0.313[b]
Smoker (n, %)	3 (15%)	3 (15.79%)	3 (16.67%)	1[c]
FMPS	15.10 ± 6.45	16.16 ± 6.11	16.33 ± 5.65	0.869[a]
FMBS	20.50 ± 4.32	20.16 ± 4.13	21.89 ± 2.11	0.608[a]
PPD = 4 mm (n, %)	46 (57.50%)	48 (63.16%)	39 (54.17%)	
PPD = 5 mm (n, %)	26 (23.50%)	22 (28.95%)	26 (36.11%)	
PPD = 6 mm (n, %)	5 (6.25%)	6 (7.89%)	6 (8.33%)	
PPD = 7 mm (n, %)	3 (3.75%)	0 (0%)	1 (1.39%)	

[a]Kruskal-Wallis test

[b]Chi-squared test

[c]Fisher's exact test

Table 2 Mean probing pocket depth (PPD) ± standard deviation (mm) at baseline and 3-, 6-, 9-, and 12-month timepoints in the treatment and control groups and p values of Kruskal–Wallis tests for intergroup comparisons

	PERISOLV	CHX	placebo	p-value
Baseline	4.56 ± 0.46	4.48 ± 0.36	4.57 ± 0.46	0.669
3 months	3.59 ± 0.42	3.66 ± 0.52	3.89 ± 0.64	0.127
Difference to baseline	0.98 ± 0.31	0.79 ± 0.36	0.68 ± 0.73	0.065
6 months	3.58 ± 0.35	3.76 ± 0.53	3.79 ± 0.72	0.343
Difference to baseline	0.99 ± 0.31	0.68 ± 0.45	0.78 ± 0.71	0.069
9 months	3.65 ± 0.43	3.71 ± 0.65	3.82 ± 0.58	0.524
Difference to baseline	0.91 ± 0.42	0.74 ± 0.58	0.75 ± 0.56	0.310
12 months	3.75 ± 0.47	3.84 ± 0.61	3.82 ± 0.57	0.934
Difference to baseline	0.81 ± 0.38	0.61 ± 0.52	0.75 ± 0.58	0.356

Table 3 Proportion of sites with BOP and p values of chi-squared tests for intergroup comparison

	PERISOLV	CHX	placebo	p-value
Baseline	67/80 (83.75%)	72/76 (94.74%)	69/72 (95.83%)	0.013
3 months	12/80 (15.00%)	15/76 (19.74%)	20/72 (27.78%)	0.147
6 months	18/80 (22.50%)	25/76 (32.89%)	20/72 (27.78%)	0.349
9 months	18/80 (22.50%)	22/76 (28.95%)	17/72 (23.61%)	0.615
12 months	10/80 (12.50%)	22/76 (28.95%)	23/72 (31.94%)	0.010

were treated. The four reference teeth were in different quadrants in 24 patients, and each reference site belonged to one

Table 4 Proportion of sites with pocket closure and p-values of chi-square tests for intergroup comparisons

	PERISOLV	CHX	placebo	p value
Baseline	0/80	0/76	0/72	–
3 months	64/80 (80.00%)	53/76 (69.74%)	46/72 (63.89%)	0.082
6 months	61/80 (76.25%)	51/76 (67.10%)	47/72 (65.28%)	0.281
9 months	61/80 (76.25%)	48/76 (63.16%)	46/72 (63.89%)	0.144
1 months	62/80 (77.50%)	48/76 (6 3.16%)	43/72 (59.72%)	0.044

reference tooth. The other 33 patients had a maximum of two reference teeth on the same quadrant (at least three teeth apart from each other), while the other two reference teeth were situated in the remaining three quadrants.

The primary outcome variable, pocket closure (Table 4), defined as the transition of sites with PPD > 5 mm or 4 mm with BOP to non-bleeding sites with PPD ≤ 4 mm, was attained in 77.5% of Perisolv® sites after 12 months. The reduction was higher in the CHX group than in the sodium hypochlorite gel group. However, a significant adjunctive effect of Perisolv® ($P=0.028$) was observed, when compared with the placebo group only at the 12-month timepoint. Therefore, the hypothesis tested could be confirmed only for one arm.

Periodontal re-instrumentation caused clinical improvements in both control and test groups, showing reductions in mean PPD value at test and control sites between baseline and 3-month follow-up timepoint. The results were maintained at subsequent re-evaluations (Table 2). However, these improvements, as well as differences between groups, were not statistically significant at any time point. Marginally, statistically significant differences were observed at the 3- and 6-month timepoints, favoring Perisolv® over

CHX and placebo. After 12 months of maintenance therapy, the mean PPD value of the study sites was reduced by 0.81 ± 0.38 mm in the test group, by 0.61 ± 0.52 mm in the CHX group, and by 0.75 ± 0.58 mm in the placebo group.

The analysis of BOP changes at test and control sites (Table 3) shows that the proportion of BOP sites in the Perisolv® group was significantly lower than in the CHX and placebo groups at baseline and at the 12-month timepoint. No difference in BOP incidence was recorded at 3-, 6-, and 9-month timepoints among study groups. The intra-group analysis showed an important decrease in the number of sites with BOP at the 3-month timepoint, followed by a stabilization tendency in all groups.

No statistically significant differences were identified in terms of REC changes among the study groups at any timepoint (Table 5). The intra-group analysis showed a statistically significant increase at 3-, 6-, and 9-month timepoint (Wilcoxon test, $P < 0.05$) from 0.29 ± 0.43 and 0.30 ± 0.57 to 0.40 ± 0.44 and 0.51 ± 0.67 for Perisolv and CHX group, respectively.

Although no statistically significant differences in terms of CAL changes were found among the groups at any timepoint (Table 6), an improvement occurred in all three groups compared to baseline (Wilcoxon tests, $P < 0.005$). Differences were observed among the groups when comparing the values from baseline with those from the 6-month timepoint (Kruskal–Wallis test, $P = 0.010$). Mann–Whitney post-hoc tests revealed that these differences were due to the more important 6-month CAL gain in the Perisolv® group than in the CHX group ($P = 0.0026$).

The intra-group analysis reveals a statistically significant decrease in detection scores from baseline to 12 months for *P.g.* (Perisolv®, CHX, and placebo group with *P* values of 0.015, 0.004, 0.002, respectively), *P.i.* (placebo group, $P = 0.049$), *T.f.* (Perisolv®, CHX, and placebo group, *P* value of 0.004, 0.003, and 0.010, respectively), and *T.d.* (Perisolv® and placebo groups with *P* value of 0.005 and 0.040, respectively). The inter-group analysis showed no statistically significant differences in the detection scores for *A.a.*, *P.g.*, *P.i.*, *T.f.*, and *T.d.* among the three groups, either at baseline or after 12 months (Table 7). In all three groups, pathogen detection scores either decreased over time or remained constant, with very few exceptions.

Table 5 Mean gingival recession (REC) ± standard deviation (mm) at baseline, 3, 6, 9, and 12 months in the treatment and control groups and p-values of Kruskal–Wallis tests for intergroup comparisons

	PERISOLV	CHX	placebo	*p*
Baseline	0.29 ± 0.43	0.30 ± 0.57	0.47 ± 0.69	0.635
3 months	0.43 ± 0.45	0.46 ± 0.66	0.58 ± 0.72	0.875
Difference to baseline	0.14 ± 0.19	0.16 ± 0.28	0.11 ± 0.23	0.656
6 months	0.40 ± 0.44	0.57 ± 0.67	0.61 ± 0.70	0.787
Difference to baseline	0.11 ± 0.21	0.26 ± 0.36	0.14 ± 0.25	0.299
9 months	0.36 ± 0.36	0.55 ± 0.69	0.61 ± 0.71	0.731
Difference to baseline	0.08 ± 0.28	0.25 ± 0.39	0.14 ± 0.26	0.496
12 months	0.40 ± 0.44	0.51 ± 0.67	0.65 ± 0.71	0.683
Difference to baseline	0.11 ± 0.15	0.21 ± 0.35	0.18 ± 0.32	0.781

Table 6 Mean clinical attachment level (CAL) ± standard deviation (mm) at baseline and 3-, 6-, 9-, and 12-month timepoints in the treatment and control groups and *p* values of Kruskal–Wallis tests for intergroup comparisons

	PERISOLV	CHX	placebo	*p*-value
Baseline	4.85 ± 0.70	4.75 ± 0.61	5.04 ± 0.82	0.531
3 months	4.01 ± 0.68	4.12 ± 0.65	4.47 ± 0.83	0.161
Difference to baseline	0.84 ± 0.37	0.63 ± 0.36	0.57 ± 0.60	0.078
6 months	3.98 ± 0.60	4.33 ± 0.64	4.40 ± 0.96	0.191
Difference to baseline	0.88 ± 0.35	0.42 ± 0.37	0.64 ± 0.62	0.010
9 months	4.01 ± 0.68	4.26 ± 0.70	4.43 ± 0.78	0.276
Difference to baseline	0.84 ± 0.46	0.49 ± 0.43	0.61 ± 0.46	0.062
12 months	4.15 ± 0.73	4.36 ± 0.69	4.47 ± 0.78	0.460
Difference to baseline	0.70 ± 0.40	0.39 ± 0.38	0.57 ± 0.50	0.095

Discussion

This study sought to evaluate the benefit of a single subgingival application of a low concentration hypochlorite/amino acid gel associated with subgingival USI and air polish in residual pockets ≥ 4 mm with positive BOP or residual pockets > 5 mm over a year of SPT.

The rationale for supplementary efforts aiming at improving periodontal maintenance and early intervention during SPT is confirmed by earlier observations that the current standard, based on repeated mechanical re-instrumentation of sites ≥ 4 mm and positive BOP, patient motivation, and oral hygiene instructions, is unable to control inflammation in more than 50% of sites. Although mechanical treatment substantially decreases the counts of subgingival microorganisms, it does not necessarily eliminate all periodontal pathogens [57].

The recently published S3-level clinical guideline for the treatment of periodontitis [20] tackles decision-making for retreatment after step 2 therapy (initial non-surgical phase). Based on the findings from a systematic review [58], it is recommended to re-instrument residual pockets with a PPD of 5 mm by a non-surgical approach. Residual pockets of ≥ 6 mm should be reduced by periodontal surgery to reach the endpoint of active therapy (PPD ≤ 4 mm, without BOP).

Table 7 Detection frequency scores for *A.a*, *P.g*, *P.i*, *T.f*, *T.d* at baseline and 12-month timepoint

Species	Timepoint	Detection score	PERISOLV	CHX	placebo	*p*-value**
A.a	Baseline	0	15 (75%)	14 (73.68%)	16 (88.88%)	0.408
		1	1 (5%)	1 (5.26%)	–	
		2	–	–	1 (5.56%)	
		3	1 (5%)	2 (10.53%)	1 (5.56%)	
		4	3 (15%)	2 (10.53%)	–	
	12 months	0	17 (85%)	16 (84.21%)	18 (100%)	0.218
		1	2 (10%)	1 (5.26%)	–	
		2	–	1 (5.26%)	–	
		3	1 (5%)	–	–	
		4	–	1 (5.26%)	–	
	p value*		0.098	0.181	0.371	
P.g	Baseline	0	6 (30%)	3 (15.79%)	1 (5.56%)	0.935
		1	1 (5%)	3 (15.79%)	1 (5.56%)	
		2	1 (5%)	1 (5.26%)	4 (22.22%)	
		3	3 (15%)	5 (26.32%)	6 (33.33%)	
		4	9 (45%)	7 (36.84%)	6 (33.33%)	
	12 months	0	11 (55%)	12 (63.16%)	9 (50%)	0.529
		1	1 (5%)	3 (15.79%)	–	
		2	2 (10%)	1 (5.26%)	2 (11.11%)	
		3	4 (20%)	–	3 (16.67%)	
		4	2 (10%)	3 (15.79%)	4 (22.22%)	
	p value*		**0.015**	**0.004**	**0.002**	
P.i	Baseline	0	5 (25%)	8 (42.10%)	6 (33.33%)	0.529
		1	4 (20%)	2 (10.53%)	1 (5.56%)	
		2	5 (25%)	6 (31.58%)	6 (33.33%)	
		3	6 (30%)	3 (15.79%)	5 (27.78%)	
		4	–	–	–	
	12 months	0	9 (45%)	12 (63.16%)	11 (61.11%)	0.354
		1	4 (20%)	3 (15.79%)	–	
		2	2 (10%)	4 (21.05%)	3 (16.67%)	
		3	5 (25%)	–	4 (22.22%)	
		4	–	–	–	
	p value*		0.121	0.095	**0.049**	
T.f	Baseline	0	–	–	–	0.325
		1	1 (5%)	1 (5.26%)	–	
		2	2 (10%)	2 (10.53%)	1 (5.56%)	
		3	4 (20%)	4 (21.05%)	11 (61.11%)	
		4	13 (65%)	12 (63.16%)	6 (33.33%)	
	12 months	0	8 (40%)	9 (47.37%)	6 (33.33%)	0.877
		1	1 (5%)	1 (5.26%)	1 (5.56%)	
		2	-	1 (5.26%)	1 (5.56%)	
		3	5 (25%)	2 (10.53%)	5 (27.78%)	
		4	6 (30%)	6 (31.58%)	5 (27.78%)	
	p value*		**0.004**	**0.003**	**0.010**	

Table 7 (continued)

Species	Timepoint	Detection score	PERISOLV	CHX	placebo	*p*-value**
T.d	Baseline	0	3 (15%)	4 (21.05%)	2 (11.11%)	0.121
		1	–	4 (21.05%)	7 (38.89%)	
		2	11 (55%)	9 (47.37%)	6 (33.33%)	
		3	6 (30%)	2 (10.53%)	3 (16.67%)	
		4	–	–	–	
	12 months	0	9 (45%)	8 (42.10%)	6 (33.33%)	0.860
		1	3 (15%)	5 (26.32%)	5 (27.78%)	
		2	4 (20%)	5 (26.32%)	6 (27.78%)	
		3	4 (20%)	1 (5.26%)	1 (5.56%)	
		4	–	–	–	
	p value*		**0.005**	0.078	**0.040**	

Data presented as frequencies (%)

* Corresponding to Wilcoxon tests for intra-group comparison of pathogen detection scores between successive timepoints

** Corresponding to Kruskal–Wallis tests for inter-group comparisons of pathogen detection scores for each timepoint

However, in the present study, a reduced number of sites with PD = 7 mm (3 in the test and one in the placebo group) were re-instrumented.

In a clinical trial from 1998 on chronic periodontitis [7], the authors noted that the average number of bleeding pockets per patient doubled over 5 years of SPT. PPD of 5 mm seemed to represent a risk factor for tooth loss, whereas residual PPD ≥ 6 mm represented an incomplete periodontal treatment outcome requiring further therapy [8]. The most relevant parameters used to assess the capacity of maintaining periodontal health and making supportive treatment useful are the percentage of sites with BOP and prevalence of residual pockets > 4 mm [59, 60]. These two parameters are easily affected by therapy.

Concurrently, the influence residual inflammation evidenced by BOP on tooth loss was addressed in many studies [60, 61]. Thus, the absence of BOP and PPD ≤ 4 mm (closed pockets) as clinical endpoints of treatment success is justified [17, 18]. According to Chapple et al. [19], periodontal stability is defined by a successful treatment resulting in minimal BOP (< 10% of sites) and PPD < 4 mm. For other authors [62], the reduction of PPD on a physiological level of up to 3 mm, which is the clinical pocket closure, remains the most important end parameter for clinically applicable success estimation after periodontal treatment.

Previous studies have assessed the effect of various adjunctive topical antimicrobial products in enhancing the outcomes of subgingival re-instrumentation of residual pockets during SPT [6, 30–32]. A recent study about the benefit of enamel matrix derivative (EMD) as an adjunct to re-instrumentation of residual pockets [35] was conducted according to the recently published S3-level clinical guideline for the treatment of periodontitis [20]. In that study, the authors explored the benefits of EMD as an adjunct to re-instrumentation of residual deep pockets with a PPD of 5–8 mm. The primary outcome was the change in mean PPD after 6 months. A statistically significant additional benefit of 0.79 ± 1.3 mm was observed in the test group and could be maintained until 12 months (0.85 ± 1.1 mm). In the present study, an additional benefit of 0.99 ± 0.31 mm was attained after 6 months for the test group and was maintained at the 12-month timepoint (0.81 ± 0.38 mm), although it was not statistically significant.

Regarding the change of residual deep sites to sites with shallow probing depth (PPD ≤ 4 mm), the frequency of conversion amounted to 76% at the 6-month timepoint and 80% at the 12-month timepoint for the test sites, compared to 46% and 45% for the control sites. In the present study, the frequency of PPD reduction was 76.25% at the 6-month timepoint and 77.50% at the 12-month timepoint for the test group and 63.89% at the 6-month timepoint and 59.72% at the 12-month timepoint for the placebo group. In addition, for the primary outcome, pocket closure at the 12-month timepoint, a statistically significant effect was demonstrated in favor of the test group when compared with the placebo group ($P < 0.05$). Hence, the hypothesis of the study could be confirmed.

In our study, patients' level of hygiene improved markedly during the SPT. The intra-group analysis showed a statistically significant reduction in FMPS at the 12-month timepoint, compared to the baseline in all three groups (Wilcoxon test, $P < 0.05$), which in turn points to the excellent compliance of the patients.

In a previous study, the authors tested the probability of pocket closure after using locally delivered doxycycline as an adjunct to subgingival re-instrumentation [56]. The estimated probability for a site to reach the successful treatment endpoint of pocket closure (defined in the study as PPD ≤ 4 mm regardless BOP) was 45% at 3 months and 53% at 9 months for the test sites, compared to 46% and 45%, respectively, for the control sites. In the present study, the frequency of conversion of residual deep sites to sites with shallow probing depth (PPD ≤ 4 mm) attained 80.00% at 3 months and 76.25% at 9 months for test group, and 63.89% at 3 months and 63.89% at 9 months for placebo group, respectively. Previous studies [56] reported that the probability of pocket closure was not improved by the adjunctive topical doxycycline therapy. However, in our study, a statistically significant effect was demonstrated in favor of the test group, when compared to the placebo group at the 12-month timepoint. In the same study, the test group showed a mean PPD reduction of 1.1 mm after 9 months, which is consistent with our results. An additional benefit of 0.91 ± 0.42 mm was attained after 9 months in the test group and was maintained at the 12-month timepoint (0.81 ± 0.38) but was not statistically significant.

Our study revealed that repeated short USI during periodontal maintenance, with or without single adjunctive administration of antimicrobials, resulted in statistically significant improvements in mean CAL in all three groups at all timepoints, compared to baseline ($P < 0.05$). The inter-group analysis showed minor CAL improvements in favor of the Perisolv® group, when compared with both CHX and placebo groups (mean change, 0.70 ± 0.40 mm vs. 0.39 ± 0.38 mm and vs. 0.57 ± 0.50 mm at the 12-month timepoint). However, no statistically significant differences were found, except for the CAL changes in the Perisolv® group compared to the CHX group at the 6-month re-timepoint evaluation ($P = 0.0026$). These results are consistent with those reported in a previous clinical study with repeated topical administration of Perisolv® in 32 patients with at least 3 months of SPT [44]. The authors reported clinically relevant CAL gain and PD reduction of 1 mm in 1 year, without inducing further recession after 3 repeated short (1 min) USI with adjunctive administration of the antimicrobial product. Despite the measured improvements, no statistically significant difference was observed between the test and control (USI only). These results appear to suggest that a single topical administration of Perisolv® during periodontal re-instrumentation is sufficient to induce a clinically measurable effect.

It is important to consider that the participants of this study presented residual periodontal pockets, following active periodontal treatment consisting of nonsurgical or/and surgical therapy. A previous study [44] has suggested that the persistence of the pockets was caused by incomplete removal of microbial deposits during nonsurgical therapy.

Another study reporting on 202 periodontal maintenance participants (minimum of 6 months of SPT) with recurrent or persistent pockets, treated using USI (with [test] or without [control]). Participants received a slow-released doxycycline (SRD) in all residual periodontal pockets of > 4 mm [6]. Although the patients received a full cycle of periodontal therapy with periodontal surgery if indicated, a single topical administration of SRD caused a modest adjunctive benefit for 3 months only. These differences may on one hand be explained by differences in baseline PPD values (i.e., in the aforementioned study the PPD values measured ≥ 5 mm at baseline while in the present study the baseline values measured at least PPD ≥ 4 mm with BOP(+). One the other hand, the results might have also been influenced by the locally applied materials (i.e., SRD, Perisolv® and CHX, respectively).

Findings of a previous "in-vitro" study revealed that cell survival and repopulation of root surfaces is possible following either air polishing or application with Perisolv®. Moreover, it has been also shown that Perisolv® clearly reduces the vitality of the microorganisms despite failing to completely eliminate the biofilm [63]. Thus, the present study used air polishing only supragingivally to avoid influencing the outcomes of the use of Perisolv® in pockets deeper than 4 mm. At this point, it is important to mention that a statistically significant CAL gain was measured event after 6 months which in turn, points to the potential clinical relevance of using Perisolv® in residual pockets in patients enrolled in SPT.

The choice of the PCR method in the context of the currently accepted host-mediated dysbiosis of the subgingival microbiota associated with the exaggerated host response was based on the finding that recolonization by the key stone pathogen *P.g.* might play an important role in the pathogenesis of recurrent periodontitis during SPT [64] while other microbiological assessments of patients under SPT focused on the same bacteria as in our study [32, 44].The microbiological results showed no statistically significant differences among the groups at any timepoint. The intra-group comparison revealed a significant decrease in detection scores between baseline and the 12-month timepoint for *P.g.*, *P.i.*, *T.f.*, and *T.d.*. A statistically significant decrease was observed in the bacterial species, which presented relatively high counts at baseline. However, this was not the situation for *A.a.* which presented low counts at baseline with low frequency detection scores. These intra-group microbiological results compare favorably with those obtained in a similar study with repeated applications of Perisolv® [44]. The authors observed a statistically significant longitudinal reduction for only *T.f.* in the test group from baseline to day 7 and for *T.d.* from baseline to month 4. This reduction in the numbers of *T.f.* seems to correlate with the constantly improved FMPS score observed in all groups during the follow-up timepoints. Like in the above-mentioned study, no inter-group statistically significant differences were observed in our study.

Time of application and the costs of the antimicrobials are other factors that should be taken into consideration, even if not specifically addressed in our study. Since the time of

application for both products seem to be similar, an eventual cost difference between the two products could be compensated in time by the reduction of the number of residual pockets, as shown by our results in the Perisolv group. This may lead to fewer sites in need of re-instrumentation during the continuous care follow-up appointments.

Conclusion

Within their limits, the present results suggest that in patients treated for stage III–IV periodontitis and enrolled in SPT, treatment of residual pockets by means of subgingival USI and a single application of a sodium hypochlorite gel may lead to substantial clinical benefits evidenced by pocket closure.

Author contribution Conceptualization: Viorelia Radulescu, Stefan-Ioan Stratul; methodology: Darian Rusu, Giorgios Kardaras; formal analysis and investigation: Viorelia Radulescu; writing—original draft preparation: Marius Ion Boariu, Vincenzo Iorio Siciliano, Octavia Vela; writing—review and editing: Alexandra Roman, Petra Surlin, Andreea Cristiana Didilescu; supervision: Stefan-Ioan Stratul, Anton Sculean, Holger Jentsch, Luca Ramaglia.Viorelia Radulescu and Darian Rusu have equally contributed and can be both considered as first authors. All authors commented on previous versions of the manuscript, read, and approved the final manuscript.

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Declarations

Ethics approval The study was approved by the Research Ethics Committee of the Victor Babes University of Medicine and Pharmacy Timisoara (approval no.1/21.01.2018).

Informed consent All study participants provided written informed consent.

Conflict of interest The authors declare conflict of interest.

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Authors and Affiliations

Viorelia Radulescu[1] · Marius Ion Boariu[2] · Darian Rusu[1] · Alexandra Roman[3] · Petra Surlin[4] · Adrian Voicu[5] · Andreea Cristiana Didilescu[6] · Holger Jentsch[7] · Vincenzo Iorio Siciliano[8] · Luca Ramaglia[8] · Octavia Vela[1] · Giorgios Kardaras[1] · Anton Sculean[9] · Stefan-Ioan Stratul[1]

1 Department of Periodontology, Faculty of Dental Medicine, Anton Sculean Research Center for Periodontal and Peri-Implant Diseases, Victor Babes University of Medicine and Pharmacy, , Timisoara, Romania

2 Department of Endodontics, Faculty of Dental Medicine, TADERP Research Center, Victor Babes University of Medicine and Pharmacy, Timisoara, Romania

3 Department of Periodontology, Faculty of Dental Medicine, Applicative Periodontal Regeneration Research Unit, Iuliu Hatieganu University of Medicine and Pharmacy, Cluj Napoca, Romania

4 Department of Periodontology, Faculty of Dental Medicine, University of Medicine and Pharmacy, Craiova, Romania

5 Department of Informatics and Medical Biostatistics, Victor Babes University of Medicine and Pharmacy, Timisoara, Romania

6 Department of Embryology, Faculty of Dental Medicine, Carol Davila University of Medicine and Pharmacy, Bucuresti, Romania

7 Department of Cariology, Endodontology and Periodontology, Centre for Periodontology, University Hospital of Leipzig, Leipzig, Germany

8 Department of Periodontology, School of Dental Medicine, University of Naples Federico II, Naples, Italy

9 Department of Periodontology, University of Bern, Bern, Switzerland