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ORIGINAL ARTICLE

Treatment of residual pockets using an oscillating chitosan device versus regular curettes alone—A randomized, feasibility parallel-arm clinical trial

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Abstract

Background: A brush made of chitosan has shown to be an effective and harmless device for non-surgical treatment of mild to moderate peri-implantitis. To date, no study has evaluated the use of a chitosan brush in the non-surgical treatment of residual pockets in periodontal treatment.

Methods: Seventy-eight patients with periodontitis were included in this multicenter, randomized, examiner-blind clinical trial of 6 months duration. Patients with residual probing pocket depth (PPD) of ≥5 mm and ≤7 mm following previous active periodontal treatment were included. Patients were assigned either subgingival treatment with curettes (control) or an oscillating chitosan brush (test). Changes in bleeding on probing (BoP) and PPD between baseline and terminal evaluation at 6 months were evaluated.

Results: A significant reduction in both PPD and BoP was seen within both groups. There was no significant difference in BoP between test and control groups after 6 months, but the reduction in PPD was significantly improved in the test group ($P \leq 0.01$). The combined outcome of no BOP and PPD ≤4 mm was significantly better in the test group ($P \leq 0.01$). No adverse reactions were seen.

Conclusion: Treatment of residual periodontal pockets (PPD = 5 to 7 mm) with a chitosan brush disclosed equal or better clinical results as compared to regular curettes. This study supports that a chitosan brush can be used for subgingival biofilm removal and soft tissue curretage in the treatment of periodontitis.

KEYWORDS
chitosan, clinical trial, periodontal debridement, periodontitis, subgingival curettage

1 | INTRODUCTION

Periodontal disease, characterized by soft-tissue inflammation and the loss of attachment around teeth,[1] is associated with plaque biofilm dysbiosis.[2] Active treatment of periodontitis involves initial professional mechanical debridement and infection control together with meticulous patient homecare, individualized measures of oral hygiene[3] and further surgical treatment according to the individual needs in the more advanced cases.[4] The loss of periodontal support is manifested through clinical attachment loss (AL), alveolar bone loss as seen

radiographically and the presence of probing pocket depths (PPDs).[2] Bleeding on probing (BoP) is also an indication of inflammation.[2,5]

A longstanding goal has been to control and prevent disease progression by means of improvements in clinical parameters (such as PPD and BoP) and hence avoid tooth loss. Research on the non-surgical treatment of periodontitis has revealed varying results.[6–8] Although some new treatment methods and devices have shown promising results; they have generally not been found to be significantly better than the conventional mechanical approaches, such as scaling and root planing.[3,9] Various numbers of remaining deep and inflamed sites are also common following non-surgical treatment. Such residual pockets are associated with disease progression, and the treatment for such sites is unpredictable.[10] Periodontal pockets not responding to non-surgical therapy may again be reduced surgically, but the cost and morbidity is relatively high.[10] The development of more efficient methods for non-surgical periodontal therapy is thus of significant interest and is still an active research area.

Chitosan, a biodegradable and biocompatible biopolymer, may potentially be an useful candidate for various type of treatment of periodontal disease.[11] The chitosan used in the brush filaments is derived from chitin from the shell of marine crustaceans. Chitosan has been approved for use in, for example, surgical bandages, as a hemostatic agent and as a dietary supplement in several nutritional and health products.[11] Moreover chitosan has been documented to be non-allergenic, and it has been suggested that chitosan has anti-inflammatory properties[12] and antimicrobial effects.[13] In an experimental study on rats, the antibacterial activity as well as improvements in alveolar bone properties have been reported.[14] Additionally, a recent study revealed the potential of chitosan to facilitate bone remodeling.[15] The aforementioned studies clearly indicate a potential for chitosan in periodontal treatment; however, there have been limited clinical studies evaluating the effects of chitosan in the treatment of periodontal disease. In one clinical study, a chitosan gel was used as a carrier for antibiotics and evaluated as an active agent in the treatment of periodontitis.[16] The study revealed significant improvements in clinical parameters, such as PPD.[16] It has in addition been demonstrated that a chitosan brush is an effective and harmless device for non-surgical treatment of peri-implant disease.[17] Chitosan may offer potential in the treatment of periodontal disease beyond its mechanical cleaning effect on root surfaces, and further clinical studies are of significant interest.

The aim of the study was to evaluate non-surgical treatment using a novel chitosan brush versus conventional curettes in patients with moderate to severe periodontitis and the primary outcome was an improvement in clinical parameters of periodontal inflammation (PPD and BoP) up to 6 months after initial therapy. The null hypothesis was no significant difference in the reduction in periodontal parameters after subgingival debridement with a chitosan brush versus subgingival debridement with curettes after 6 months.

2 | MATERIALS AND METHODS

The study was registered at ClinicalTrials.gov (NCT04173156) and approved by the regional ethical board (2017/707/REK Sør-Øst D), Oslo, Norway. The study was conducted in accordance with the Helsinki Declaration as revised in 2013. Signed informed consent was obtained before the start of the study, and patients were enrolled and treated consecutively between October 2017 and December 2019 at two different specialist clinics for periodontology: Department of Periodontology, Yeditepe University School of Dentistry, Istanbul, Turkey and Bjerke Tannmedisin, Oslo, Norway.

2.1 | Study design and examinations

Patients with Stage III and IV, Grade B periodontitis[2] were included in this prospective, multicentre, parallel-arm, feasibility randomized clinical trial of 6 months' duration. All included subjects had previously undergone active periodontal treatment, including either non-surgical or surgical therapy, but this treatment had been terminated at least 6 months before inclusion. The patients had persistent or reoccurring deep residual periodontal pockets. The eligibility of the patients for the study was initially evaluated with the following inclusion criteria: at least three, but less than eight teeth presenting sites with clinical AL ≥5 mm, a residual probing pocket depth (PPD) of ≥5 mm and ≤7 mm and inflammation demonstrated by the presence of BoP.[18] The included sites should be plaque-free (supraginigvally) and the full-mouth scores should be ≤20% before final inclusion and treatment. All patients were individually instructed in plaque removal techniques prior to inclusion. Modified Stillman and Bass technique was instructed,[19] and appropriate interdental brushes were recommended based on the size of the interdental space and anatomy (presence of furcations, root surface concavities and tooth alignment).[19] Instructions included insertion of the brush through the interproximal space and movement of the brush, back and forth, between the teeth with short strokes.[19]

Screened patients were included if they met the following conditions:

1. Had periodontitis as previously defined on at least three teeth but less than eight teeth;

2. were > 18 years of age;
3. were eligible for treatment in an outpatient dental clinic (i.e., ASA I and II);
4. had full-mouth plaque scores ≤20% before final inclusion;
5. provided informed consent before starting;
6. was psychologically fit; and
7. consented to complete all follow-up visits.

The patients were excluded if they met any of the following conditions:

1. Had prosthetic constructions with technical complications that according to the examiner's judgement had contributed to the disease state and were not possible to resolve before final inclusion;
2. had received systemic antibiotics within 3 months of starting the study;
3. were pregnant or lactating;
4. had any underlying condition or were receiving treatment, which in the opinion of the investigator or consulting physician, may constitute an unwarranted risk;
5. presented psychological characteristics, such as an inappropriate attitude or a lack of motivation, that in the opinion of the investigator were incompatible with the protocol;
6. were unwilling to undergo treatment;
7. were undergoing or had radiotherapy in the head–neck region; and
8. were undergoing chemotherapy.

The plaque index (PI),[20] PPD and BoP as clinical parameters were recorded at baseline and 6 months. The intraoral radiographies were taken and general dental status was also recorded. Clinical screening included a routine history and physical examination, meeting the admission criteria and providing signed informed consent. Patient screening, inclusions and all clinical examinations were performed by a board-certified specialist in periodontology at the test centres and all the study examiners were blinded (one examiner at each treatment center, JCW and BEK). Treatment was performed by a registered dentist or dental hygienist (HG and DE) separate from the examiners and all clinical procedures were conducted according to a standardised protocoll agreed upon between the participating therapists. Treatment was performed by the same therapist at baseline and at 6 months with the same examiner at 6 months and baseline.

Patients were allocated to one of the treatment groups (control or test), and the allocation was done by computer-generated block randomization to ensure equal sample sizes. The main outcome measure (change in PPD from baseline to 6 months) was used to determine the sample size. Detecting a 1 mm difference in PPD change between the group was set and $\alpha = 0.05$ and a power of $\beta = 0.9$, the appropriate number of subjects per group would be 23. Inclusion of 40 subjects in each treatment center was done to stay within the limit, because of possible drop-outs.

2.2 | Treatment procedure

Full-mouth, supra-gingival debridement to remove supragingival calculus was performed on all patients using USS (ultrasonic scaling). Thereafter, the following treatments were applied to the allocated patients.

1. Control group: Periodontal pockets were debrided using commercially available, area-specific periodontal curettes[*] for 2 minutes. Debridement included scaling, removal of any calculus detected and planing of the roots.
2. Test group: The periodontal pockets were debrided with the chitosan brush[†] seated in an oscillating dental handpiece,[‡] with a gentle probing movement in a circular fashion around each included tooth, for 2 minutes per tooth. The chitosan brush aims at soft tissue curettage and primarily removing biofilm subgingivally.

All sites were irrigated with sterile saline after the completion of sub-gingival instrumentation in both groups. Debridement was performed at baseline and repeated at 3 months with the terminal examination undertaken at 6 months. The treatment- and evaluation timeline is disclosed in Figure 1.

2.3 | Outcome measures

The primary outcome variable was the change in PPD and BoP after 6 months. PPD was recorded at six sites (mesio-buccal, buccal, disto-buccal, disto-palatal, palatal, mesio-palatal) around each included tooth using a regular periodontal probe.[§] BoP was assessed using a modified four-graded index[21] (0 = no bleeding; 1 = a bleeding spot; 2 = a bleeding line; 3 = pronounced bleeding) within 30 seconds following probing of the pocket. However, for the statistical analysis it was created a dichotmous scale (BoP/no BoP).[18] Suppuration at the included sites was

[*] Gracey system, Hu-Friedy Mfg LLC, Chicago, IL.
[†] Labrida BioClean, Labrida AS, Oslo, Norway.
[‡] NSK, NAKANISHI INC., Kanuma, Japan.
[§] American Eagle Instruments, Algonquin, IL.

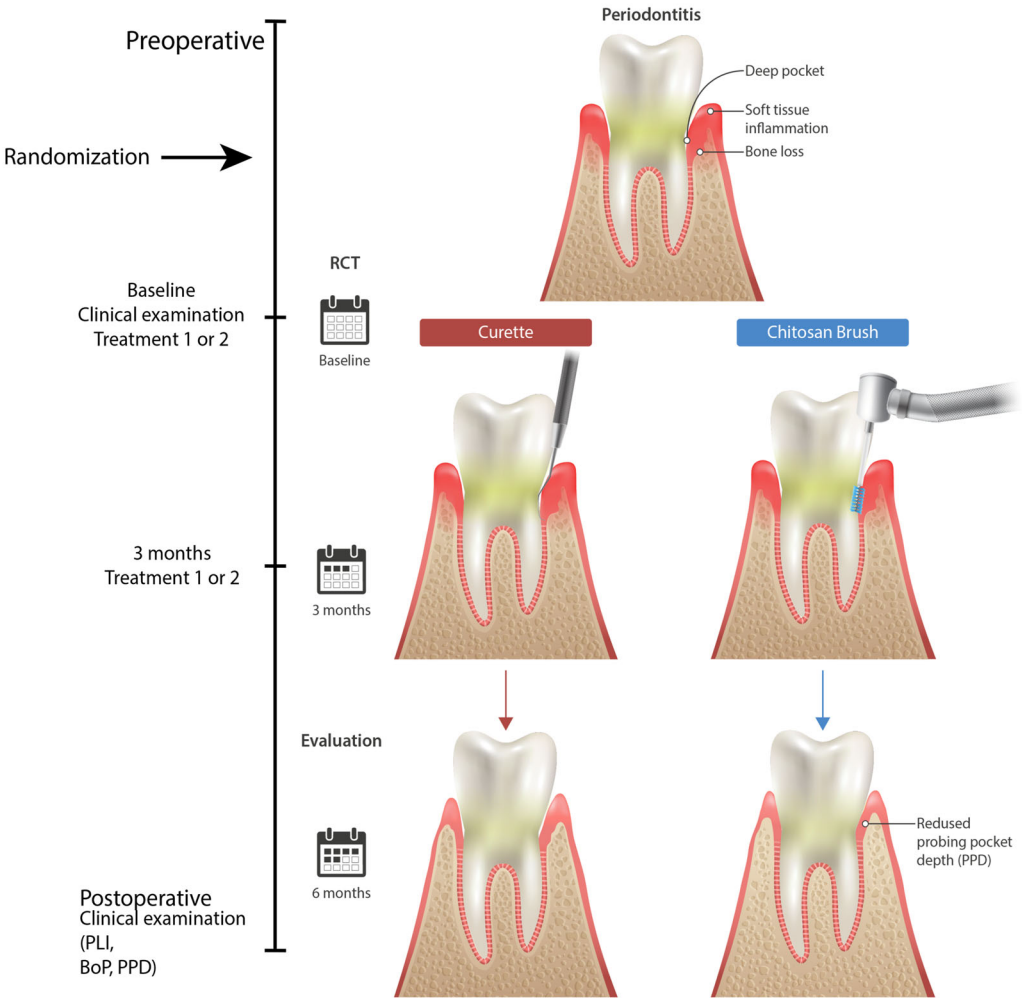

FIGURE 1 Treatment and evaluation timeline

recorded using dichotomous scoring. The furcations on a scale of I–III[22] were recorded with a Nabers probe. Plaque score were recorded both for the full dentition and separately at the included sites using the PI system (scale from 0 to 3).[20]

A comparison between the test and control sites over the 6 months was performed by recording changes in PPD and BoP.

2.4 | Adverse event evaluation and reporting

The recording of any adverse event, injury or negative effect was performed at 3 and 6 months. All patients were asked if they had experienced any discomfort or swelling.

2.5 | Statistical analysis

Clinical parameters evaluated on a periodontal site basis, were compared between baseline and 6 months, first within each group, then between the groups by using StataSE 16 (StataCorp, College Station, Texas, USA). A difference variable was generated in the groups for each parameter (difference between 6 months and baseline). This variable was in good agreement with the normal distribution (Shapiro Wilk) of the main outcome variable (PPD), hence paired and independent *t*-tests were used for each of the groups and between the groups, respectively. A two-sided statistical test was used because both positive and potential negative outcomes were possible. Results are presented as mean values and standard deviations.

Non-parametric analysis (Mann-Whitney) was performed as a control and for the variables that were not normally distributed. Additionally, the pockets at 6 months

that were ≤4 mm were compared between the test and control groups for evaluating the need for surgery using non-parametric analysis (Mann-Whitney). A chi-square test was performed to evaluate sites with an outcome showing the composite of PPD ≤4 mm and no BoP.

Further, statistical analysis was also conducted on each treatment centre separately as a control to check for center effects.

Regression models were computed on patient level, using longituidal analysis of covariance.[23] The periodontal parameters (PPD and BoP) were used as outcome/dependent variable and treatment as the exposure variable. One regression analysis for each of the clinical parameter was conducted. A stepwise linear regression was computed for PPD and a logistic regression for BoP, for this dichotomous outcome the OR was converted to coefficient values. Baseline values were adjusted for in these models.[23] Adjustment for cofounding variables was evaluated and adjusted if necessary in order to get the best fitted model (former smoker, current smoker, sex, diabetes).

Data were analyzed on an intention to treat basis and included all randomized patients were the outcome was available.

A P-value < 0.05 was considered statistically significant in all analyses.

3 | RESULTS

Eighty-three patients were enrolled, 40 in Istanbul and 43 in Oslo. After the exclusion of five patients, 40 patients in the test group and 38 patients in the control groups were finally included in the analysis as disclosed in Figure 2. There were 291 sites in the test group to be evaluated and 269 sites in the control group.

The demographics of the patients are presented in Table . The distribution of BoP and PPD in the two groups was not different at baseline ($P = 0.689$ and $P = 0.252$, respectively). The mean reduction in PPD and BoP with the standard deviation and confidence interval (CI) is presented in Table 2. Both groups demonstrated significant reductions in clinical parameters (BoP and PPD) between the baseline and 6 months' post-intervention ($P \leq 0.01$) (Table 2 and Figure 3A). The distribution of PPD at baseline and at 6 months is presented in Table 1 and Supplementary Table S1 (in the online *Journal of Periodontology*), respectively. The test sites treated with the chitosan brush demonstrated significantly more reduction in PPD at 6 months compared with the sites treated with the control method ($P \leq 0.01$) (Table 2) (Figure 3B). No significant difference in BoP was observed between the groups.

Supplementary Table S1 displays the frequency distribution for change in PPD; the negative values present a decrease in PPD, whereas positive values indicate an increase in PPD. Of the sites in the test group, 78% of the sites demonstrated a reduction in PPD of ≥1 mm as compared to the control group, where a reduction of ≥1 mm was seen in 69% of the patients' sites ($P \leq 0.02$).

In the test group, 65% of sites had a PPD ≤4 mm at 6 months, compared to 45% in the control group ($P \leq 0.01$). The composite outcome of PPD ≤4 mm and the absence of BoP was significantly improved in the test group, with 51% of the pockets compared to 32% in the control group ($P \leq 0.01$) (Table 3).

No significant difference was seen in the results between the two treatment centers (Oslo and Istanbul). No adverse reactions were observed based on clinical observations.

Regression coefficients are reported in Supplementary Table S2 and Table S3 in the online *Journal of Periodontology*, analysis conducted on patient-level. Test treatment showed a significant reduction in PPD as reported at site level, the coefficients for cofounding variables were in addition evaluated and the adjusted values for the main outcome measure was −0.62, with CI [−0.92 to −0.31], P value ($P \leq 0.001$). Even though alone sex and furcation were significant when evaluating PPD at 6 months, in the adjusted model (with the best fit) they did not show significant values.

The difference in BoP was not significant and none of the cofounding variables displayed significant coefficient values (Supplementary Table S3).

The tests on patient level is in line with the tests on site level.

4 | DISCUSSION

Chitosan has shown many favorable qualities in lab- and preclinical studies,[13–15] yet research on the clinical use of chitosan in periodontal treatment is scarce. Results from the present study indicate that using a chitosan brush subgingivally is beneficial in terms of improvement in pocket depth. Both the test and control groups showed a statistically significant reduction in BoP and PPD, but a significant improvement in PPD was seen at sites treated with the chitosan brush. Clinically pocket depths are used as a guideline in treatment modality decision;[24] when evaluating PPD at 6 months, it was disclosed that 66% of the pockets were ≤4 mm in the test group (Supplementary Table S1) hence, making surgery unnecessary[25] compared to 45% in the control group (Supplementary Table S1). Studies have suggested that patients with PPD of ≥5 mm after periodontal treatment should undergo surgical treatment.[25–28]

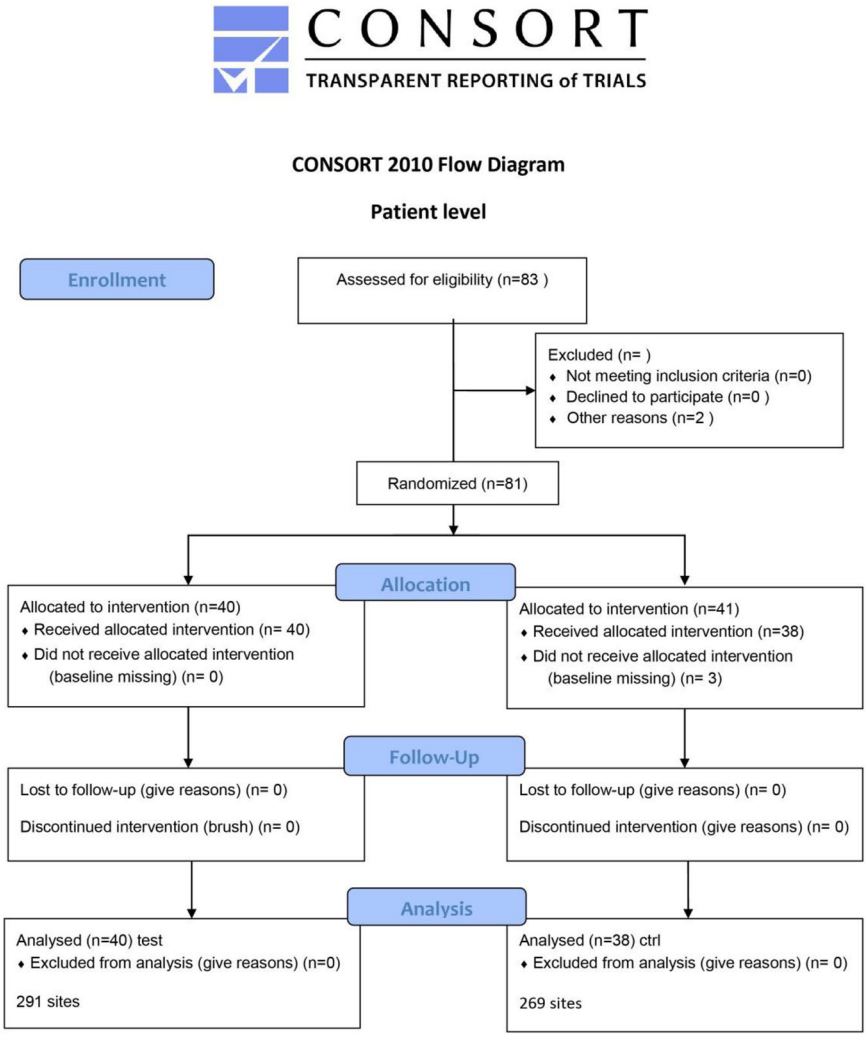

FIGURE 2 CONSORT diagram (flow diagram)

Based on the results from this study, it is suggested that in 66% of the sites in the test group surgery could be avoided compared to 45% in the control group. A significant number of patients find surgical treatment painful,[29,30] thus reducing the need for periodontal surgery is of significant interest from the perspectives of patient morbidity, debilitation and economic factors.[31] The combined outcome of no BoP and PPD ≤4 mm were in addition significantly improved in the test group, resulting in 51% healthy sites in the test group compared to 32% in the control group (Table 3). This analysis is based on the values at 6 months, and to validate this result a calibration should have been done, questioning the significant result of this specific outcome.

The presence of deep residual pockets is a common finding in periodontal practice, and further treatment is recommended.[32] It has been reported that surgery provides more stable PPD reduction over time[33] compared to non-surgical treatment, where the results vary. Although deep residual periodontal pockets along with a positive BoP score has been reported to represent a risk for progression in bone loss,[32] the literature on this field is relatively deficient;[10] which highlights the importance of further studies on the treatment of residual pockets. The regression analysis in the present study also emphasized that molars and teeth with furcation involvement grade I had less PPD reduction than other sites. This is a common finding in periodontal treatment, where treatment of multirooted teeth is more challenging,[34] making it even more crucial to evaluate treatment of these sites and pockets.

The present study has strengths and limitations. Among the strengths is the multicenter design with both a private practice and a university clinic in two different countries. In addition, no center effect was seen, and the number of patients were evenly distributed between the centers. Only a few studies provide sufficient follow-up when

TABLE 1 Demographic data of patients and baseline measurements (BoP and PPD)

Demographic data of patients		Test group	Control group
	Variable		
Patients	Male/Female	13/27	18/20
	Smoker	5	5
	Former smoker	15	10
	Diabetes	1	1
Site level	Anterior/Premolar/Molar	43/37/211	59/53/157
	Furcation involvement	94	79
BoP baseline			
0 (n)		9	7
1 (n)		126	126
2 (n)		135	96
3 (n)		21	40
Mean BoP		1.57 (SD: 0.67)	1.63 (SD:0.76)
Median BoP		2 [1-2]	2 [1-2]
P-value			0.689[a]
PPD baseline			
5 mm (n)		195	156
6 mm (n)		59	85
7 mm (n)		37	28
Mean PPD		5.46 (SD:0.04)	5.45 (SD:0.71)
Median PPD		5 [5-5]	5 [5-5]
P-value			0.253[a]

Abbreviations: BoP, bleeding on probing; PPD, probing pocket depth.
[a]Statistical test Mann-Whitney.

TABLE 2 Mean, standard deviation, and CI for reduction in PPD and BoP (6 months ÷ baseline)

Variable	Test group	Control group	Intra-group mean (difference)
Reduction in PPD (mean mm±SD) [CI]	−1.37 ± 0.07 [−1.52– −1.24]	−0.86 ± 0.06 [−0.98 – −0.74]	0.51 ± 0.09 [0.32 – 0.69]
P-value[a]	≤ 0.01	≤ 0.01	≤ 0.01
Reduction in BoP (mean value ± SD) [CI]	−0.53 ± 0.04 [−0.60 – −0.45]	−0.51 ± 0.04 [−0.60 – −0.43]	0.01 ± 0.06 [−0.09 – 0.123]
P-value[b]	≤ 0.01	≤ 0.01	= 0.841

Abbreviations: BoP, bleeding on probing; PPD, probing pocket depth.
[a]*t*-test (mean comparison test).
[b]Mann-Whitney intra-group and Wilcoxon matched-pair signed rank intergroup.

evaluating non-surgical treatment of residual pockets, which is among the limitations of our study. Another limitation is the possible heterogeneity among patients.

TABLE 3 Proportion of sites with PPD ≤4 mm and no BOP

	Test	Control	*P*-value[a]
Baseline	0/291	0/269	
6 months	147/291	85/291	≤0.01
	51%	32%	

Abbreviations: BoP, bleeding on probing; PPD, probing pocket depth.
[a]Chi-square test.

Patients have had periodontal treatment at least 6 months before the inclusion; ideally, this initial periodontal treatment should have been a part of the protocol. However, the treatment was terminated at least 6 months before inclusion and teeth included had remaining residual pockets.

The clinical effect of the brush seen in this study is attributed to subgingival biofilm removal on the root surface, without damaging the root surface and in addtion soft tissue curettage. A site-spesific curette, as used in the present study, will not currettage soft tissue hence the significant reduction may be attributed to gingival curretage. Although the American Academy of

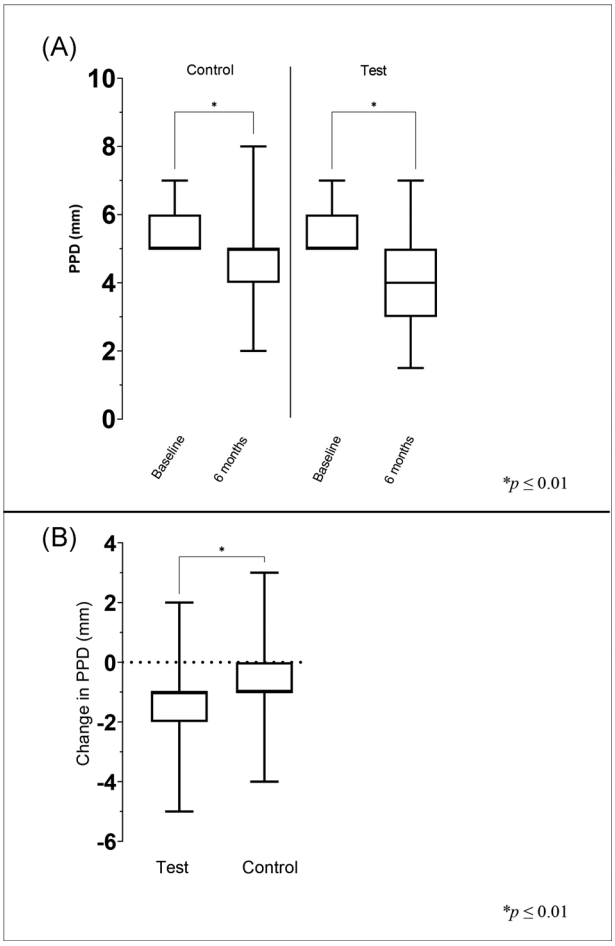

FIGURE 3 (**A**) Probing pocket depth (PPD) at baseline and 6 months for the control and test groups. (**B**) Change in PPD (6 months ÷ baseline) for the test and control groups

Periodontology (AAP) has stated that there is no benefit to subgingival curettage,[35] this study shows that there is a significant reduction in PPD with curettage. Further research combining a chitosan brush with adjunct chemical agents would be interesting to consider in non-surgical treatment of periodontitis. A number of studies on adjunctive antibiotics in addition to non-surgical treatment for poor responders have been published.[36,37] One recent systematic review provided a low level of evidence for the adjunctive use of systemic antibiotics in non-surgical treatment.[38] Similarly, adjunctive use of local antibiotics showed limited results,[39] in line with a study conducted by Tomasi et al.[40] However, other studies have shown beneficial effects of using antimicrobials[41] depending on the type of antimicrobial.[42] The use of adjunctive antiseptics, like chlorhexidine, has revealed additional beneficial effects in non-surgical treatment,[43,44] but such results have been debated by other authors.[45,46]

In this study, the broadly accepted metric of recording changes in PPD and BoP was used as a surrogate marker for active periodontal disease.[2] However, several studies have suggested other biomarkers for disease activity and for monitoring treatment outcome.[47–49] Although such biomarkers might be better indicators for future disease progression,[50] research is still in the early phases. One recent study looked at salivary proteins C3 and C3cy, and high levels of these proteins correlated with poor responses to treatment.[50] Evaluating other biomarkers in addition to these clinical results may be interesting from the perspective of detailed information on the treatment outcome. In addition, evaluating the consistency of PPD over a more extended follow-up period would provide a better prediction of the maintenance interval and outcome. Hence, long-term studies combining the chitosan brush with antimicrobial agents or evaluation of biochemical markers for change in inflammation after treatment are of future interest.

5 | CONCLUSION

Within the limits of this study, a chitosan brush for the treatment of residual deep periodontal pockets in patients with moderate to severe periodontal disease demonstrated significantly improved PPD reductions up to 6 months after baseline, as compared to a conventional treatment. Improvement in BoP was seen in both groups and no adverse events were observed.

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CONFLICTS OF INTEREST

Dr. Wohlfahrt is the inventor and patent holder of Labrida BioClean and is a shareholder in Labrida AS (Oslo, Norway). The test devices (Labrida BioClean) were provided by Labrida AS. Prof. Håvard J. Haugen is a minor shareholder in Labrida AS. The remaining authors report no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available because of privacy or ethical restrictions.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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