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Non-surgical treatment of mild to moderate peri-implantitis with an oscillating chitosan brush or a titanium curette—12-month follow-up of a multicenter randomized clinical trial

Sadia N. Khan[1] | Odd Carsten Koldsland[2] | Ann-Marie Roos-Jansåker[3,4] | Johan Caspar Wohlfahrt[2] | Anders Verket[2] | Ibrahimu Mdala[5] | Anna Magnusson[6] | Eirik Salvesen[7] | Carl Hjortsjö[1]

[1]Department of Prosthetics and Oral Function, Institute of Clinical Dentistry, Faculty of Dentistry, University of Oslo, Oslo, Norway

[2]Department of Periodontology, Institute of Clinical Dentistry, Faculty of Dentistry, University of Oslo, Oslo, Norway

[3]Department of Periodontology, Faculty of Odontology, Malmö University, Malmö, Sweden

[4]Department of Periodontology, Blekinge Hospital, Karlskrona, Sweden

[5]Department of General Practice, University of Oslo, Oslo, Norway

[6]Department of Periodontology, Faculty of Medicine and Health, School of Medical Sciences, Orebro University, Orebro, Sweden

[7]Private Practice, Stavanger, Norway

Correspondence
Sadia N. Khan, Department of Prosthetics and Oral Function, Institute for Clinical Dentistry, Faculty of Dentistry, University of Oslo, PO. Box 1109, Oslo 0317, Norway.
Email: sadiak@odont.uio.no

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Abstract

Objectives: To study clinical and radiographic outcomes after non-surgical treatment of peri-implantitis using either an oscillating chitosan brush (OCB) or titanium curette (TC) and to observe changes in clinical signs of inflammation after repeated treatment.

Methods: Thirty-nine patients with dental implants (n = 39) presented with radiographic bone level (RBL) of 2–4 mm, bleeding index (BI) ≥ 2, and probing pocket depth (PPD) ≥ 4 mm were randomly assigned to mechanical debridement with OCB (test) or TC (control). Treatment was performed at baseline and repeated at 3, 6, and 9 months in cases with > 1 implant site with BI ≥ 1 and PPD≥4 mm. Blinded examiners recorded PPD, BI, pus, and plaque. The radiographic bone level change between baseline and 12 months was calculated. A multistate model was used to calculate transitions of BI.

Results: Thirty-one patients completed the study. Both groups exhibited a significant reduction in PPD, BI, and pus at 12 months compared to baseline. Radiographic analysis showed stable mean RBL in both groups at 12 months. There was no statistically significant difference in any of the parameters between the groups.

Conclusions: Within the limitations of this 12-month multicenter randomized clinical trial, non-surgical treatment of peri-implantitis with OCB or TC showed no statistically significant differences between the groups. Clinical improvements and, in some cases, disease resolution, was observed in both groups. However, persistent inflammation was a common finding which further puts emphasis on the need for further treatment.

KEYWORDS
clinical trial, dental implants, peri-implantitis, titanium

Key findings: Clinical signs of inflammation were reduced in both groups at 12 months compared to baseline, but no statistically significant intergroup differences were observed.

Clinical trials registration: The study was registered at ClinicalTrials.gov (12/08/2017, NCT03373448).

1 | INTRODUCTION

Peri-implantitis, defined as biofilm-associated inflammation in peri-implant mucosa and progressive peri-implant bone loss (Berglundh et al., 1992, 2018), affects approximately 30% of all dental implants (Romandini et al., 2021). It is a widespread but false understanding that 'implants are for life' and that implants are better than teeth. Many patients have exaggerated expectations of rehabilitation with dental implants. Thus, biological complications such as peri-implantitis can be challenging for patients and clinicians (Abrahamsson et al., 2017; Insua et al., 2017).

The prevalence of peri-implantitis has been reported to vary between 1% and 47% on the patient level. Various disease definitions explain the significant variations in reported prevalence numbers (Derks & Tomasi, 2015). This issue was addressed at the World Workshop on the Classification of Periodontal and Peri-implant Diseases and Conditions (Berglundh et al., 2018). A case definition was proposed based on three criteria; (1) the presence of peri-implant signs of inflammation, (2) radiographic evidence of bone loss following initial bone remodeling, and (3) increased probing pocket depth (PPD) compared to probing depth measurements after prosthetic loading of the implant. Since baseline radiographs and probing depths are not always available, it was proposed that peri-implantitis diagnosis be based on radiographic bone level ≥3 mm combined with bleeding on probing (BoP) and PPD ≥ 6 mm. Studies employing similar definitions reported prevalence numbers of approximately 15% on the patient level after 9–14 years of function (Derks et al., 2016; Roos-Jansaker et al., 2006).

Biofilm accumulation is considered the main etiological factor for the inflammatory response in peri-implant soft- and hard tissues (Berglundh et al., 1992, 2018). The treatment focuses on controlling the inflammation by reducing the bacterial load around the infected implant (Renvert et al., 2019). A comparison of surgical versus non-surgical treatment has demonstrated superior outcomes for surgical approaches in cases with deeper peri-implant pockets (Polyzois, 2019). Although the non-surgical treatment of peri-implantitis is unpredictable, studies have also reported efficacious non-surgical protocols (Machtei et al., 2021). Early intervention, at a bone loss of 2–4 mm, is preferable as the outcome of surgical intervention largely depends on the amount of bone loss at the implant (Koldsland et al., 2018; Serino & Turri, 2011). Given the prevalence of peri-implantitis, non-surgical methods may reduce the treatment burden on specialist teams as general practitioners and dental hygienists may perform the treatment.

Furthermore, non-surgical methods generally require fewer resources from the dental team. Non-surgical treatment may be performed before surgical treatment, allowing the clinician to assess the peri-implant tissues´ response to treatment (Polyzois, 2019) and reduce the microbial load before surgery. Non-surgical intervention may also reduce the degree of inflammation and thereby facilitate surgical treatment (Schwarz et al., 2015). Developing effective non-surgical treatment methods is essential for treating patients where surgical treatment is contraindicated or for patients unwilling to undergo surgery. Surgical treatment may lead to soft tissue recession and influence the esthetic outcome in cases with high smile lines (Montero et al., 2022).

The affected implant's short- and long-term re-evaluation is indicated due to constant changes in plaque and inflammation (Polyzois, 2019). Outcomes of a recent multicenter randomized controlled clinical trial (RCT) demonstrated reductions in inflammatory parameters but rarely disease resolution when treatment was performed non-surgically with an oscillating chitosan brush (OCB) or titanium curettes (TC; Khan et al., 2022). Similar findings with a reduction in bleeding sites but no reduction in PPD and stable RBL were observed when implants were non-surgically treated with carbon fiber curettes or a Vector® system (Karring et al., 2005). Karring et al. (2005) defined peri-implantitis as BOP, PPD ≥5 mm, 1.5 mm radiographic bone loss, and exposed implant threads. Renvert et al. (2009) reported equivalent findings, with incomplete resolution of peri-implant inflammation 6 months after initial non-surgical treatment with titanium curettes or an ultrasonic device. Although eradication of the disease is rare, a decrease in inflammation seems to be a common feature in RCTs with shorter follow-up times and repeated non-surgical intervention (Karring et al., 2005; Sahm et al., 2011). The efficacy of repeated therapy over time has been evaluated for peri-implant mucositis, peri-implantitis, and after peri-implantitis surgery (Bassetti et al., 2014; Koldsland & Aass, 2020; Riben-Grundstrom et al., 2015). Despite post-surgical follow-up and repeated treatments every third month, peri-implant bleeding was observed 18 months after the first follow-up (Koldsland & Aass, 2020). For mucositis and peri-implantitis, a decrease in diseased sites was observed after repeated treatments and follow-up for 12 months. Clinical follow-ups and retreatments seem crucial considering the non-linear and progressive bone loss pattern in peri-implantitis (Berglundh et al., 2018).

Using a graded bleeding score may be beneficial in evaluating patients´ risk of destructive disease (Newbrun, 1996). Bleeding Index (BI; Roos-Jansåker et al., 2007) allows for identifying sites at risk of further bone destruction. Because BI includes four degrees of bleeding scores (0 = no bleeding, 1 = bleeding spot, 2 = bleeding line, 3 = profuse bleeding), it may be used to estimate the probability of transitions from one state to another. The likelihood of disease progression for periodontitis has been estimated using multistate Markov models (Mdala et al., 2014). Markov models are helpful when a condition involves a persistent risk. Markov models estimate the transition from one state to another for chronic diseases with a staged progression. There is a need to understand disease development in healthy and diseased peri-implant sites to reduce mortality and choose the proper treatment intervention and frequency. To our knowledge, transition analysis for clinical inflammation parameters for peri-implantitis has not been performed per se.

The present multicenter RCT aimed to evaluate repeated non-surgical treatment of peri-implantitis with an OCB or a TC. This study assessed changes in the following parameters: PPD, BI, presence of pus, and RBL 12 months after initial treatment (Sanz & Chapple, 2012). Furthermore, implant sites with and without inflammation were evaluated by assessing the transitions for BI scores during the study period.

2 | MATERIALS AND METHODS

2.1 | Study design

This randomized, prospective, two-arm, multicenter, controlled clinical trial including five specialist dental practices. The study was registered at clinicaltrials.gov (NCT03373448). Research ethical boards approved the trial in Norway and Sweden (REK south-east 2017/710, Linköping (EPN 2017/36–31). The study was conducted according to the principles in the Declaration of Helsinki (Fortaleza, Brazil). Good clinical practice (GCP) for medical devices and the Consolidation Standards of Reporting Trials (CONSORT) guidelines for clinical trials were followed (Schulz et al., 2010). A calibration meeting was held to discuss the study protocol prior to the study start. The detailed clinical protocol and study design have been published (Khan et al., 2022).

2.2 | Primary and secondary outcome variables

The primary outcome was a change in PPD. Secondary outcome variables included changes in BI, pus, and RBL.

2.3 | Sample size assessment and power

The calculation of the required sample size was based on the primary outcome; PPD. Alpha was set as 5%. To detect a difference of 1 mm for PPD between the groups, 17 patients per group were required to provide 80% statistical power (ß = 0.2).

2.4 | Study population

Patients diagnosed with peri-implantitis (mild/moderate) in dental specialist practices between April 2018 and February 2020 were invited to participate in the study. Mild to moderate peri-implantitis was defined as 2–4 mm radiographic reduction in peri-implant bone level, PPD ≥4 mm, and BI ≥2. One implant per patient was included in the study. Once patients had given written informed consent, they were randomly allocated to the test or control group.

Patients were included based on the following criteria:

1. Peri-implantitis as defined on an implant in function for more than 12 months.
2. Age ≥ 18 years.
3. Eligible for treatment in a dental clinic (ASA I and II, American Society of Anesthesiologists).
4. Full-mouth plaque scores ≤20% at the study start.
5. No plaque at the included implant.
6. Informed consent.
7. Consent to complete all follow-ups.

Patients were excluded based on the following criteria:

1. Supraconstructions that made it impossible to access the implant for clinical measurements.
2. Technical complications which had contributed to peri-implantitis and were not possible to resolve before final inclusion.
3. Mobile implant.
4. Active periodontal disease.
5. Implants treated for peri-implantitis with grafting materials.
6. Mucosal hyperplasia-inducing medications.
7. Systemic antibiotics ≤3 months prior to inclusion.
8. Acute or chronic medical conditions that would limit the patients´ ability to participate in the trial.
9. Advanced and uncontrolled peri-implantitis on proximate implants.
10. Patients presented with severely overloaded implants.
11. Previous or current radiotherapy to the head–neck region.
12. Current chemotherapy.
13. Current corticosteroid treatment.

Complementary inclusion and exclusion criteria were published in a previous publication (Khan et al., 2022).

2.5 | Null hypothesis

The null hypothesis was no statistically significant difference in the reduction of peri-implant inflammation (PPD, BI, and pus) 12 months after initial debridement between the two intervention groups.

2.6 | Randomization and allocation concealment

The allocation concealment between the two groups was conducted by the study administrator using computer-generated block randomization (RANDOM.ORG., Randomness and Integrity Services Ltd., Dublin, Ireland). Patients were randomly assigned to treatment in blocks of 10.

2.7 | Clinical and radiographic assessment

Probing pocket depth, BI, pus, Plaque Index (PI), and height of keratinized mucosa (KM) were registered at baseline before treatment and at 1, 3, 6, and 12 months after initial treatment.

Probing pocket depth, BI, and PI (Plaque Index) were measured at six sites per implant (mesiobuccal, buccal, distobuccal, mesiolingual, lingual, and distolingual) using a manual 0.20 N defined force periodontal probe (University of North Carolina, DB764R, AESCULAP, B Braun, Germany). Specialists in periodontology performed the assessment. The examiners were blinded to treatment allocation. The implant-retained supra-constructions were not removed for clinical examination or treatment.

Radiographic examinations were performed at baseline, 6- and 12 months post-treatment. Periapical radiographs were obtained using the long-cone paralleling technique with digital X-rays. ImageJ® image processing and analysis software program was used to measure changes in peri-implant RBL (Preus et al., 2015). Intraoral phosphor plates and sensors were used to calibrate the radiographs. Three examiners assessed the RBL twice for radiographs taken at baseline and 12 months. Information on patient data, time of examination, and clinic affiliation was removed from the radiographs before the analysis. The size of the sensor and phosphor plates were used to calibrate the radiographs. ImageJ® roentgenological attachment analyzer plugin converted markings on the radiographs to numeric data. The RBL was calculated as the distance from the implant neck to the first bone-to-implant contact.

2.8 | Clinical outcomes

The outcome variables were assessed at baseline before treatment and 3, 6, and 12 months after initial treatment.

The following clinical variables were assessed at the affected implant:

1. PI—presence or absence of plaque (O'Leary et al., 1972). Registered by running the probe along the marginal surface of the implant (Mombelli et al., 1987).
2. Pus—presence or absence of pus/suppuration.
3. BI—registered 30 s after probing. The bleeding scores were categorized into four categories; score 0 = no bleeding, score 1 = isolated bleeding spot, score 2 = blood forming a red line, and score 3 = profuse bleeding (Roos-Jansåker et al., 2007).
4. PPD registered in millimeters.
5. Height of keratinized mucosa (KM) was assessed midbuccaly with a periodontal probe.

2.9 | Treatment interventions and protocol

There were two parallel treatment arms. Prior to inclusion, all study patients underwent an initial hygiene phase with oral hygiene instructions. At the baseline registration and intervention, the PI was 0 for all implant surfaces. Implants in the test group were treated with an OCB for 2 min. The OCB was soaked in sterile saline prior to treatment. The control group treatment was performed using TC for 2 min (Langer and Langer, Rønvig, Denmark). Peri-implant pockets were irrigated with saline after mechanical treatment in both groups. Treatment was performed at baseline and repeated at 3, 6, and 9 months in cases with >1 implant site with BI ≥ 1 and (PPD) ≥ 4 mm (Figure 1). Local infiltration anesthesia was administrated when required by the patients. Both treatment modalities were performed non-surgically. Treatment was performed by five authorized dental hygienists.

2.10 | Treatment outcomes

Disease eradication: PPD <4 mm, BI 0, and no reduction in RBL compared to baseline.Treatment success: ≤1 implant site with BI ≤1, absence of pus, PPD ≤5 mm, and absence of progressive bone loss.Resolution of inflammation: BI 0.Disease improvement: BI = 1. Peri-implantitis recurrence/progression: RBL increase, and/or PPD increase, and/or BI ≥2.

2.11 | Data management and statistical analysis

Calculations and analysis were performed using Stata Statistical Software, Version 16.1 (StataCorp.2001. Statistical Software: Release 7.0. Stata Corporation). A *p*-value less than .05 was considered statistically significant.

Data were analyzed by per-protocol (PP) analysis on assessed patients at all time points. In addition, the intention-to-treat (ITT) principle was used, meaning that all randomized patients were included in the analysis using multiple imputations generated in R (R app 4.0.3 GUI Mac OS, R Foundation for Statistical Computing, Vienna, Austria). Implant and patient characteristics were described with percentages for categorical variables and means with standard deviations (SD) for continuous data.

Probing pocket depth, BI, pus, and PI data were obtained at baseline, 1, 3, 6, and 12 months for one implant in each patient. Patients were included in five different dental practices. The mean of PPD sites ≥4 mm was calculated for all implants at each study time point. A three-level linear regression model for PPD and a logistic regression model for BI with random intercept and random effect of time (level 3) were used to account for possible

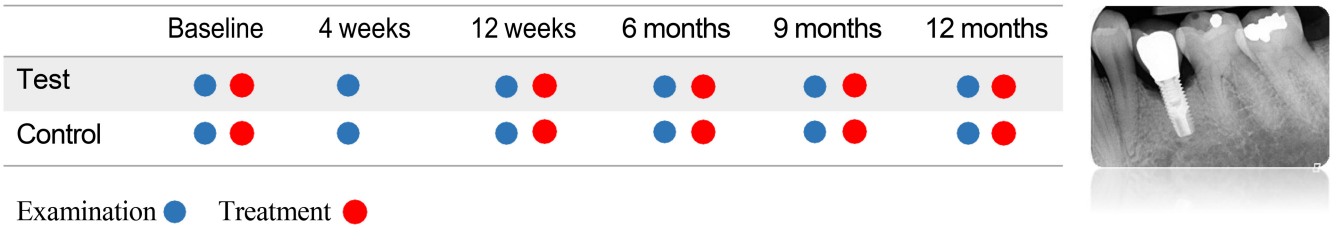

FIGURE 1 Patients were examined at baseline, 1, 3, 6, 9 and 12 months. Treatment was performed at baseline and retreated every third month in cases with PPD ≥ 4 mm and BI ≥ 1.

dependences of the data within the patients (level 2) who were nested within the clinics (level 1). Within and between the group changes in PPD and BI at each study time point were obtained from the two-way interaction of time with the groups. Variability in PPD and BI attributed to differences in patients, and clinics were described using estimates of ICC.

The transitions between BI states were modeled using a three-state Markov model. For the Markov analysis, BI 0 was considered healthy, and BI 1 was a state between health and disease. BI 2 and BI 3 were merged into one state and categorized as sick. All states were considered transient. The analysis was performed at the site level for both groups. Each implant was presented with six site measurements (mesiobuccal, buccal, distobuccal, distopalatal, palatal, and mesiopalatal). In addition, BI transitions at the implant level were performed based on the highest BI at baseline and 12 months. Markov analysis was performed with the msm package in R (R app 4.0.3 GUI Mac OS, R Foundation for Statistical Computing).

3 | RESULTS

A total of 31 patients with peri-implantitis, as defined above, completed the scheduled 12 months examination appointment. The study flow chart is presented in Figure 2. The baseline implant and patient characteristics for both groups and the dropouts are presented in Table 1. No adverse reactions related to the treatments were reported.

3.1 | Clinical withdrawal

A total of eight patients were withdrawn from the study by the clinicians (Figure 2). In the test group, one patient was excluded at the follow-up between 3 and 6 months, and three patients between 6 and 12 months. All withdrawals in the control group were at the follow-ups between 6 and 12 months. Radiographic and clinical data at baseline for the dropouts are presented in Table 2.

3.2 | Clinical and radiographic changes between the study groups (per-protocol; $n = 31$)

The changes in PPD, BI, PI, pus, plaque, KM, and RBL from baseline to 6 and 12 months are presented in Table 3.

3.2.1 | Probing pocket depth

Changes in the mean PPD at 6 and 12 months are reported in Table 3. Differences in PPD between the groups are presented in Table 4. Changes in mean PPD at each study point from baseline to 12 months between and within the groups are demonstrated in Figure 3. Both treatments resulted in a statistically significant reduction in PPD at 3, 6, and 12 months compared to baseline ($p < .05$). No statistically significant differences between the groups were registered at any time point. Reduction in PPD was statistically significant between 6 and 12 months for the test group ($p < .05$).

3.2.2 | Bleeding index

The results from the ordinal logistic regression model with the following comparisons: no bleeding (BI 0) and spot bleeding (BI 1) combined vs line and profuse bleeding combined, demonstrated a statistically significant decrease in BI 2 and BI 3 at the implant level in the test and the control group from baseline to 12 months (Figure 3b). The differences between the groups were not a statistically significant at 1, 3, 6, or 12 months ($p > .05$; Table 4).

3.2.3 | Pus

The number of implants with pus decreased significantly in both study groups between baseline to 12 months (Table 3). However, there was no statistically significant difference between the groups ($p > .05$).

3.2.4 | Radiographic bone level

At baseline, three patients in the test group and six patients in the control group had RBL ≥ 3 mm. The mean RBL for both study groups at baseline, 6, and 12 months are presented in Table 3. The radiographic bone level was stable in all patients, and the change in bone levels between baseline and 12 months was not statistically significant for any of the groups. The intraclass correlation coefficient (ICC) describing the intra-examiner agreement was 0.98.

3.2.5 | Composite outcome

At 12 months, one implant in the test group and none in the control group presented disease eradication according to the criteria: PPD <4 mm, no bleeding (BI 0), and no changes in RBL compared to baseline. Treatment success was defined as ≤1 implant site with BI ≤ 1, absence of pus, PPD ≤ 5 mm, and no progressive bone loss was achieved for three implants in the test group and one implant in the control group. The differences between the groups were not statistically significant ($p > .05$).

3.2.6 | Height of keratinized mucosa

The mean KM at baseline, 6 and 12 months for both groups is presented in Table 3.

At baseline, about 70% of implants in the test group and 60% in the control group had KM ≥ 2 mm. At 12 months, the number of

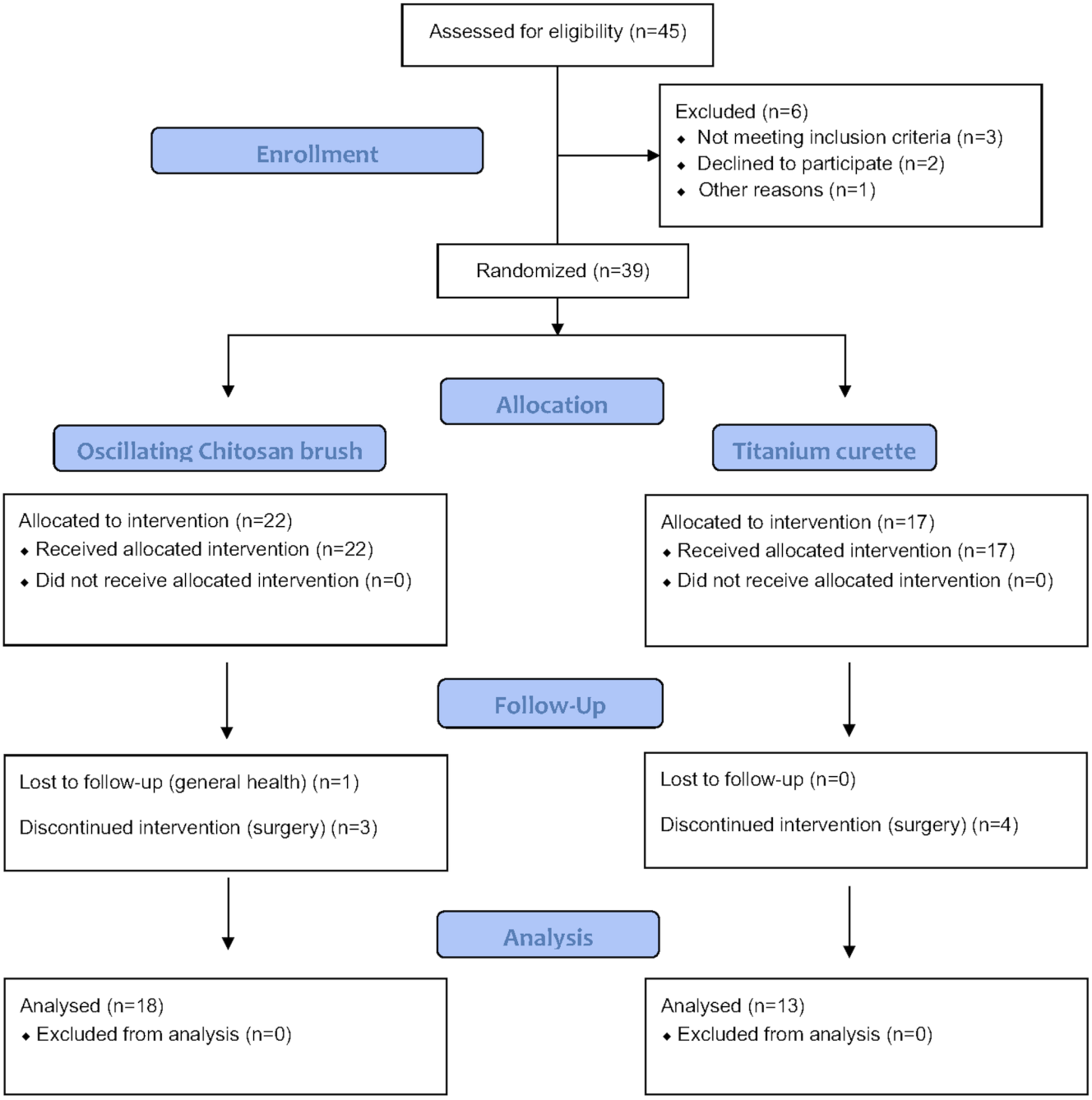

FIGURE 2 A CONSORT flowchart of enrollment, allocation, follow-up, and analysis.

implants with KM ≥ 2 mm decreased to approximately 60% in the test group and to 40% in the control group.

3.2.7 | Plaque index

Plaque scores at the included implants changed throughout the study period, without significant differences between the study time points ($p > .05$) Figure 4. At the site level, an association between bleeding on probing and the presence of plaque was not observed.

3.3 | Clinical and radiographic changes between the study groups (intention-to-treat; $n = 39$)

Study group differences derived from the intention-to-treat (ITT) analysis are presented in Tables 5 and 6. In both study groups, the radiographic bone level remained stable throughout the study period. No statistically significant differences between the groups were observed for PPD, BI, presence of pus, or RBL. PPD, BI, and plaque changes are presented in included implants changed throughout S1-S3.

TABLE 1 Baseline characteristics of all randomized study patients ($n=39$) and dropouts ($n=8$).

	Patients randomized to the study		Dropouts		*p*-values	
Variable	**OCB**	**TC**	**OCB**	**TC**	**OCB**	**TC**
Subjects/Implants (*n*)	22	17	4	4		
Mean age (± SD)	62.86 (±12.2)	61.12 (±3.7)	61.5 (±9.0)	65.5 (±11.4)	.84	.18
Gender						
Male (M), *n* patients (%)	5 (22.7)	9 (52.9)	0 (0.0)	1 (25.0)	.29	.31
Female (F), *n* patients (%)	17 (77.3)	8 (47.1)	4 (100.0)	3 (75.0)	.01	.31
Daily smoker; *n* patients (%)	4 (18.2)	1 (5.9)	0 (0.0)	0 (0.0)	.35	.62
Diabetes; *n* patients (%)	5 (22.7)	3 (17.6)	2 (75.0)	0 (0.0)	.04	.36
Tooth loss due to periodontitis; *n* patients (%)	6 (27.3)	5 (29.4)	1 (25.0)	0 (0.0)	.92	.21
Front; *n* implants (%)	8 (36.4)	9 (52.9)	1 (25.0)	2 (50.0)	.66	.92
Premolar; *n* implants (%)	11 (50.0)	7 (41.2)	2 (50.0)	2 (50.0)	1.0	.74
Molar; *n* implants (%)	3 (13.6)	1 (5.9)	1 (25.0)	0 (0.0)	.56	.62
Screw-retained; *n* implants (%)	17 (77.3)	15 (88.2)	4 (100.0)	4 (100.0)	.01	.01
Cement-retained; *n* implants (%)	5 (22.7)	1 (5.9)	–	–		
Not reported; *n* implants (%)	0 (0.0)	1 (5.9)	–	–		
Implant-retained crown; *n* implants (%)	10 (45.5)	5 (33.3)	1 (25.0)	2 (50.0)	.87	.53
Implant-retained fixed dental prosthesis; *n* implants (%)	12 (54.5)	12 (52.2)	3 (75.0)	2 (50.0)	.44	.94

Abbreviations: OCB, oscillating chitosan brush; TC, titanium curettes.

TABLE 2 Radiographic and clinical data of the complete cases and dropout patients at baseline ($n=8$).

	Complete cases ($n=31$)		Dropouts ($n=8$)		*p* values	
Variable	**OCB**	**TC**	**OCB**	**TC**	**OCB**	**TC**
Subjects/Implants (*n*)	18	13	4	4		
Radiographic bone level (±SD)	2.4 (±0.7)	2.9 (±0.5)	2.6 (±0.2)	2.5 (±0.5)	.58	.29
PPD[§] mean (mm)[a]	5.0 (±0.8)	5.3 (±1.4)	5.0 (±0.3)	5.3 (±0.6)	1.00	1.00
Mean (PPD ≥ 4 mm)[a] (±SD)	5.2 (±0.9)	5.6 (±0.1)	5.4 (±0.5)	5.3 (±0.6)	.73	.08
Mean (PPD ≥ 6 mm)[a] (±SD)	6.7 (±0.5)	6.5 (±0.9)	8.0 (±1.7)	6.2 (±0.3)	.01	.53
BI ≥ 2 (%)	100.0	100.0	100.0	100.0	1.00	1.00
BI 0 (%)	0.0	0.0	0.0	0.0	-	-
BI 1 (%)	0.0	0.0	0.0	0.0	-	-
BI 2 (%)	61.1	76.9	100.0	75.0	.06	.93
BI 3 (%)	38.9	23.1	0.0	25.0	.13	.93
Pus (%)	50	53.8	25.0	100.0	.36	.12
Plaque (%)	2.8	9.0	0.0	0.0	.73	.01
Keratinized mucosa ≥ 2 mm (%)	72.2	61.5	25.0	75.0	.08	.62

Abbreviations: BI, bleeding index; OCB, oscillating chitosan brush; PPD, probing pocket depth; TC, titanium curettes.

[a]PPD mean = mean of 6 measurements at selected sites, whereas mean (PPD ≥ 4 mm) = mean of measurements ≥4 mm, and mean (PPD ≥ 6 mm) is the mean of measurements 6 ≥ mm.

3.4 | Markov models

During the 12-month interval, a large number of healthy sites (BI0), remained healthy. Comparably, a large number of inflamed sites (BI2 + BI3) remained inflamed. The transitions between the BI states for both groups at the site level are demonstrated in Figure 5. BI transitions at the implant level between baseline and 12 months are presented in Figure 6.

TABLE 3 Changes in mean PPD and BI between the groups at each time point obtained from the linear and ordinal logistic multilevel regression model with clinic (level 1), patient random effects (level 2), and time (level 3), based on per-protocol analysis ($n = 31$).

	Baseline		6 months		12 months			
	OCB ($n = 18$)	TC ($n = 13$)	OCB ($n = 18$)	TC ($n = 13$)	OCB ($n = 18$)	TC ($n = 13$)	p value[a]	p value[b]
Clinical parameters								
Radiographic bone level (±SD)	2.4 (±0.7)	2.9 (±0.5)	2.5 (±0.5)	2.7(±0.7)	2.5 (±0.5)	3.1 (±0.7)	.62	.41
PPD[§] mean (mm)[c]	5.0 (±0.8)	5.3 (±1.4)	4.5 (±1.1)	4.7 (±0.1)	3.9(±1.2)	3.9 (±1.1)	.01	.01
Mean (PPD ≥ 4 mm) (±SD)[c]	5.2 (±0.9)	5.6 (±0.1)	4.5 (±1.1)	4.3 (±0.9)	4.0 (± 1.2)	4.0 (± 1.1)	.01	.01
Mean (PPD ≥ 6 mm) (±SD)[c]	6.7 (±0.5)	6.5 (±0.9)	6.8 (±0.7)	6.3(±0.6)	6.7 (±0.7)	6.6 (±0.7)		
BI ≥ 2 (%)	100.0	100.0	77.8	61.5	44.4	76.9	.02	.01
BI 0 (%)	–	–	–	15.4	11.1	0	–	–
BI 1 (%)	–	–	22.2	23.1	44.4	23.1	–	–
BI 2 (%)	61.1	76.9	77.8	61.5	38.9	76.9		
BI 3 (%)	38.9	23.1	-	-	5.6	0	.01	.07
Pus (%)	50	53.8	33.3	53.8	16.7	0	.05	.01
Plaque (%)	2.8	9.0	4.6	19.2	10.2	5.1	.4	.7
Keratinized mucosa ≥ 2 mm (%)	72.2	61.5	77.8	69.2	77.8	38.5	.70	.24

Abbreviations: BI, bleeding index; OCB, oscillating chitosan brush; PPD, probing pocket depth; TC, titanium curettes.

[a]Difference between baseline and 12 months for OCB.

[b]Difference between baseline and 12 months for TC.

[c]PPD mean = mean of 6 measurements at selected sites, whereas mean (PPD ≥ 4 mm) = mean of measurements ≥4 mm, and mean (PPD ≥ 6 mm) is the mean of measurements 6 ≥ mm.

TABLE 4 Changes in mean PPD and BI between the groups at each time point obtained from the linear and ordinal logistic multilevel regression model with clinic (level 1), patient random effects (level 2), and time (level 3), based on per-protocol analysis ($n = 31$).

	Baseline		1 month		3 months		6 months		12 months	
	ß (95% CI)	p-value	ß (95% CI)	p-value	ß (95% CI)	p-value	ß (95% CI)	p-value	ß (95% CI)	p-value
Group (ref.: TC)										
PPD OCB	0.5 (−0.3, 1.2)	.4	0.3 (−0.4, 1.0)	.4	−0.1 (−0.8, 0.6)	.8	−0.2 (−0.9, 0.5)	.6	0.1(0.7, 0.8)	.9
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	
Between the groups (ref.: TC)										
BI 0–1 vs. BI 2–3	0.8(0.2, 3.3)	.7	0.8(0.2, 3.5)	.8	0.7(0.2, 3.0)	.6	2.9(0.7, 12.4)	.1	0.3(0.1, 1.3)	.1

Abbreviations: BI, bleeding index; CI, confidence interval; OCB, oscillating chitosan brush; PPD, probing pocket depth; TC, titanium curettes.

4 | DISCUSSION

This 12-month multicenter, single-blinded RCT aimed to evaluate the efficacy of repeated non-surgical mechanical treatment of peri-implantitis performed with an OCB or TC after an initial hygiene phase. Implants in both groups demonstrated a statistically significant reduction in BI and PPD at 3, 6, and 12 months after initial treatment. Pus was significantly reduced in both groups at 12 months compared to baseline. The null hypothesis was not rejected as the difference in the reduction of inflammation parameters between the groups was not statistically significant at any time point.

It is demonstrated that disease resolution is unpredictable after non-surgical peri-implantitis treatment; thus, novel methods should be developed and tested (Roccuzzo et al., 2020). Non-surgical treatment of mucositis and peri-implantitis with OCB compared to TC has been evaluated in clinical studies with equal efficacy for both treatment modalities (Khan et al., 2022; Koldsland & Aass, 2020; Wohlfahrt et al., 2017) The presence of pus was resolved in 19.1% of the implants in the OCB group and with no reduction in the TC group when the treatments were compared in an RCT with a 6-month follow-up (2022). Further reduction in the presence of pus following repeated treatments over 12 months was observed in the present study (2022).

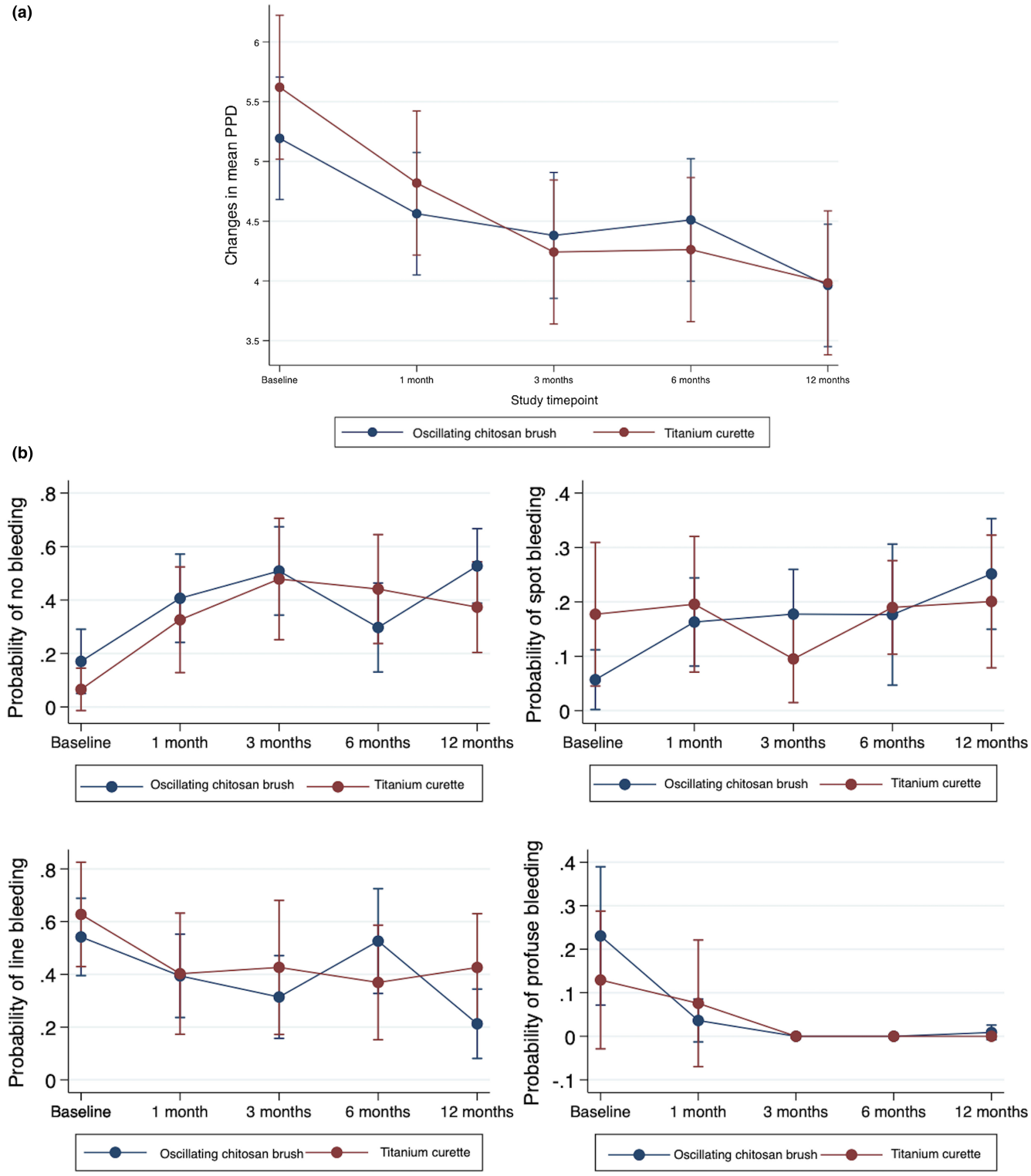

FIGURE 3 (a) Changes in mean PPD ≥ 4 mm, from baseline to 12 months between and within the groups (per-protocol; $n = 31$). (b) The probability of BI 0–3 at implant level between and within the groups at each time point between baseline and 12 months (per-protocol; $n = 31$).

Peri-implantitis has been reported to progress in a non-linear, accelerating pattern if no treatment is performed (Fransson et al., 2010). Patients with peri-implant mucositis who are not provided adequate preventive maintenance care show an increase in total bacterial load and a higher prevalence of peri-implantitis after 5 years (Costa et al., 2019). As of today, there has yet to be a consensus on a protocol for peri-implant maintenance or supportive therapy, both concerning instruments that should be applied and the frequency of care.

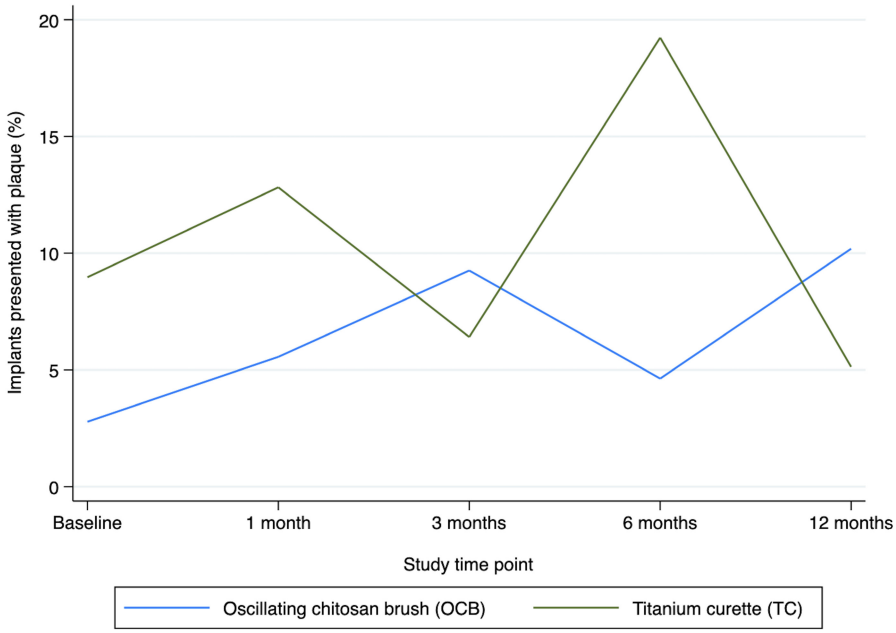

FIGURE 4 Implants with plaque at all study timepoints (per-protocol; $n = 31$).

TABLE 5 Radiographic and clinical data based on *intention-to-treat* analysis at baseline, 6 months and 12 months for both study groups ($n = 39$).

	Baseline		6 months		12 months			
	OCB ($n = 22$)	TC ($n = 17$)	OCB ($n = 22$)	TC ($n = 17$)	OCB ($n = 22$)	TC ($n = 17$)	*p* value[a]	*p* value[b]
Clinical parameters								
Radiographic bone level (±SD)	2.4 (±0.1)	2.8 (±0.1)	2.5 (±0.5)	2.6 (±0.7)	2.5 (±0.7)	3.0 (±0.5)	.51	.12
PPD mean (mm)[c]	5.1 (±0.9)	5.3 (±1.6)	4.5 (±1.1)	4.4 (±1.0)	3.9 (±1.2)	3.9 (±1.1)	.01	.01
Mean (PPD ≥ 4 mm), (±SD)[c]	5.3 (±0.7)	5.6 (±1.4)	4.9 (±0.1)	5.0 (±0.1)	4.7 (±0.6)	4.6 (±0.1)	.01	.01
Mean (PPD ≥ 6 mm), (±SD) [c]	6.8 (±0.6)	6.5 (±0.9)	6.7 (±0.7)	6.3 (±0.6)	6.5 (±0.7)	6.5 (±0.5)	.16	1.00
BI ≥ 2 (%)	88.7	93.3	51.6	40.9	22.0	38.3	.01	.01
BI 0 (%)	2.3	1.3	17.2	24.5	50.6	31.9	.01	.01
BI 1 (%)	9.0	5.4	31.2	34.6	27.4	29.8	.11	.06
BI 2 (%)	85.3	87.4	51.2	40.3	21.6	37.4	.01	.01
BI 3 (%)	3.4	5.9	0.4	0.6	0.4	0.9	.52	.42
Pus (%)	47.5	64.7	33.3	64.7	17.5	8.4	.03	.01
Plaque (%)	2.4	6.7	4.2	20.6	9.9	5.7	.27	.9
Keratinized mucosa ≥ 2 (mm) (%)	71.6	68.6	66.9	58.9	75.3	71.9	.78	.83

Abbreviations: BI, bleeding index; OCB, oscillating chitosan brush; TC, titanium curettes.

[a]Difference between baseline and 12 months for OCB.

[b]Difference between baseline and 12 months for TC.

[c]PPD mean = mean of 6 measurements at selected sites, whereas mean (PPD ≥ 4 mm) = mean of measurements ≥4 mm, and mean (PPD ≥ 6 mm) is the mean of measurements ≥6 mm.

Treatment of both peri-implant mucositis and peri-implantitis aims to reduce the bacterial load and control the inflammation. In the present study, FMPS < 20% and no plaque at the included implants at baseline were prerequisites. At baseline, the test group had the lowest plaque scores, with an increasing trend throughout the study period. The control group had a higher number of implants with plaque at baseline compared to the test group and showed a reduction in plaque at 3 months. The number of implants with plaque

TABLE 6 Changes in mean PPD and BI between the groups at each time point obtained from the linear and ordinal logistic multilevel regression model with clinic (level 1), patient random effects (level 2), and time (level 3) based on imputed data ($n = 39$).

	Baseline		1 month		3 months		6 months		12 months	
	ß (95% CI)	*p*-value	ß (95% CI)	*p*-value	ß (95% CI)	*p*-value	ß (95% CI)	*p*-value	ß (95% CI)	*p*-value
Group (ref.: TC)										
PPD OCB	- 0.3 (−1.2, 0.5)	.48	0.1 (−0.7, 1.0)	.80	0.1 (−1.0, 0.8)	.82	0.1 (−0.8, 1.0)	.78	0.2 (−1.4, 0.9)	.71
	OR (95% CI)	***p*-value**	**OR (95% CI)**	***p*-value**	**OR (95% CI)**	***p*-value**	**OR (95% CI)**	***p*-value**	**OR (95% CI)**	
Between the groups (ref.: TC)										
BI 0–1 vs. BI 2–3	0.2 (0.1, 0.9)	.03	0.5 (0.2, 1.5)	.24	0.5 (0.2, 1.4)	.20	1.0 (0.4, 3.0)	.97	0.5 (0.1, 1.4)	.16

Abbreviations: BI, bleeding index; CI, confidence interval; OCB, oscillating chitosan brush; PPD, probing pocket depth; TC, titanium curettes.

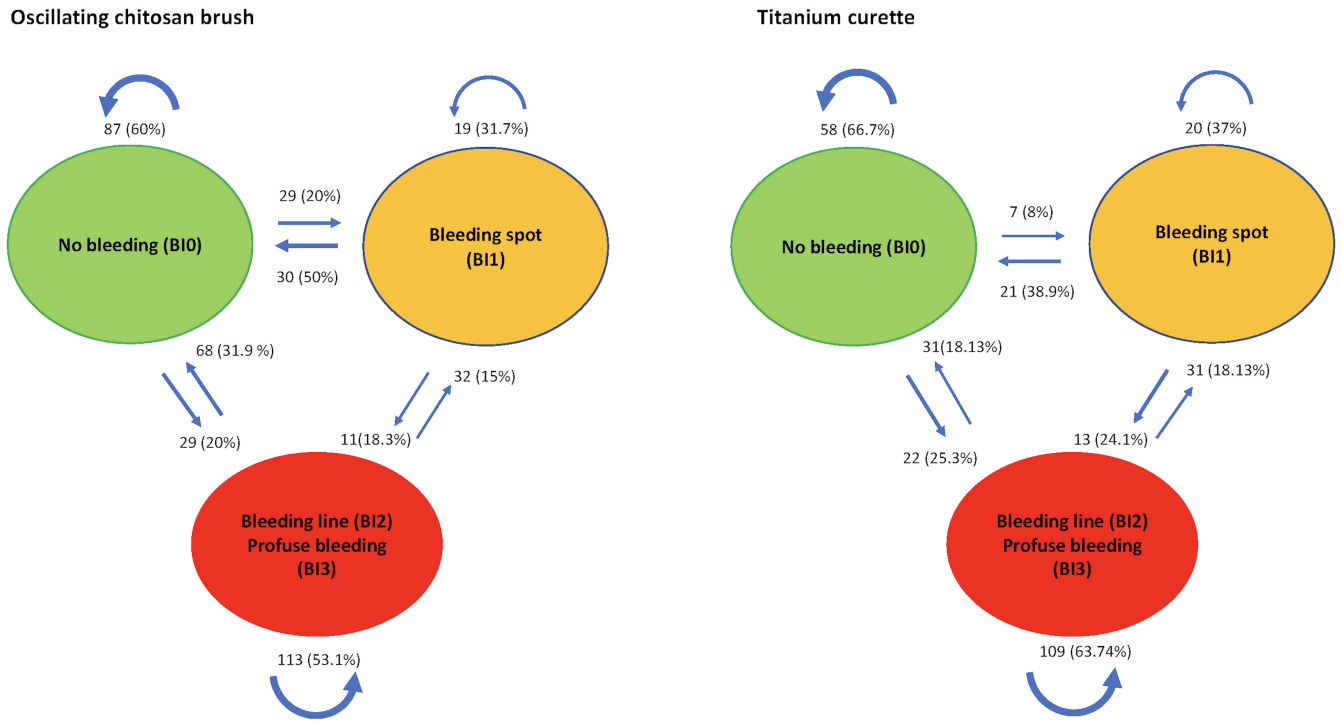

FIGURE 5 A multi-state Markov model for peri-implantitis. BI 0 correspond to health, BI 1 to a state between health and disease and BI 2 and 3 as disease. The number and percentage of site transitions between the different states are represented by the arrows. The model shows all transitions through the study period of 12 months ($n = 31$).

in the control group increased significantly from 3 to 6 months. At 12 months, the implants in the control group showed a significant reduction in the presence of plaque, with values lower than at baseline. A causal relationship between plaque and peri-implant inflammation has been reported in previous studies (Pontoriero et al., 1994; Serino & Ström, 2009). The difference in plaque levels may have affected the results in the present study.

In the present study, 53.1% of the implant sites in the test group and 63.7% of the sites in the control group remained at BI 2–3 through the study period despite four active treatments. Furthermore, transition of healthy implant sites (BI 0) to diseased sites (B1 2–3) was observed in both groups. Contrary to the within-group results from the regression analysis, results from the Markov model indicated active disease. The transition from health to disease (BI 0 to BI 2–3) and infrequent improvement of sites with BI 2–3 is an important finding in the present study, as complete disease improvement was not achieved according to the BI transitions. In comparison, the regression analysis showed a statistically significant reduction in BI and PPD at 6 and 12 months within both groups. Transitions analysis at the implant level showed that most implants had BI2-3 at 12 months. Bleeding improvement from BI2-3 to BI1 was a common finding in both study groups. While transitions from BI2-3 to BI0 were observed in 11.2% of the implants in the test group, no implants in the control group showed improvement from BI2-3 to BI0. Transitions between the different BI scores are not reported for either peri-implant mucositis or peri-implantitis in the literature. The present study is the first attempt to estimate the disease initiation of healthy sites. Although, after the examinations

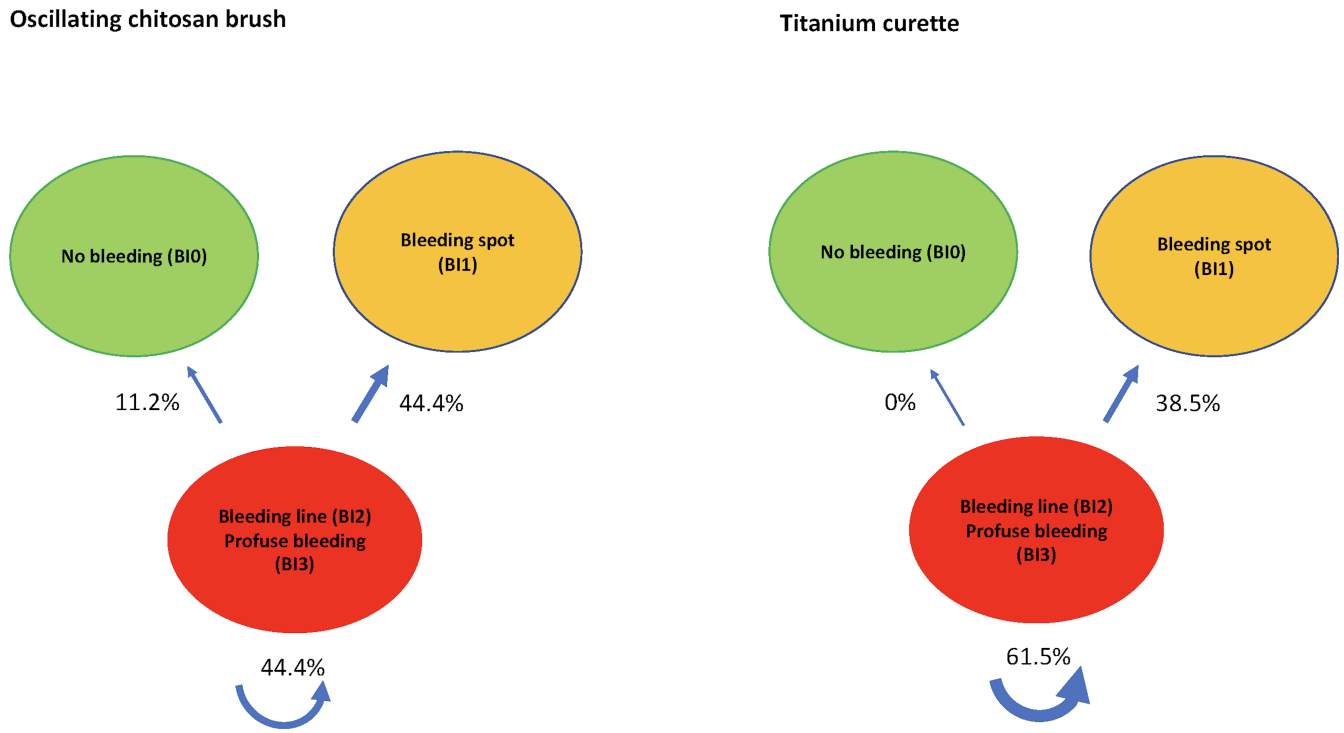

FIGURE 6 Transitions between BI states reported on implant level between baseline and 12 months. Each implant is presented with the highest BI score at each study timepoint ($n = 31$).

at 3 and 6 months, only sites presented with bleeding on probing were retreated, it is conceivable that the patients´ hygiene routines were positively influenced by the fact that they participated in a study with repeated follow-ups, known as the Hawthorne effect (Sedgwick & Greenwood, 2015).

The PPD reduction in the test group was statistically significant from 6 to 12 months in the present study. Contrary to the control group, the test group showed an increase in PPD between 3 to 6 months. The statistically significant PPD decrease in the test group between 6 to 12 months could be related to the PPD increase between 3 and 6 months.

In the present study, the baseline RBL was 2.4 (±0.7) mm and 2.9 (±0.5) mm for the test and the control group, respectively, leading to a difference in baseline characteristics among the groups. However, the CONSORT guidelines do not encourage significance testing of the baseline characteristics and describe the differences as 'results by chance' and not bias (Schulz et al., 2010). At 12 months, the RBL increased to 2.5 (±0.5) mm and 3.1 (±0.7) mm for the test and control groups, respectively. The registered RBL may have been influenced by the inter-examiner difference in radiographic technique and various digital x-ray equipment in all five clinics participating in the present multicenter study. Radiographs from the time of prosthetic loading were not available. The first radiographs were obtained at the time of study recruitment. Thus, a different threshold for peri-implantitis should have been used since baseline radiographic data were lacking, namely 3 mm bone loss and 6 mm PPD.

The required sample size to achieve 80% study power was calculated to be 17 patients in each group. At baseline, 21 patients were included in the test group and 17 in the control group (Khan et al., 2022). At 12 months, the test group consisted of 18 patients and the control group 13 patients. The multicenter randomization process leading to differential attrition rates between the test and control group was caused by separate randomizations at the five clinics. The skewing is a limitation of the present study, and significant differences may have been present with a high number of patients.

Intention-to-treat analysis with imputed data was compared to the results derived from the per-protocol analysis of complete cases. Analyses based on the per-protocol method run the risk of attrition bias as dropout patients may differ from those who remain. In the present study, one patient dropped out, and seven were excluded during the study period. The reason for exclusion was mainly recurrence or worsening of the disease and indication for surgical intervention, but the dropout rates were not significantly different in the two groups (4/22 vs. 4/17). Systematic differences in baseline data of complete cases and the dropouts were compared using regression analysis. For the radiographic and clinical data at baseline, a statistically significant difference was observed in the presence of plaque and the odds of being in BI0-1 vs. BI2-3 for the control group.

Within the limitations of this 12 months multicenter randomized clinical trial, non-surgical treatment of peri-implantitis with OCB and TC demonstrated no statistically significant difference between the treatment groups. Although this finding does not demonstrate an equivalence between the treatment methods, in view of the small sample sizes, it should be noted from the figures showing the time development of various features that none of the treatments seems

superior to each other. Clinical improvements in both groups and some cases disease resolution were achieved. Differences between test and control groups in changes in inflammation were not statistically significant but due to withdrawals, power was low. However, persistent inflammation was a common finding that further puts emphasis on the need for further treatment. Studies with larger sample sizes are important in the future.

AUTHOR CONTRIBUTIONS

J.C.W. conceived the idea. A.V., A.M.R.J., A.M., E.S., and S.N.K collected the data. I.M. and S.N.K. analyzed the data. S.N.K. led the writing. All co-authors have approved the manuscript.

FUNDING INFORMATION

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CONFLICT OF INTEREST STATEMENT

Caspar Wohlfahrt is the inventor and patent holder of the chitosan brush (Labrida Bioclean®, Labrida AS Oslo, Norway). Ann Marie Roos-Jansåker and Caspar Wohlfahrt are shareholders in Labrida AS. Drs Khan, Koldsland, Verket, Mdala, Magnusson, Salvesen and Hjortsjö report no conflicts of interest related to this study.

DATA AVAILABILITY STATEMENT

Data are stored at a central university facility and are available upon request from the corresponding author, S.K.

ETHICS STATEMENT

The study was approved by the Regional Committee for Medical and Health Research Ethics, South-East Norway (REK sør-øst 2017/710) and by the Swedish Ethical Review Authority, Linköping (EPN 2017/36–31).

PATIENT CONSENT STATEMENT

Informed consent forms were signed by participants prior to the study start.

PERMISSION TO REPRODUCE MATERIAL FROM OTHER SOURCES

Not applicable.

ORCID

Sadia N. Khan https://orcid.org/0000-0003-3925-326X
Odd Carsten Koldsland https://orcid.org/0000-0001-6842-8255

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SUPPORTING INFORMATION

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

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