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Domiciliary Use of Chlorhexidine vs. Postbiotic Gels in Patients with Peri-Implant Mucositis: A Split-Mouth Randomized Clinical Trial

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Abstract: Peri-implant mucositis is a pathological condition characterized by an inflammatory process in the peri-implant soft tissues. Progression to peri-implantitis takes place in case of peri-implant bone resorption. Recently, an aid for non-surgical treatment by mechanical debridement (SRP) has been identified in probiotics. As there are no recent studies regarding their use for peri-implant mucositis, the aim of this study was to test a new postbiotic gel for this clinical condition. A split-mouth randomized clinical trial was performed. Twenty patients undergoing SRP were randomly assigned to two treatments based on the following oral gels: chlorhexidine-based Curasept Periodontal Gel (Group 1) and postbiotic-based Biorepair Parodontgel Intensive (Group 2). At baseline (T0) and after three (T1) and six (T2) months, the following peri-implant mucositis indexes were recorded: Probing Pocket Depth (PPD), Plaque Index (PI), Gingival Bleeding Index (GBI), Bleeding Score (BS), Marginal Mucosal Condition (MMC). A significant decrease is reported for both postbiotic and chlorhexidine for all peri-implant mucositis indices studied. Quite the opposite, no significant variation was present in intergroup comparisons. Greater improvements for BS, GBI and MMC inflammatory indices of the postbiotic gel compared to chlorhexidine suggest the importance of further studies to investigate the relevance of the product alone.

Keywords: dentistry; peri-implant mucositis; mechanical debridement; non-surgical peri-implant mucositis treatment; probiotics; postbiotics; chlorhexidine; implantology; randomized clinical trial

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1. Introduction

Dental prosthetic rehabilitation supported by osseo-integrated implants has increased considerably in recent decades [1]. Consequently, the biological complications that can occur with them, mainly infectious-inflammatory processes, raise great interest in contemporary dentistry [2]. It is possible to recognize two clinical conditions: peri-implant mucositis and, subsequently, peri-implantitis [3]. Peri-implant mucositis is a pathological condition characterized by the development of an inflammatory process in the soft tissues surrounding the implant surfaces, without affecting the bone structure in which the implant is located [2]. Otherwise, if peri-implant bone resorption is associated, there is a progression into peri-implantitis, leading to implant loss and, consequently, failure of the prosthetic work [4,5]. From a clinical point of view, the diagnosis of peri-implant mucositis requires the presence of bleeding and/or suppuration on gentle probing and

the absence of bone resorption; the diagnosis of peri-implantitis requires the presence of bleeding and/or suppuration on gentle probing, increased probing depth and the presence of bone resorption [6].

Like the progression of gingivitis into periodontitis, peri-implant mucositis is supposed to precede peri-implantitis, but currently, the causes that favor this evolution have not been identified [2]. Peri-implant soft tissue reactions to plaque formation have been widely evaluated in both animal and human studies [7,8]. Thus, plaque formation has consistently led to peri-implant soft tissue inflammation, associated with clinical signs of inflammation, such as erythema and edema [9]. The histopathological and clinical conditions leading to the conversion from peri-implant mucositis to peri-implantitis are not completely understood [2].

Risk factors related to peri-implant disease are: history of periodontitis [10]; smoking [11]; diabetes [12]; poor plaque control/lack of regular maintenance therapy [13]; keratinized mucosa < 2 mm [14]; genetic factors [15]; excess cement [16]; systemic conditions [17]; iatrogenic factors [18]; occlusal overload [19]; and titanium particles [20].

Non-surgical treatment of peri-implant mucositis usually includes mechanical debridement of dental plaque and calculus, either by professional oral hygiene or home oral hygiene techniques, with or without the additional use of antimicrobials [2]. Scaling and root planing (SRP) peri-implant mucositis sites, using curette and ultrasound devices in titanium or polyether-ether-ketone (PEEK) coated tips, with or without antimicrobials, has been shown to significantly reduce inflammation of peri-implant tissues and reduce bleeding upon probing [21]. In the case of oral hygiene products for home use, mechanical plaque control, together with the use of an antiseptic, may provide benefit in the treatment of peri-implant mucositis, reducing probing bleeding and sometimes also the plaque index [2].

SRP has a few shortcomings, the most represented of which is bacterial recolonization [22]. Consequently, antibiotics [23], ozone application [24], photodynamic treatment [25], and probiotics [26] have been proposed as additional therapeutic approaches. Regarding the latter, they have been increasingly used in recent years for the treatment of periodontal disease, and recently, peri-implant pathologies, due to the absence of side effects associated with conventional antibiotic therapy [27]. Probiotics are supposed to compete with pathogens for nutritional sources and adhesion sites, enhancing mucosal barrier function and producing antimicrobial and immunomodulatory substances [28].

Regarding 'biotic' agents, a subsequent formulation is represented by postbiotics, i.e., products of the metabolic activity of the micro-organism, which, by exerting an antioxidant action, lead to a positive effect on the host [29].

Therefore, the aim of the present study is to compare the efficacy of two different oral gels for home oral hygiene, containing a postbiotic and chlorhexidine respectively, in combination with mechanical debridement, comparing their ability to improve indices of peri-implant mucositis. The statistical null hypothesis of the study is the absence of significant differences for each group considered and between them in the improvement of peri-implant mucositis indices at the different times considered.

2. Materials and Methods

2.1. Trial Design

A randomized, controlled, single-centre, split-mouth trial with an allocation ratio of 1:1 was carried out, validated by the unit's Internal Review Board (2021-0127), and recorded on Clinicaltrials.gov (NCT04899986).

2.2. Participants

A total of twenty patients were recruited at the Unit of Dental Hygiene, Section of Dentistry, Department of Clinical, Surgical, Diagnostic and Pediatric Sciences of the University of Pavia (Pavia, Italy) in May 2021 after informed consent was signed, ending in January 2022. Each phase of the study was performed by the same Unit. No patient

selection procedure was performed regarding the type of implants, their location, type of prosthesis, and date of insertion.

Table 1 shows the inclusion and exclusion criteria chosen in this study.

Table 1. Inclusion and exclusion criteria.

Inclusion Criteria
Age between 18 and 70 years
Written informed consent to take part of the study
Presence of peri-implant mucositis according to the recent 2018 classification (2017 World Workshop on the Classification of Periodontal and Peri-Implant Disease and Condition) [6]: presence of bleeding and/or suppuration on gentle probing with or without increased probing depth compared to previous examinations
absence of bone loss beyond crestal bone level changes resulting from initial bone remodeling
Presence of peri-implant mucositis in both sides of the mouth
Regular oral hygiene at home
Exclusion Criteria
Heart arrhythmias monitored through implantation of electronic devices
Mental and neurologic diseases
Pregnant or nursing in the last year
Lack of compliance or motivation
Lifestyle factors such as use illicit substances and alcohol drinking
Treatment with antibiotics 6 months before
Peri-implant mucositis diagnosis in one side of the mouth

2.3. Interventions and Outcomes

Patients at T0 had signed an informed consent, which was mandatory to participate in the study. Then, an instructed operator collected peri-implant mucositis indexes using a millimetre probe (UNC 15 probe; Hu-Friedy, Chicago, IL, USA): PPD (distance between the margin of the peri-implant mucosa and the base of the peri-implant sulcus) [30]; PI (percentage of plaque surfaces to total tooth surfaces) [31]; GBI (presence or absence of gingival inflammation after flossing unwaxed in the proximal grooves) [32]; BS (presence of bleeding on probing on a scale of 0 to 3) [33]; and MMC (presence of qualitative changes in the mucosa on a scale of 0 to 3) [34]. After that, professional supra- and subgingival oral hygiene was performed using a piezoelectric instrument (Multipiezo, Mectron S.p.a., Carasco, Italy), Gracey curette (Hu-Friedy, Chicago, IL, USA), PEEK ultrasonic tip (Implant Cleaning Set S, Mectron S.p.a., Carasco, Italy) and titanium curette for implant sites (Implant Curette TIS2CN, Arnold Deppeler SA, Rolle, Switzerland), followed by peri-implant mucositis sites decontamination with glycine powder (Glycine Powder, Mectron S.p.a., Carasco, Italy).

Patients from Group 1 were treated with Curasept Periodontal Gel at the sites of peri-implant mucositis in quadrants Q1 and Q3, while Biorepair Parodontgel Intensive was used for quadrants Q2 and Q4. The quadrants were inverted for patients in Group 2. Random number tables were used to decide the sides. The compositions of the two gels used are shown in Table 2.

Once mechanical debridement was performed, the peri-implant mucosal sites were rinsed. Drying and isolation was performed, and finally assigned product was applied. Two minutes later, the patient was discharged.

Patients were seen after one (T1), three (T2), and six (T3) months. The same steps were performed, except for professional oral hygiene, which was repeated after six months (T3). After each visit, the two gels, contained in two different syringes provided of plastic blunt needle with a diameter of 5–6 mm, were used by patients until the sites with peri-implant mucositis were filled, for the next two weeks once a day after home oral hygiene procedure, following the protocol provided for chlorhexidine.

Table 3 shows the protocol followed to carry out the study.

Table 2. Products used in the study.

Gel	Manufacturer	Composition
Biorepair Parodontgel Intensive	Coswell SPA, Funo di Argelato, BO, Italy	Aqua, Propylene Glycol, Peg-40 Hydrogenated Castor Oil, Xylitol, Xanthan Gum, Silica, Zinc Hydroxyapatite, Zinc PCA, Aloe Barbadensis Leaf Juice Powder, *Lactobacillus Ferment*, Sodium Hyaluronate, Lactoferrin, Solidago Virgaurea Extract, Aroma, Sodium Benzoate, Phenylpropanol, Benzyl Alcohol, Hydroxyacetophenone, Sodium Saccharin, *O*-Cymen-5-ol, Mannitol, Decylene Glycol, Sodium Myristoyl Sarcosinate, Sodium Methyl Cocoyl Taurate, Citric Acid, Potassium Sorbate, Phenoxyethanol, Linalool, Benzyl Benzoate, Limonene.
Curasept Periodontal Gel (with 1% chlorhexidine)	Curasept S.p.A, Saronno, VA, Italy	Purified water, Propylene glycol, Hydroxy Ethyl Cellulose, PVP/VA copolymer, PEG-40 hydrogenated castor oil, Chlorhexidine digluconate, Sodium acetate, Aroma, Acetic acid, Sodium metabisulfite, Ascorbic acid.

Table 3. Protocol designed for the study.

Appointment	Procedures
	Signature to the informed consent for the study Assessment of peri-implant mucositis indexes
Baseline (T0)	Professional supragingival and subgingival oral hygiene Peri-implant mucositis sites decontamination with glycine powders Group 1: Chlorhexidine was applied to peri-implant sites in quadrants Q1 and Q3; probiotic was applied to peri-implant sites in quadrants Q2 and Q4 Group 2: Probiotic was applied to peri-implant sites in quadrants Q1 and Q3; Chlorhexidine was applied to peri-implant sites in quadrants Q2 and Q4 Home use of the two products for the same sites for two weeks following the examination
After 1 month (T1) After 3 months (T2)	Reassessment of peri-implant mucositis indexes Peri-implant mucositis sites decontamination with glycine powders Group 1: Chlorhexidine was applied to peri-implant sites in quadrants Q1 and Q3;
After 1 month (T1) After 3 months (T2)	probiotic was applied to peri-implant sites in quadrants Q2 and Q4 Group 2: Probiotic was applied to peri-implant sites in quadrants Q1 and Q3; Chlorhexidine was applied to peri-implant sites in quadrants Q2 and Q4 Further oral hygiene motivation and continuation of the home treatment assigned
After 6 months (T3)	Professional supragingival and subgingival oral hygiene Peri-implant mucositis sites decontamination with glycine powders Reassessment of peri-implant mucositis indexes

Implant placement and professional oral hygiene and treatment procedures with the two gels were performed by two different operators. As only one operator detected the results, error between operators has not been evaluated. A negative control group was not considered due to the inability to avoid treating patients with sites of peri-implant mucositis.

2.4. Sample Size

Sample size calculation (Alpha = 0.05; Power = 95%) for two independent study groups and a continuous primary endpoint was calculated.

The following mathematical formula was used for sample size calculation:

$$\text{Sample size} = \frac{Z^2_{(1-\frac{\alpha}{2})} p(1-p)}{d^2}$$

where $Z_{(1-\frac{\alpha}{2})}$ is the standard normal variate corresponding to 1.96 at 5% type 1 error, p is the expected proportion in population expressed as decimal and based on previous studies, and finally d is the confidence level decided by the researcher and expressed as decimal too.

Concerning the variable Probing Depth (primary outcome), the expected difference between the means was supposed to be 0.57 with a standard deviation of 0.5 [35], requiring 40 quadrants per group and, therefore, 20 patients for the split-mouth study.

2.5. Randomization and Blinding

Considering a permuted block of 20 participants, the data analyst developed a randomization sequence using a block randomization table. Opaque envelopes were previously prepared, sealed and numbered sequentially (SNOSE); afterwards. For home-based procedures, the two products were hidden and therefore there were no differences between the two solutions; consequently, neither the operator, the patients or the data analyst were aware of the treatment administered. For the home protocol, the two syringes were of different colors to make it easier for patients, and the quadrant where the gel was to be applied was indicated on the box to avoid errors.

2.6. Statistical Methods

Using R software (R version 3.1.3, R Development Core Team, R Foundation for Statistical Computing, Wien, Austria), data were evaluated. In all groups and variables, descriptive statistics were computed (mean, standard deviation, minimum, median, and maximum). Through the Kolmogorov–Smirnov test, the normality of the distributions was computed. An ANOVA test for repeated measures was then applied, followed in case of significance by Tukey's post hoc test.

Significance was predetermined as $p < 0.05$ for all the tests performed.

3. Results

3.1. Participant Flow and Baseline Data

Twenty patients who satisfied the inclusion and exclusion criteria were selected to take part in the trial. All of them accepted to be part of the study, given assigned treatment. No patients were left out of the analysis. Figure 1 explains the flowchart of the study. At T0, sample had a mean age of 52.6 $\pm$ 9.79 years (8 females and 12 males).

The following sections show the average values achieved for all variables. Intergroup and intra-group comparisons were made using letter-based comparisons, whereby the same the same letter(s) assigned in the presence of non-significant differences [36].

3.2. Probing Pocket Depth (PPD)

After six months, PPD measurements showed a significant decrease for either product ($p < 0.05$). Regarding differences in the probiotic and chlorhexidine group, a statistically significant decrease was seen in the BPI at T1 and T2, whereas for the CHX it was evaluated at T1 ($p < 0.05$). No significant difference between the two treatments applied was found ($p > 0.05$); however, considering that at T0 the PPD value was higher in the trial group, the improvement at T3 in the trial group was higher than in the control group (Table 4 and Figure 2).

3.3. Plaque Index (PI)

Plaque index decreased significantly with both probiotic and chlorhexidine from baseline to three months later (T2) ($p < 0.05$). In the BPI, a significant improvement has been seen at T2 ($p < 0.05$). Regarding the differences between BPI and CHX, there were no significant differences between the two products employed ($p > 0.05$) (Table 5 and Figure 3).

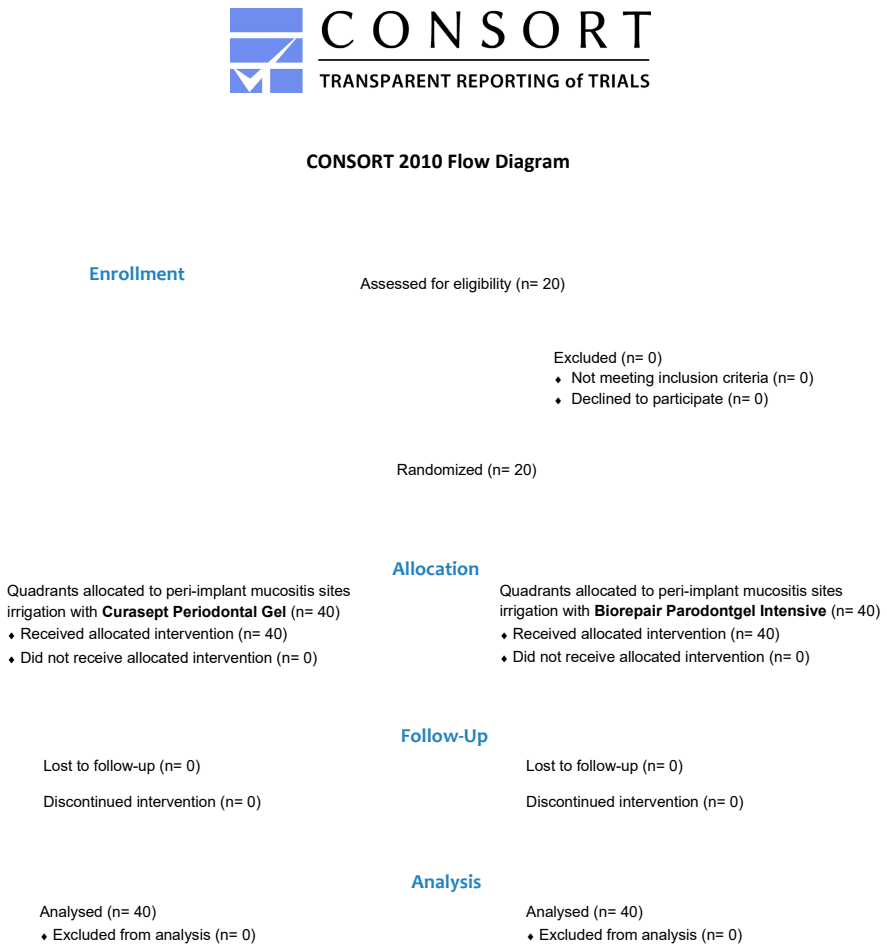

Figure 1. Flow chart of the study.

Table 4. Descriptive statistics of probing pocket depth (PPD).

Group	Time	Mean	St Dev	Min	Median	Max	Significance *
Control (CHX)	T0	3.72	1.32	1.00	4.00	7.00	A
	T1	3.33	1.34	1.00	3.00	7.00	B,C
	T2	3.16	1.30	1.00	3.00	9.00	B,C
	T3	3.21	1.25	1.00	3.00	8.00	B,C
Trial (BPI)	T0	3.94	1.35	1.00	4.00	7.00	A
	T1	3.23	1.19	1.00	3.00	6.00	B
	T2	2.97	1.17	1.00	3.00	6.00	C
	T3	2.89	1.14	1.00	3.00	6.00	C

* Use of various letters indicates significant differences between the two products ($p < 0.05$).

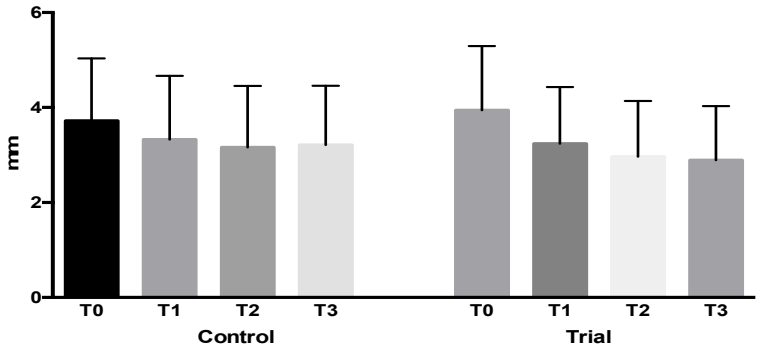

Figure 2. PPD values.

Table 5. Descriptive statistics of plaque index (PI).

Group	Time	Mean	St Dev	Min	Median	Max	Significance *
Control (CHX)	T0	52.15	32.20	10.00	47.50	100.00	A
	T1	37.90	19.85	5.00	37.50	75.00	A,B,C
	T2	30.75	20.48	5.00	22.50	85.00	C
	T3	30.75	21.52	5.00	26.50	77.00	A,B,C
Trial (BPI)	T0	52.25	33.62	10.00	45.00	100.00	A,B
	T1	36.45	20.52	5.00	40.00	75.00	B,C
	T2	26.90	19.09	5.00	20.00	85.00	C
	T3	30.75	21.56	0.00	23.50	77.00	A,C

* Use of various letters indicates significant differences between the two products ($p < 0.05$).

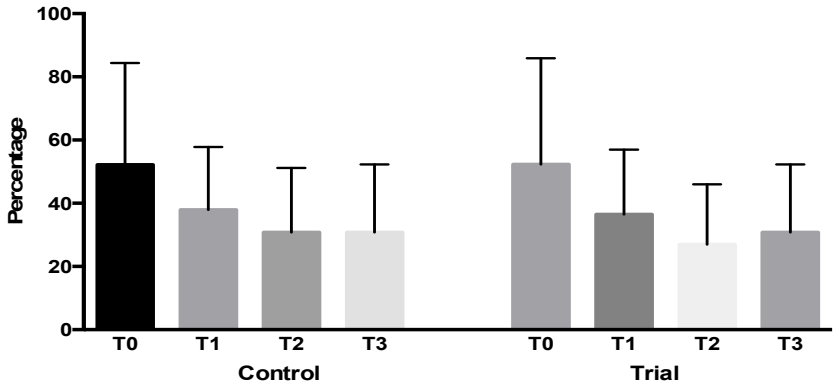

Figure 3. PI values.

3.4. Gingival Bleeding Index (GBI)

The gingival bleeding index decreased significantly for the trial gel at the end of the study ($p < 0.05$). Concerning intragroup differences, no statistically significant difference was found in the control group ($p > 0.05$), but, for BPI, a significant reduction was noted at T2 ($p < 0.05$). For differences between BPI and CHX, no significantly observed difference was found for the two products applied ($p > 0.05$); however, comparing the variation of the index between T0 and T3 in the two groups, there was a more marked reduction in the GBI value in the trial group (Table 6 and Figure 4).

3.5. Bleeding Score (BS)

For the bleeding score, a more significant reduction was evidenced at T3 than at T0 ($p < 0.05$). This outcome was greater after probiotic application, as a significant decrease is seen already at T1, whereas after CHX application is seen only at T2 ($p < 0.05$). There were no significantly observed differences between BPI and CHX at any stage of the present study ($p > 0.05$) (Table 7 and Figure 5).

3.6. Marginal Mucosal Conditions (MMC)

MMC measurements showed a significant reduction after both postbiotic and chlorhexidine application from baseline until six months later ($p < 0.05$). Significantly present differences were observed between baseline and T1 after application of BPI and between baseline and T2 after application of CHX ($p < 0.05$). There were no significant intergroup differences in any time point ($p > 0.05$) (Table 8 and Figure 6).

Table 6. Descriptive statistics of gingival bleeding index (GBI).

Group	Time	Mean	St Dev	Min	Median	Max	Significance *
Control (CHX)	T0	0.95	0.22	0.00	1.00	1.00	A
	T1	0.75	0.44	0.00	1.00	1.00	A
	T2	0.60	0.50	0.00	1.00	1.00	A,B
	T3	0.60	0.50	0.00	1.00	1.00	A,B
Trial (BPI)	T0	0.90	0.31	0.00	1.00	1.00	A
	T1	0.60	0.50	0.00	1.00	1.00	A,B
	T2	0.30	0.47	0.00	0.00	1.00	B
	T3	0.20	0.41	0.00	0.00	1.00	B

* Use of various letters indicates significant differences between the two products ($p < 0.05$).

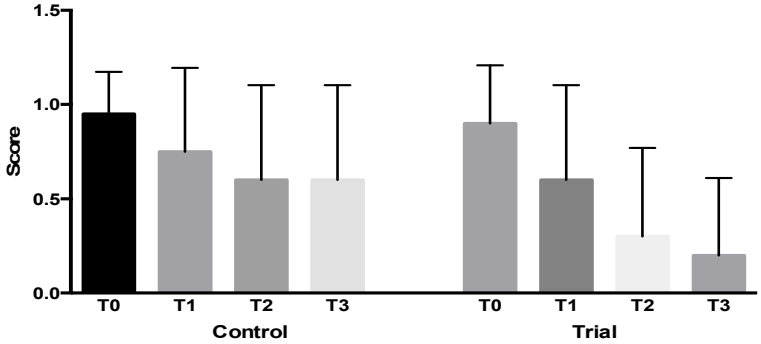

Figure 4. GBI values.

Table 7. Descriptive statistics of bleeding score (BS).

Group	Time	Mean	St Dev	Min	Median	Max	Significance *
Control (CHX)	T0	1.55	0.60	1.00	1.50	3.00	A,B
	T1	1.05	0.83	0.00	1.00	2.00	B,C,D
	T2	0.88	0.65	0.00	1.00	2.00	C,D
	T3	0.75	0.72	0.00	1.00	2.00	C,D
Trial (BPI)	T0	1.75	0.72	1.00	2.00	3.00	A
	T1	1.30	0.86	0.00	1.00	3.00	B,C
	T2	0.75	0.72	0.00	1.00	2.00	C,D
	T3	0.65	0.67	0.00	1.00	2.00	D

* Use of various letters indicates significant differences between the two products ($p < 0.05$).

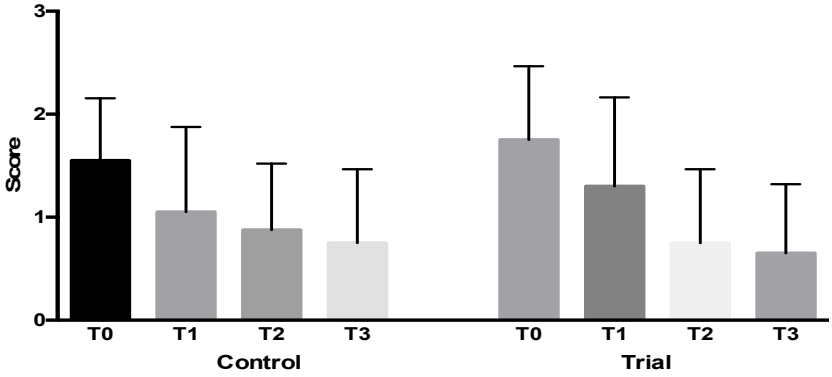

Figure 5. BS values.

Table 8. Descriptive statistics of marginal mucosal conditions (MMC).

Group	Time	Mean	St Dev	Min	Median	Max	Significance *
Control (CHX)	T0	1.30	0.57	0.00	1.00	2.00	A,C
	T1	1.00	0.56	0.00	1.00	2.00	A,B
	T2	0.65	0.59	0.00	1.00	2.00	B,D
	T3	0.60	0.68	0.00	0.50	2.00	B,D
Trial (BPI)	T0	1.60	0.60	0.00	2.00	2.00	C
	T1	1.00	0.65	0.00	1.00	2.00	A,B,D
	T2	0.60	0.60	0.00	1.00	2.00	B,D
	T3	0.50	0.51	0.00	0.50	1.00	D

* Use of various letters indicates significant differences between the two products ($p < 0.05$).

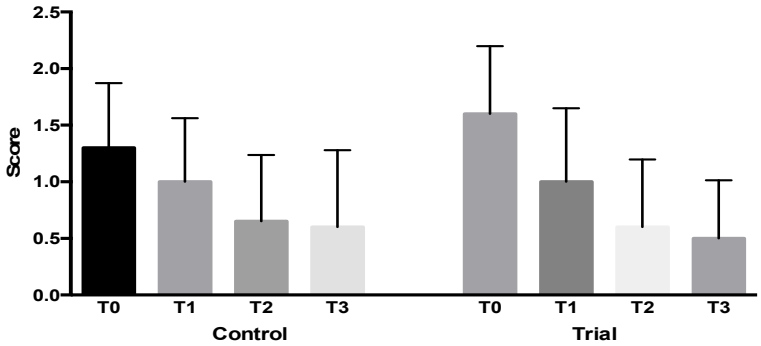

Figure 6. MMC values.

4. Discussion

For the replacement of missing teeth, osseo-integrated implants are one of the most frequently used treatment solutions, showing high efficacy, a positive long-term prognosis, and a survival rate ranging from 95% to 99% [37].

As the number of implants positioned rises, so does the frequency of relative complications leading to implant loss: loss of osseointegration; implant fracture; fracture of the screw connecting the abutment to the implant; fracture of the screw connecting the crown to the abutment (if it is a screw-retained prosthesis); peri-implant mucositis; and peri-implantitis [38].

The prevalence of peri-implant mucositis is higher than that of peri-implantitis: 80% of patients and 50% of sites respectively, compared with 28–56% of patients and 12–43% of sites [39].

Clinically, the risk factors for periodontitis can be considered an analogue for peri-implant disease; in particular, patients susceptible to periodontal disease appear to be more affected by peri-implant disease [40].

The pathogenesis appears to be related to the presence of a biofilm consisting of microorganisms, especially anaerobic Gram-, comparable to those found in periodontal disease; moreover, if periodontal pockets are present close to the implant site, they may act as foci of infection [41].

The proposed treatment of peri-implant disease is based on similar therapies followed in periodontal disease: non-surgical mechanical therapy (SRP) can be effective in treating mucositis, but the addition of topical antimicrobials increases the chance of successful treatment because reducing the bacterial load to allow healing is difficult to achieve by mechanical means alone, thus leading to bacterial recolonization [42].

Probiotics are the newest additional therapy and contain specific bacteria that have positive influences on health, including avoiding the side effects of antibiotics [43]. By modulating the local environment, symbiotic bacteria enable SRP efficiency [44].

To date, a few studies have been conducted to evaluate the effect of probiotics in peri-implant mucositis. They suggest that the oral and intestinal microbiota may be relevant to the development and treatment of mucositis, but a clear high-risk model has not yet been

identified and no single probiotic formulation has emerged for this indication. Preliminary results are promising for the positive effects of *Lactobacillus* species, particularly *L. reuteri* in the treatment of peri-implant mucositis and *L. brevi CD2* in the prevention of oral mucositis related to chemo/radiotherapy. Further studies are needed to address limitations but also to investigate the potential adjuvant role of prebiotics [45,46].

Since there are no studies assessing postbiotics in implantology, the aim of this work was to evaluate the effect of a recently developed antioxidant-acting postbiotic-based gel in supplement to mechanical debridement to improve clinical values of peri-implant mucositis.

The study's statistical null hypothesis was confirmed in part. Regarding differences found after probiotic and chlorhexidine application, dissimilarities and a significantly gradual reduction in probing pocket depth (PPD) was assessed for both products as well as: plaque index (PI); gingival bleeding index (GBI); bleeding score (BS); and marginal mucosal conditions (MMC). There were no significant intergroup changes; however, regarding PPD and GBI, comparing the changes for the two groups from T0 to T3, there was a higher reduction in values using Biorepair Parodontgel Intensive compared to Curasept Periodontal Gel.

On the basis of these results, both gels appear to be valuable tools for the management of peri-implant mucositis. However, until now, the effectiveness of these new products in dentistry has been under-researched.

In dentistry, a very common antiseptic agent is chlorhexidine thanks to its wide-spectrum antibacterial properties. It reduces dental plaque, gum inflammation and bleeding [47]. However, several side effects are linked to its prolonged and excessive use, including tooth discoloration, dysgeusia, oral burning, bacterial resistance, and mucosal inflammation [48]. Consequently, the introduction of new bioactive biomolecules, such as 'biotics', is recommended. However, no extensive literature is present. Currently, there are few studies related to postbiotics in the periodontal setting [49–52]; conversely, their use in implantology has not been investigated to date. The outcomes of this study illustrate that postbiotics are as effective as chlorhexidine. To the best of our knowledge, no clinical studies have been performed previously.

It was not possible comparing these results with other studies because, to date, they have not been performed. The products used in the present study were effective to reduce the clinical indexes of peri-implant mucositis because chlorhexidine has a high antiseptic power, while the postbiotics have both antiseptic and antioxidant and immunomodulating properties, leading to an antiphlogistic effect on peri-implant tissues. Thus, it is possible to suggest that postbiotics may lead a positive effect for a longer time than chlorhexidine. In addition, it must be considered that chlorhexidine should be used for a maximum of 15 days, thus avoiding the previously described side effects, unlike postbiotics.

Several critical points emerged during the preparation, conduct and processing of the data for this study. It would have been interesting to make analyses using variables such as the type of prosthesis supported by implants, average age and sex, all factors that the small number of patients included did not allow for.

Another limitation was the absence of a radiographic control that led to a partial evaluation of the importance that could be given to the PPD index; the literature of the last years in fact clearly expresses the variability of the probing depth among the various implant sites, influenced by the positioning of the implant, the type of connection, the shape of the prosthesis and the width of the mucous tunnel decided during surgery. Not only single crown implants were considered, but also bridge abutment or circular implants: obviously in the latter type of patient, plaque control is more difficult and consequently, also the maintenance of low inflammatory indices.

Furthermore, during home applications of chlorhexidine and probiotic products, contamination of sites by the control product with the test product and vice versa cannot be ruled out, although the emergence of intergroup differences might suggest that this contamination is not so significant, but further in-depth studies would be needed to verify this consideration.

The findings that the tested postbiotic gel could be effective in improving inflammatory indices should be further investigated.

Based on these observations and because of the lack of comparable studies, it is not possible to draw definitive conclusions about their use in implantology. Several research are needed to evaluate specific individual chemical compounds to permit comparison without bias and if implant type, their location, prosthesis type, and date of insertion can affect the results obtained by using postbiotics.

5. Conclusions

This study shows that the use of postbiotic gels is effective in reducing inflammatory indices. The greater improvements in BS, GBI and MMC inflammatory indices of the postbiotic gel compared to chlorhexidine suggest the importance of further studies to investigate the relevance of the product alone. The role of probiotics in maintaining the homeostasis of the oral microbiome may makes these compounds suitable for long-term therapy.

The ability of postbiotics to prevent the onset of peri-implant mucositis and their ability to maintain the reduction of inflammatory indices over time should be evaluated through further research.

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Data Availability Statement: Upon request of the corresponding author, the data are available for use.

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References

1. Jung, R.E.; Pjetursson, B.E.; Glauser, R.; Zembic, A.; Zwahlen, M.; Lang, N.P. A systematic review of the 5-year survival and complication rates of implant-supported single crowns. *Clin. Oral Implants Res.* **2008**, *19*, 119–130. [CrossRef] [PubMed]
2. Jepsen, S.; Berglundh, T.; Genco, R.; Aass, A.M.; Demirel, K.; Derks, J.; Figuero, E.; Giovannoli, J.L.; Goldstein, M.; Lambert, F.; et al. Primary prevention of peri-implantitis: Managing peri-implant mucositis. *J. Clin. Periodontol.* **2015**, *42*, S152–S157. [CrossRef] [PubMed]
3. Schwarz, F.; Derks, J.; Monje, A.; Wang, H.L. Peri-implantitis. *J. Clin. Periodontol.* **2018**, *45*, S246–S266. [CrossRef]
4. Liaw, K.; Delfini, R.H.; Abrahams, J.J. Dental Implant Complications. *Semin. Ultrasound CT MR* **2015**, *36*, 427–433. [CrossRef] [PubMed]
5. Lindhe, J.; Meyle, J.; Group DoEWoP. Peri-implant diseases: Consensus Report of the Sixth European Workshop on Periodontology. *J. Clin. Periodontol.* **2008**, *35*, 282–285. [CrossRef]
6. Berglundh, T.; Armitage, G.; Araujo, M.G.; Avila-Ortiz, G.; Blanco, J.; Camargo, P.M.; Chen, S.; Cochran, D.; Derks, J.; Figuero, E.; et al. Peri-implant diseases and conditions: Consensus report of workgroup 4 of the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions. *J. Clin. Periodontol.* **2018**, *45*, S286–S291. [CrossRef]
7. Berglundh, T.; Lindhe, J.; Marinello, C.; Ericsson, I.; Liljenberg, B. Soft tissue reaction to de novo plaque formation on implants and teeth. *An experimental study in the dog. Clin. Oral Implant. Res.* **1992**, *3*, 1–8. [CrossRef]

8. Salvi, G.E.; Aglietta, M.; Eick, S.; Sculean, A.; Lang, N.P.; Ramseier, C.A. Reversibility of experimental peri-implant mucositis compared with experimental gingivitis in humans. *Clin. Oral Implant. Res.* **2012**, *23*, 182–190. [CrossRef]
9. Schwarz, F.; Mihatovic, I.; Golubovic, V.; Eick, S.; Iglhaut, T.; Becker, J. Experimental peri-implant mucositis at different implant surfaces. *J. Clin. Periodontol.* **2014**, *41*, 513–520. [CrossRef]
10. Roccuzzo, M.; Bonino, F.; Aglietta, M.; Dalmasso, P. Ten-year results of a three arms prospective cohort study on implants in periodontally compromised patients. Part 2: Clinical results. *Clin. Oral Implants Res.* **2012**, *23*, 389–395. [CrossRef]
11. Lindquist, L.W.; Carlsson, G.E.; Jemt, T. A prospective 15-year follow-up study of mandibular fixed prostheses supported by osseointegrated implants. *Clinical results and marginal bone loss. Clin. Oral Implants Res.* **1996**, *7*, 329–336. [CrossRef] [PubMed]
12. Ferreira, S.D.; Silva, G.L.M.; Cortelli, J.R.; Costa, J.E.; Costa, F.O. Prevalence and risk variables for peri-implant disease in Brazilian subjects. *J. Clin. Periodontol.* **2006**, *33*, 929–935. [CrossRef] [PubMed]
13. Costa, F.O.; Takenaka-Martinez, S.; Cota, L.O.M.; Ferreira, S.D.; Silva, G.L.M.; Costa, J.E. Peri-implant disease in subjects with and without preventive maintenance: A 5-year follow-up. *J. Clin. Periodontol.* **2012**, *39*, 173–181. [CrossRef] [PubMed]
14. Gobbato, L.; Avila-Ortiz, G.; Sohrabi, K.; Wang, C.W.; Karimbux, N. The effect of keratinized mucosa width on peri-implant health: A systematic review. *Int. J. Oral Maxillofac. Implants.* **2013**, *28*, 1536–1545. [CrossRef]
15. Laine, M.L.; Leonhardt, Å.; Roos-Jansåker, A.M.; Peña, A.S.; Van Winkelhoff, A.J.; Winkel, E.G.; Renvert, S. IL-1RN gene polymorphism is associated with peri-implantitis. *Clin. Oral Implant. Res.* **2006**, *17*, 380–385. [CrossRef]
16. Korsch, M.; Obst, U.; Walther, W. Cement-associated peri-implantitis: A retrospective clinical observational study of fixed implant-supported restorations using a methacrylate cement. *Clin. Oral Implant. Res.* **2014**, *25*, 797–802. [CrossRef]
17. Renvert, S.; Aghazadeh, A.; Hallstrom, H.; Persson, G.R. Factors related to peri-implantitis-A retrospective study. *Clin. Oral Implant. Res.* **2014**, *25*, 522–529. [CrossRef]
18. Lang, N.P.; Berglundh, T.; Working Group 4 of Seventh European Workshop on Periodontology. Periimplant diseases: Where are we now?—Consensus of the Seventh European Workshop on Periodontology. *J. Clin. Periodontol.* **2011**, *38*, 178–181. [CrossRef]
19. Kozlovsky, A.; Tal, H.; Laufer, B.-Z.; Leshem, R.; Rohrer, M.D.; Weinreb, M.; Artzi, Z. Impact of implant overloading on the peri-implant bone in inflamed and non-inflamed peri-implant mucosa. *Clin. Oral Implant. Res.* **2007**, *18*, 601–610. [CrossRef]
20. Fretwurst, T.; Buzanich, G.; Nahles, S.; Woelber, J.P.; Riesemeier, H.; Nelson, K. Metal elements in tissue with dental peri-implantitis: A pilot study. *Clin. Oral Implant. Res.* **2016**, *27*, 1178–1186. [CrossRef]
21. Bassetti, M.; Schär, D.; Wicki, B.; Eick, S.; Ramseier, C.A.; Arweiler, N.B.; Sculean, A.; Salvi, G.E. Anti-infective therapy of peri-implantitis with adjunctive local drug delivery or photodynamic therapy: 12-month outcomes of a randomized controlled clinical trial. *Clin. Oral Implant. Res.* **2014**, *25*, 279–287. [CrossRef]
22. Mombelli, A. Microbial colonization of the periodontal pocket and its significance for periodontal therapy. *Periodontology 2000* **2018**, *76*, 85–96. [CrossRef] [PubMed]
23. Feres, M. Antibiotics in the treatment of periodontal diseases: Microbiological basis and clinical applications. *Ann. R Australas. Coll. Dent. Surg.* **2008**, *19*, 37–44. [PubMed]
24. Butera, A.; Gallo, S.; Pascadopoli, M.; Luraghi, G.; Scribante, A. Ozonized Water Administration in Peri-Implant Mucositis Sites: A Randomized Clinical Trial. *Appl. Sci.* **2021**, *11*, 7812. [CrossRef]
25. Meimandi, M.; Talebi Ardakani, M.R.; Esmaeil Nejad, A.; Yousefnejad, P.; Saebi, K.; Tayeed, M.H. The Effect of Photodynamic Therapy in the Treatment of Chronic Periodontitis: A Review of Literature. *J. Lasers Med. Sci.* **2017**, *8*, S7–S11. [CrossRef]
26. Invernici, M.M.; Salvador, S.L.; Silva, P.; Soares, M.; Casarin, R.; Palioto, D.B.; Souza, S.; Taba, M., Jr.; Novaes, A.B., Jr.; Furlaneto, F.; et al. Effects of Bifidobacterium probiotic on the treatment of chronic periodontitis: A randomized clinical trial. *J. Clin. Periodontol.* **2018**, *45*, 1198–1210. [CrossRef]
27. Francino, M. Antibiotics and the Human Gut Microbiome: Dysbioses and Accumulation of Resistances. *Front. Microbiol.* **2016**, *6*, 1543–1545. [CrossRef]
28. Ince, G.; Gürsoy, H.; Ipçi, S.D.; Cakar, G.; Emekli-Alturfan, E.; Yılmaz, S. Clinical and Biochemical Evaluation of Lozenges Containing Lactobacillus reuteri as an Adjunct to Non-Surgical Periodontal Therapy in Chronic Periodontitis. *J. Periodontol.* **2015**, *86*, 746–754. [CrossRef]
29. Żółkiewicz, J.; Marzec, A.; Ruszczyński, M.; Feleszko, W. Postbiotics-A Step beyond Pre-and Probiotics. *Nutrients* **2020**, *12*, 2189. [CrossRef]
30. Laugisch, O.; Auschill, T.M.; Heumann, C.; Sculean, A.; Arweiler, N.B. Clinical Evaluation of a New Electronic Periodontal Probe: A Randomized Controlled Clinical Trial. *Diagnostics* **2022**, *12*, 42. [CrossRef]
31. O'Leary, T.J.; Drake, R.B.; Naylor, J.E. The plaque control record. *J. Periodontol.* **1972**, *43*, 38. [CrossRef] [PubMed]
32. Ainamo, J.; Bay, I. Problems and proposals for recording gingivitis and plaque. *Int. Dent. J.* **1975**, *25*, 229–235. [PubMed]
33. Mombelli, A.; van Oosten, M.A.; Schurch, E., Jr.; Land, N.P. The microbiota associated with successful or failing osseointegrated titanium implants. *Oral Microbiol. Immunol.* **1987**, *2*, 145–151. [CrossRef] [PubMed]
34. Apse, P.; Zarb, G.A.; Schmitt, A.; Lewis, D.W. The longitudinal effectiveness of osseointegrated dental implants. The Toronto Study: Peri-implant mucosal response. *Int. J. Periodontics Restor. Dent.* **1991**, *11*, 94–111. [CrossRef]
35. De Siena, F.; Corbella, S.; Taschieri, S.; Del Fabbro, M.; Francetti, L. Adjunctive glycine powder air-polishing for the treatment of peri-implant mucositis: An observational clinical trial. *Int. J. Dent. Hyg.* **2015**, *13*, 170–176. [CrossRef]
36. Piepho, H.P. An Algorithm for a Letter-Based Representation of All-Pairwise Comparisons. *J. Comput. Graph. Stat.* **2004**, *13*, 456–466. [CrossRef]

37. Berglundh, T.; Persson, L.; Klinge, B. A systematic review of the incidence of biological and technical complications in implant dentistry reported in prospective longitudinal studies of the least 5 years. *J. Clin. Periodontol.* **2002**, *29*, 197–212. [CrossRef]
38. Turkyilmaz, I. A Proposal of New Classification for Dental Implant Complications. *J. Contemp. Dent. Pract.* **2018**, *19*, 1025–1033. [CrossRef]
39. Fransson, C.; Lekholm, U.; Jemt, T.; Berglundh, T. Prevalence of subjects with progressive bone loss at implants. *Clin. Oral Implant. Res.* **2005**, *16*, 440–446. [CrossRef]
40. Ong, C.T.T.; Ivanoski, S.; Needleman, I.G.; Retzepi, M.; Moles, D.R.; Tonetti, M.S.; Donos, N. Systematic review of implant outcomes in treated periodontitis subjects. *J. Clin. Periodontol.* **2008**, *35*, 438–462. [CrossRef]
41. Heitz-Mayfield, L.J.A.; Lang, N.P. Comparative biology of chronic and aggressive periodontitis vs. peri-implantitis. *Periodontology 2000* **2010**, *53*, 167–181. [CrossRef] [PubMed]
42. Lang, N.P.; Berglundh, T.; Heitz-Mayfield, L.J.; Pjetursson, B.E.; Salvi, G.E.; Sanz, M. Consensus statements and recommended clinical procedures regarding implant survival and complications. *Int. J. Oral Maxillofac. Implant.* **2004**, *19*, 150–154.
43. Ikram, S.; Hassan, N.; Raffat, M.A.; Mirza, S.; Akram, Z. Systematic review and meta-analysis of double- blind, placebo-controlled, randomized clinical trials using probiotics in chronic periodontitis. *J. Investig. Clin. Dent.* **2018**, *9*, e12338. [CrossRef] [PubMed]
44. Vivekananda, M.R.; Vandana, K.L.; Bhat, K.G. Effect of the probiotic Lactobacilli reuteri (Prodentis) in the management of periodontal disease: A preliminary randomized clinical trial. *J. Oral Microbiol.* **2010**, *2*, 5344. [CrossRef]
45. Cereda, E.; Caraccia, M.; Caccialanza, R. Probiotics and mucositis. *Curr. Opin. Clin. Nutr. Metab. Care* **2018**, *21*, 399–404. [CrossRef]
46. Zhao, R.; Hu, H.; Wang, Y.; Lai, W.; Jian, F. Efficacy of Probiotics as Adjunctive Therapy to Nonsurgical Treatment of Peri-Implant Mucositis: A Systematic Review and Meta-Analysis. *Front. Pharmacol.* **2021**, *11*, 541752. [CrossRef]
47. Varoni, E.; Tarce, M.; Lodi, G.; Carrassi, A. Chlorhexidine (CHX) in dentistry: State of the art. *Minerva Stomatol.* **2012**, *61*, 399–419.
48. Haydari, M.; Bardakci, A.G.; Koldsland, O.C.; Aass, A.M.; Sandvik, L.; Preus, H.R. Comparing the effect of 0.06%-, 0.12% and 0.2% Chlorhexidine on plaque, bleeding and side effects in an experimental gingivitis model: A parallel group, double masked randomized clinical trial. *BMC Oral Health* **2017**, *17*, 118. [CrossRef]
49. Ishikawa, K.H.; Bueno, M.R.; Kawamoto, D.; Simionato, M.R.L.; Mayer, M.P.A. Lactobacilli postbiotics reduce biofilm formation and alter transcription of virulence genes of Aggregatibacter actinomycetemcomitans. *Mol. Oral Microbiol.* **2021**, *36*, 92–102. [CrossRef]
50. Vale, G.C.; Mayer, M.P.A. Effect of probiotic Lactobacillus rhamnosus by-products on gingival epithelial cells challenged with Prphyromonas gingivalis. *Arch. Oral Biol.* **2021**, *128*, 105174. [CrossRef]
51. Butera, A.; Gallo, S.; Pascadopoli, M.; Taccardi, D.; Scribante, A. Home Oral Care of Periodontal Patients Using Antimicrobial Gel with Postbiotics, Lactoferrin, and Aloe Barbadensis Leaf Juice Powder vs. Conventional Chlorhexidine Gel: A Split-Mouth Randomized Clinical Trial. *Antibiotics* **2022**, *11*, 118. [CrossRef] [PubMed]
52. Lee, J.; Park, S.; Oh, N.; Park, J.; Kwon, M.; Seo, J.; Roh, S. Oral intake of Lactobacillus plantarum L-14 extract alleviates TLR2- and AMPK-mediated obesity- associated disorders in hight-fat-diet-induced obese C57BL/6J mice. *Cell Prolif.* **2021**, *54*, e13039. [CrossRef] [PubMed]