

Clinical Effects of the Application of an Innovative Bioadhesive Gel in the Nonsurgical Treatment of Chronic Periodontitis: A Randomized "Split Mouth" Trial



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Aims: To evaluate the additional clinical efficacy of an innovative bio-adhesive gel (Hobagel Plus, i-Res; Milan) after scaling and root planing in patients with chronic periodontitis. **Materials and methods:** in this randomized study with a "split mouth" design, 20 subjects with chronic periodontitis were evaluated after SRP treatment and application of the new bio-adhesive gel in the following five weeks. At the control sites, a 1% chlorhexidine gel was applied with the same protocol. The following parameters were taken into account: IP, BOP, PD, CAL. **Results:** The chance of having a positive BOP at sites treated with Hobagel Plus was 96% lower than at those treated with 1% chlorhexidine gel. The Plaque Index (IP) decreases with significant association with time. A reduction in PD was observed and estimated (p-value: < 0.0001) in both the test and control groups, however the CAL shows a clearer improvement with Hobagel Plus (about 24% more than with 1% chlorhexidine gel). **Conclusions:** Bio-adhesive gel has an excellent effect on soft tissue repair in patients with chronic periodontitis. In addition, the antibacterial action of the gel allows for additional clinical improvement to SRP therapy.

Keywords: Chronic periodontitis, Adjunctive therapy, Bioadhesive gel, Chlorhexidine.



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Introduction

Chronic periodontitis is universally described as an inflammatory-infectious state capable of inducing damage to the soft tissues and alveolar bone that support teeth. The therapies proposed over the years have always placed as the first indispensable clinical step an accurate elimination of soft and hard deposits along the dento-periodontal tissues and a root planing, generally carried out by quadrants of the arch. Curettage of the affected tissues is often further necessary to allow the start of a regenerative process that leads to a preliminary clot inside the periodontium, followed by the development of a connective tissue with a new attachment that is arranged on the dental slopes.

Unfortunately and for different reasons, the disease process may persist or progress with the development of additional residual or recurrent pockets for which surgical approach may be necessary. Therefore, an additional use of active substances has long been proposed, with the aim of controlling inflammation and bacterial infection. This would reduce recurrences of non-surgical treatments, improve outcomes, and limit the need for a surgical approach.

However, the clinical results of adjunctive therapy appear to be discordant and even the recent literature does not offer unanimous conclusions. Eberhard et al.¹ state, on the basis of an extensive review of Cochrane databases, that there is no definitive evidence to date to accept that local applications of substances bring additional benefits compared to the traditional mechanical approach. It has been noted^{2,3} however, that the mechanical procedure can often be difficult or ineffective and must, therefore, be integrated with what has been defined as "chemical control".

The American Dental Association (ADA) recently formed a panel of experts to determine the clinical evidence for nonsurgical treatment of patients with chronic periodontitis by mechanical therapy, with or without the use of adjunctive substances.⁴ Scaling and Root Planing (SRP) are confirmed as the basis of non-surgical treatment. The use of antimicrobial agents, on the other hand, is recommended with reservations due to "the higher risk of adverse effects at higher doses of antibacterials". Especially

Locally slow-release systems are preferable in weighing the benefits induced and the risk of adverse effects. In a further review of the recently published literature,⁵ Da Rocha et al. conclude that the additional use of local delivery systems of antibacterial substances induces a therapeutic effect in periodontal pockets only if the release is prolonged and controlled. The results of this therapeutic approach are a function of the individual clinical situation, the general state of health of the patient and any previous use of antimicrobials. There would therefore be two clinical determinants that can be considered as effective the additional application of active substances in the treatment of periodontitis: their effective persistence along the tissues to be treated and a verifiable absence of adverse effects, local or general, induced by the use of active ingredients including chlorhexidine, which has been known and used in periodontology for a long time. From the point of view of its persistence, unfortunately, chlorhexidine mouthwash at different dosages proves to be unsuitable, as well demonstrated by the research of Paolantonio and Coll.⁶ and Matesanz et al.⁷, Authors who believe that the use of the gel substance is preferable in non-surgical treatment. The sub-gingival application of chlorhexidine, after SRP, in subjects with chronic periodontitis, induces significant improvements already after one month of application only as regards the plaque index, since the positive effect on BOP and probing depth (PD) are not so evident.⁸ Also the microbiological analysis of bacterial colonies taken from periodontal pockets of subjects with moderate or severe periodontitis, together with clinical parameters, demonstrates the numerical reduction of these colonies already after one month of chlorhexidine use, after SRP, but only if the sub-gingival application is carried out with paints or gels.^{9,10}

Finally, it should be considered that the discomfort described by many patients and the many side effects related to prolonged use of chlorhexidine, especially in the high dosages typical of gel formulations, often limit its effective application and expected results.

Purposes

The main aim of the present research is to evaluate the clinical effects following the application of the

a new bioadhesive gel (Hobagel Plus, i-RES, Milan) additional to scaling, root planing and curetting procedures, by quadrants, in subjects suffering from chronic periodontitis.

A further aim of the clinical investigation is to compare the results obtained with the bioadhesive gel with those emerging from a similar procedure that made use of a 1% chlorhexidine gel.

Materials and methods

Twenty cases of moderate or severe chronic periodontitis, both sexes, were recruited and rebranded to receive scaling, root planing and periodontal curettage followed by the application of the gels examined (Hobagel Plus versus chlorhexidine gel 1%). The study was carried out with a "split mouth" design in the sense that in one quadrant of the same patient the additional procedure uses Hobagel Plus, while in another quadrant examined the protocol involved the use of chlorhexidine gel 1%.

Some clinical indices were detected during the investigation: the plaque index (IP) according to Ramfjord in numerical formula, the dichotomous Bleeding On Probing (BOP) index, the probing depth (PD) and the clinical attack level (CAL) with millimeter probe.

The evaluation times used for each individual case are at the beginning of the protocol (baseline – time 0), one week later (time 1) and five weeks later (time 2).

The inclusion criteria of the recruited subjects are: adulthood, chronic periodontitis or similar periodontal diseases, moderate/severe periodontal pockets with involvement of multiple tooth surfaces, residual pockets after RSP or relapsed after maintenance, willingness to complete the survey with "split mouth" method by the participants. The exclusion criteria are: age under 18 years, aggressive periodontitis, presence of systemic pathologies interfering with periodontal status, antibiotic therapy in the 6 weeks prior to or during the investigation time, known allergies to some component of the gels applied.

To all participants, after the clinical sessions in which the mechanical procedures and the preparation of the

In addition to the use of the gels under research, the same gels were provided to continue with domicile applications twice a day and a neutral toothpaste (Betadent, Betafarma, Milan), free of antiseptic or anti-inflammatory substances, potentially interfering with the outcome of the results, for the usual home hygiene. Specific and uniform instructions were presented to each participant.

In statistical analysis, the continuous and categorical variables appear, respectively, as a mean with standard deviation (SD) and as the number of subjects and percentage values. Baseline differences between treatment groups in BOP, IP, PD and CAL parameters were tested using the Fisher's Exact test or the Student's *t* test, respectively for categorical and continuous variables. The associations of the gels with the indicated parameters were tested using the "logistic or linear mixed effects model" for the categorical and continuous variables, respectively. The "Likelihood Ratio test" was used as a test of statistical significance and patients were considered as a random effect. Differences with a p-value of less than 0.05 were considered significant. The data were acquired and analyzed using the R v3.4.1 software.

The new bioadhesive gel "Hobagel Plus" contains several active ingredients: cetylpyridinium chloride with disinfectant action on gram+ bacteria (and partly on gram- bacteria), tea tree and manuka essential oils with a strong antiseptic action (typical of oils extracted from myrtle plants) and anti-inflammatory/healing action on ulcerated tissues, the mixed salt of Na/Ca of the methylvinyl ether/polyvinylpyrrolidone copolymer and Na carboxy-methylcellulose for prolonged adhesion of the gel to the periodontal tissues, hyaluronic acid (also in oligomers) at different molecular weights associated with and potentiated by H peroxide.

Results

The clinical characteristics of the group of 20 subjects participating in the research (of which 11 males) are summarized in figure 1.

The average of the PD and CAL parameters were respectively 4.23 mm (1.05) and 3.28 mm (1.72). At baseline there were no significant differences between the two treatment groups for BOP, PD and CAL parameters

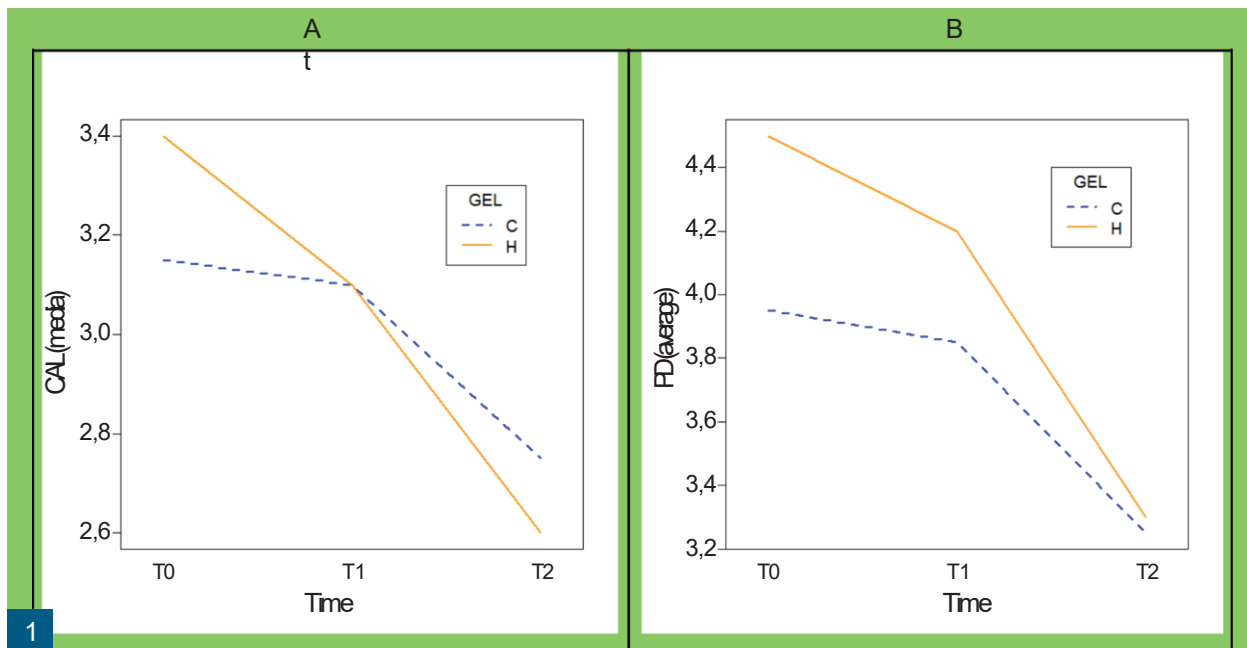


Fig. 1 Means of CAL and PD parameters at three times in the treatment groups. The level of clinical attack is much improved in sites treated with Hobagel Plus, compared to those treated with chlorhexidine gel 1%.

Table 1. Essential demographic and clinical characteristics of participants included in the research at baseline (T0). The data are expressed both in standard deviation and as a percentage of the number of subjects

Features	BOP		OR (95% CI)	p-value	IP		OR (95% CI)	p-value
	No	Yes			No	Yes		
(Intercept)			3,6 and 10 + 3 (16,79; 7,6 e 10 + 5)	0,0028				
Come here				0,0070				0,0665
Chlorhexidine 1%	29 (48,33%)	31 (51,67%)	1		27 (45%)	33 (55%)	1	
Hobagel Plus	35 (58,33%)	25 (41,67%)	0,04 (0,00 : 0,53)		32 (53,33%)	28 (46,67%)	0,29 (0,07 : 1,22)	
Time				< 0.0001				< 0.0001
1	6 (15%)	34 (85%)	1		0 (0%)	40 (100%)	1	
2	19 (47,5%)	21 (52,5%)	0,01 (0,00 : 0,05)		22 (55%)	18 (45%)	0,01 (0,00 : 0,10)	
3	39 (97,5%)	1 (2,5%)	0,01 (0,00 : 0,02)		37 (92,5%)	3 (7,5%)	0,01 (0,00 : 0,02)	

Table 2. Descriptive statistics and summary of the "linear mixed-effect model". The coefficient (95% CI) is the linear coefficient with a 95% confidence interval

Features	CAL			PD		
	Media (SD)	Coef. (95% C.I.)	p-value	Media (SD)	Coef. (95% C.I.)	p-value
(Intercept)		3,26 (2,55 : 3,97)	< 0.0001		4,07 (3,66 : 4,47)	< 0.0001
Come here			0,7555			0,0027
Chlorhexidine 1%	3,00 (1,50)	0		3,68 (0,79)	0	
Hobagel Plus	3,03 (1,75)	0,03 (-0,18 : 0,25)		4,00 (1,24)	0,32 (0,12 : 0,52)	
Time			0,0001			< 0.0001
1	3,28 (1,72)	0		4,23 (1,05)	0	
2	3,10 (1,66)	-0,18 (-0,43 : 0,08)		4,01 (0,95)	-0,2 (-0,45 : 0,05)	
3	2,68 (1,44)	-0,6 (-0,86 : -0,34)		3,28 (0,91)	-0,95 (-1,2 : -0,7)	

(p-value 0.9999, 0.0997 and 0.6527 respectively). The descriptive statistics of gels in the levels of dependent variables are given in tables 1 and 2. As regards continuous outcomes (Table 2), the mean PD value in the sample treated with Hobagel Plus was slightly higher than in the sample treated with chlorhexidine gel 1% (4 mm vs 3.68). On the contrary, the average value of CAL was substantially identical in both treatment groups. A statistically significant increase (0.32 mm) was observed when comparing the mean PD parameter in the group treated with Hobagel Plus compared to the group treated with chlorhexidine gel 1% (p-value 0.0027).

The mean CAL values at time 1 and time 2 were 3.10 mm (SD:1.66) and 2.68 mm (SD:1.44) respectively. The mean PD values at time 1 and time 2 were 4.01 mm (SD: 0.95) and 3.28 mm (SD: 0.91), respectively. Therefore, a significant trend in the time variable was observed for both parameters (p-value 0.0001 and 0.0001 respectively) as clearly shown in Figure 1.

As far as categorical outcomes are concerned (Table 1), a significant statistical association is highlighted between the IP parameter and the "time" factor (p-value 0.0001): it is highlighted, in fact, that the probability of having high IP values tends to be reduced by up to 99% in times T₁ and T₂ compared to the baseline.

A statistically significant effect related to the use of the two gels tested, in relation to the time of use, is also observed for the BOP parameter, but the probability of having a positive BOP in the group treated with Hobagel Plus is about 96% lower than in the group treated with chlorhexidine gel 1%.

In summary, therefore, the plaque index (IP) detected at sites where Hobagel Plus has been applied tends to decrease after 5 weeks in a similar way to that found at sites treated with chlorhexidine gel 1%; Probing bleeding (BOP), on the other hand, tends to be much more radically reduced, over the same period of time, in samples treated with Hobagel Plus. The probing depth (PD) improves in the sites treated with the two different gels, but the clinical attack level (CAL) shows a tendency to normalize much higher in the sites where Hobagel Plus has been applied (24% improvement in about 5 weeks). These data therefore seem to highlight the clear effectiveness of the

Hobagel Plus on the tissue repair process.

Discussion

The clinical results that emerge from the present research must be related to the characteristics of periodontal antibacterial agents (ability to inhibit the bacterial adhesion phase to tissues, potential effect of interrupting the metabolic activity of the bacteria themselves, without interfering with the other biological mechanisms of healing, low local or general toxicity) already identified in the literature since the mid-90s.¹¹ Chlorhexidine, frequently used in the chemical control of biofilms, meets the criteria of antibacterial efficacy, but is not free from a series of side effects, increasingly described in Reading,¹²⁻¹⁴ linked to the high concentration of the substance and the long regime of use proposed to periodontal patients to obtain satisfactory clinical effects.

The use of chlorhexidine, *in vitro*, on human fibroblasts of the gingiva and periodontal ligament can have toxic effects on both their survival and their migratory capacity. The undiluted chlorhexidine mouthwash, applied for 60", is in fact able to determine necrosis of fibroblasts after just 24 hours. Dilutions of 15-20% induce necrosis in 50% of cases and a reduction in migratory capacity. Diluted essential oils, on the other hand, do not induce such toxic effects.¹⁵ In addition, chlorhexidine appears to interfere with the cellular proliferation of fibroblasts and chollageneic proteins and not of the periodontium. It follows that contact with this substance, even in the 0.12% formulation, on periodontal surgical sites can negatively interfere with the healing process.¹⁶ There are also observations¹⁷ on patients in whom the use of chlorhexidine 0.12% mouthwash for two weeks was able to induce alterations in the perception of saline or bitter taste and abnormal lingual and dental pressures.^{6,19 p.m.}

The clinical results of our investigation, despite the limitation of the cases treated and the only short-term evaluation of the same, demonstrate how the application of the innovative bioadhesive gel under study is a viable alternative to the use of chlorhexidine in subjects suffering from chronic periodontitis, naturally if they undergo regular check-ups

and therapeutic procedures, including non-surgical ones. The deposition of bacterial biofilms seems to be counteracted in a similar way to that obtained with chlorhexidine, but the tissue healing effects appear even superior. The peculiar characteristics of the gel lie in the mix of active ingredients that compose it. Among them, cetylpyridinium chloride stands out, a bactericide very active on gram+ bacteria and on some gram-, which is associated in the antibacterial action with two essential oils (tea tree oil and manuka oil) which, being extracted from myrtle plants, are rich in terpenes and triketones, with a strong antiseptic and anti-inflammatory action. The regeneration of affected periodontal tissues is entrusted, in the context of the gel, to hyaluronic acid, enhanced by the presence of hydrogen peroxide, with antioxidant action. It is mainly the oligomers of hyaluronic acid, which have a very low molecular weight, that quickly penetrate the affected tissue, binding water and promoting the multiplication and migration of fibroblasts. Finally, bisabolol and allantoin have a soothing action with undoubted advantages in the patient's comfort. The gel, which comes in anhydrous form, has an exceptional ability to adhere and persist on the treated tissues. This peculiar innovation originates from a mix of salts and natural resins, easily perceptible both during **bioadhesive** application.

Hobagel Plus bioadhesive gel has an excellent effect on soft tissue repair in patients with chronic periodontitis. In these patients, moreover, the antibacterial action of the gel allows a clinical improvement in addition to the non-surgical therapy of scaling and root planing.

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Clinical effects of a new bio-adhesive gel during non-surgical treatment of chronic periodontitis: a randomized “split mouth” study

Aim: The objective of this study was to evaluate the clinical adjunctive efficacy of local application of a new bio-adhesive gel (Hobagel Plus iRES Co.- Milan, Italy) following scaling and root planning (SRP) in chronic periodontitis patients. Another purpose was to compare the clinical outcomes with those obtained through a 1% chlorhexidine gel in same patients. **Materials and Methods:** In this randomized “split mouth” study 20 subjects with chronic periodontitis were evaluated after SRP procedures. In test sites bio-adhesive gel was applied after SRP and during the next five weeks post therapy (with checks after one and five weeks). In control sites, 1% chlorhexidine gel was applied with same method and times. Plaque Index (PI), Bleeding on Probing (BOP), Probing Depth (PD) and Clinical Attachment Level (CAL) were recorded at baseline, 1 week (T1) and 5 weeks (T2). Clinical differences were tested using Fisher’s Exact test and Student’s *t* test. Associations of gels with clinical parameters were investigated by using Binomial or Linear Mixed-Effect Model. **Results:** Significant effect of gel-time on BOP were observed in all sites groups (*p*-value 0.0070 and 0.0001, respectively). However, the chance of having BOP in patients treated with Hobagel Plus was about 96% less likely than in patients treated with 1% chlorhexidine gel. A significant association was observed between PI and time factor (*p*-value 0.0001): the chance to have lower levels of plaque on sites is evident, from baseline to T1 and T2, by using both the gels. A time effect trend on PD was observed and estimated (*p*-value < 0.0001) in both test and control groups, however CAL shows a better ameliorative trend on sites where Hobagel Plus was applied (24% more than 1% CHX gel in five weeks). **Conclusions:** Bio-adhesive gel (containing hyaluronic acid, essential oils and cetilpyridinium chloride) has an optimal effect on soft tissues replacement in patients with chronic periodontitis. In addition, its antimicrobial action supplies a clinical amelioration, as an adjunct to SRP, on those patients.

Key words: Chronic periodontitis, Adjunct therapy, Bio-adhesive gel, Chlorhexidine.