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In a double-blind clinical trial vs. placebo, a new gel based on HMW sodium hyaluronate (the sodium salt of hyaluronic acid with a high mean molecular weight) was used on patients with marginal gingivitis (2 applications a day for 4 weeks) to complete oral hygiene. The product proved effective in promoting more rapid, complete remission of symptoms after an oral hygiene session; it was also very well tolerated and well accepted by patients because of its practicality and excellent sensory characteristics. The activity of HMW sodium hyaluronate can reduce the tendency to relapse in patients with plaque-generated gingivitis.

DOUBLE-BLIND CLINICAL TRIAL VS. PLACEBO OF A NEW SODIUM-HYALURONATE-BASED GINGIVAL GEL

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BACKGROUND AND PURPOSE OF TRIAL

Hyaluronic acid is a biopolymer constituted by D-glycuronic acid and N-acetyl glucosamine.

GENGIGEL® is an orthostomatological gingival gel which contains as its active constituent the sodium salt of hyaluronic acid with a high mean molecular weight (HMW), obtained by a biotechnological method (Fig. 1).

Hyaluronic acid is a "natural" substance, and is therefore devoid of toxic risks and adverse effects in general, as it is a constituent of the ground substance of connective tissue (especially in the gingival mucosa, where it performs the following physiological effects (1, 2, 3).

ANTI-HYALURONIDASE EFFECT

Hyaluronidase is a bacterial enzyme which plays an important part in "plaque-generated" disorders, because it is able to break down the proteoglycans in the ground substance of connective tissue (ie. macroaggregates of hyaluronic acid and proteins), thereby enabling bacteria to invade even the deepest periodontal structures.

HMW hyaluronic acid can therefore perform an efficient anti-hyaluronidase action as a result of its physiological macroaggregating activity.

TISSUE REPAIR AND PROTECTION EFFECT

Under physiological conditions, the proteoglycans in the ground substance of the gingival mucosa connective tissue represent an effective barrier against microbe invasion, and against the spread of bacterial toxins and cell-damaging factors generated by the consequent inflammatory and immune reaction.

If the natural barrier is damaged for the above reasons, an exogenous input of HMW hyaluronic acid can help reconstruct the barrier due to its macroaggregating effect on the proteoglycans.

ANTI-OEDEMATIGENOUS EFFECT

Oedema basically consists of an accumulation of fluid in the intercellular spaces of connective tissue. In the proteoglycans, the macroaggregating effect of hyaluronic acid gives rise to “free water binding”, ie. the capture of free water resulting from the formation of hydrogen bonds.

Figure 1: Hyaluronic acid sodium salt (sodium hyaluronate)

Aspecific plaque-generated inflammatory gingivitis is very common, and generally follows a cyclical or relapsing pattern. It is now unanimously acknowledged (4) that despite its nature, often wrongly considered "trivial" by patients, the cyclical recurrence of episodes of gingivitis causes irreversible harm to the periodontal structures, ie. the formation of increasingly deep pockets with gradual loss of attachment and bone resorption (Fig. 2), and can therefore be an even more frequent cause of tooth loss than tooth decay (5).

In uncomplicated cases of gingivitis, an oral hygiene session with removal of plaque and tartar from the diseased periodontium is generally sufficient to produce a temporary remission in symptoms. However, if the patient's oral hygiene habits are unsatisfactory, insufficient cleaning will inevitably cause a relapse and/or worsening of the gum disease. It is therefore essential for the dentist to instruct the patient correctly in how to perform and maintain effective oral hygiene, although these instructions are unfortunately not always adequately followed by patients.

The innocuity of GENGIGEL® and its favourable tissue repair and healing action have already been confirmed by the results of a preliminary trial performed on 10 patients suffering from inflammatory gingivitis and surgical wounds following odontostomatological operations (6).

The purpose of this clinical trial was to evaluate the effects of GENGIGEL® under controlled conditions in patients with marginal gingivitis when used as a complement to daily oral hygiene over a 4-week period following a professional oral hygiene session.

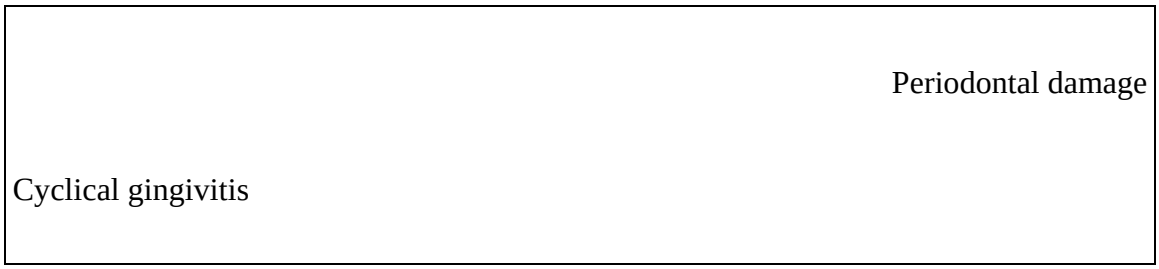

Figure 2: Ideograph showing the possible consequences of cyclical gingivitis

MATERIALS AND METHODS

A randomised, controlled double-blind trial vs. placebo was conducted on two parallel groups of patients, 30 treated with GENGIGEL® and 30 with placebo (ie. the gel excipients alone).

ADMISSION CRITERIA

- Patient's informed consent
- Age 18-35 years
- Regular use of toothbrush and toothpaste, at least morning and evening.
- Gingival pain and/or bleeding (when brushing the teeth), at least during the past 2 weeks
- Oral hygiene defined as "not ideal" on the basis of a score of at least 10 positive points for plaque and 8 positive points for bleeding (in the API and SBI determinations)
- Clinical diagnosis of aspecific gingivitis, with evident reddening and/or swelling of marginal mucosa at the level of at least 3 contiguous teeth, possibly with signs of inflammation extending to the adherent gingiva and the interdental papillae (alteration of colour, swelling, loss of characteristic stippling) but without deep gingival pockets (> 3 mm)
- Elements I-VII present in all quadrants
- Patient's undertaking to follow the dentist's instructions about correct oral hygiene with toothbrush and toothpaste as well as possible, to use a gingival gel morning and evening for 4 weeks, and to complete a personal diary and return it at the check-up visit together with the used tube of gel (see paragraphs below).

EXCLUSION CRITERIA

- Indication for immediate periodontal surgery or conservative or prosthetic odonto-stomatological treatment
- Pathological factors during the past month (e.g. illnesses treated with antibiotics, or immobilisation of arm due to fracture, etc.) which might have made a crucial contribution to the onset of the inflammation
- Chronic illnesses liable to interfere with the state of periodontal health
- Pathological tooth mobility or clinical signs of bone resorption
- Signs of atrophy or gingival retraction, gingival complications (necrosis, epulis, lacerations, etc.), or characteristic signs of acute specific gingivitis (necrotising ulcerative gingivitis, herpetic, syphilitic or streptococcal gingivitis, or gingivitis caused by candida, Actinomyces or tuberculosis).

TEST MATERIALS

Samples of GENGIGEL® and placebo (ie. the gel excipients only) in indistinguishable packs were used for the trial, together with data entry forms for the dentist and diaries for patients so that compliance and any adverse effects could be established.

The samples consisted of 60 pairs of 25 gm tubes (one pair per patient) marked with the randomisation number only.

TEST TIMES AND EXAMINATIONS

The examinations were performed on the 1st Visit (basal), the 2nd Visit (check-up after 2 weeks) and the 3rd Visit (check-up after 4 weeks).

On each visit an overall clinical evaluation of the state of the gingivae was effected, and ordinal scores were used to quantify reddening and swelling of the marginal mucosa and interdental papillae (0 = none, 1 = slight, 2 = moderate, 3 = intense). Immediately afterwards, the approximal plaque index (API) and the sulcus bleeding index (SBI) were determined in accordance with the Lange et al. method (7). At the end of the tests on the 1st Visit, an oral hygiene session was performed to ensure complete removal of plaque and tartar. On the 2nd and 3rd Visits, any adverse effects were ascertained on the basis of objective examination and symptoms reported by patients and recorded in their diaries.

TEST TREATMENT

Every day, after using toothbrush and toothpaste in the morning and evening, the patient had to apply 5 mm of gel squeezed from the tube onto the gums on the palatal and lingual side, and another 5 mm of gel on the vestibular side, with a gentle fingertip massage.

The treatment began at the end of the 1st Visit, immediately after the oral hygiene session. On that occasion the patient was instructed and assisted by the dentist in performing the first application, and was given the first diary and first tube of gel, to be returned at the 2nd Visit.

At the 2nd Visit the second tube of gel and second diary were given to the patient, to be returned at the 3rd Visit.

STATISTICAL METHODOLOGY

The homogeneity of the groups was evaluated by the chi-squared test for the patients' sex, Student's "t" test for age, actual interval between two consecutive visits and compliance (in terms of applications omitted between one visit and the next, expressed as a percentage of the theoretical number).

The Wilcoxon test was used for the intra-group study of the symptom scores and the API and SBI indexes (with comparisons versus basal value).

The Mann-Whitney U test was used for the inter-group study of the symptom scores and the API and SBI indexes (comparison performed on the same observation times).

In the case of all the statistical tests, the significance threshold was set at $P < 0.05$.

RESULTS

The mean age of the 60 patients suffering from marginal gingivitis admitted to the trial, namely 27 men and 33 women, was 27.3 years (minimum 19, maximum 35).

The treatment groups (GENGIGEL® or placebo) proved homogenous in terms of the patients' age and sex, compliance with the prescription (over 95% in both groups at both follow-up visits), and the basal values of the symptom, API and SBI scores.

One patient treated with the placebo and one treated with GENGIGEL® failed to attend for the 2nd Visit, and were therefore considered spontaneous drop-outs and excluded from the continuance of the trial. There were no other drop-outs for any reason, including non-compliance and adverse effects. The trial was therefore completed on 29 patients treated with GENGIGEL® and 29 treated with the placebo.

Table 1: SYMPTOM SCORES

The significance (P) of the differences between the means vs. basal value was calculated with the Wilcoxon text, and the inter-group significance with the Mann-Whitney U test. D = variation in mean vs. basal value.

Treatment group		**GENGIGEL®**			**Placebo**		
Experiment time		**Basal**	**2 wks**	**4 wks**	**Basal**	**2 wks**	**4 wks**
Patients studied		**30**	**29**	**29**	**30**	**29**	**29**
Approximal plaque index (API)	mean Δ vs. basal vs. placebo	47.4 NS	24.1 -49.0% P<0.001 NS	19.7 -58.4% P<0.001 NS	45.0	26.5 -41.1% P<0.001	21.1 -53.1% P<0.001
Reddening of marginal mucosa (score)	mean Δ vs. basal vs. placebo	1.50 NS	0.23 -84.4% P<0.001 P<0.001	0.03 -97.7% P<0.001 P<0.001	1.53	0.77 -50.0% P<0.001	0.41 -73.0% P<0.001
Swelling of marginal mucosa (score)	mean Δ vs. basal vs. placebo	1.87 NS	0.47 -75.0% P<0.001 P<0.001	0.03 -98.2% P<0.001 P<0.001	1.97	1.13 -42.4% P<0.001	0.76 -61.4% P<0.001
Reddening of interdental papillae (score)	mean Δ vs. basal vs. placebo	1.63 NS	0.30 -81.6% P<0.001 P<0.001	0.07 -95.8% P<0.001 P<0.001	1.63	0.97 -40.8% P<0.001	0.69 -57.8% P<0.001
Swelling of interdental papillae (score)	mean Δ vs. basal vs. placebo	2.23 NS	0.83 -62.7% P<0.001 P<0.001	0.14 -93.8% P<0.001 P<0.001	2.30	1.53 -33.3% P<0.001	1.14 -50.5% P<0.001
Sulcus bleeding index (SBI)	mean Δ vs. basal vs. placebo	43.0 NS	11.7 -72.8% P<0.001 P<0.001	3.41 -92.1% P<0.001 P<0.001	40.1	23.9 -40.5% P<0.001	17.6 -56.1% P<0.001

TOLERABILITY

No adverse effects were observed on the objective examination, reported by patients or recorded in their diaries, regardless of the type of treatment received (GENGIGEL® or placebo).

APPROXIMAL PLAQUE INDEX (API)

The API index (Table 1 and Fig. 3) in both groups presented a significant reduction (P<0.001) compared with the basal values at both follow-up visits. In the inter-group comparison between GENGIGEL® and the placebo, no statistically significant differences were found.

During the trial, the values of the index demonstrated that compared with the basal value, the oral hygiene condition had only improved by 40-60%. In fact, early re-formation of plaque accumulations amounting to an API between 20 and 30 was found (24.1 in the patients treated with GENGIGEL® and 26.5 in the control group 2 weeks after the oral hygiene session, and 19.7 and 21.1 respectively 4 weeks after the session).

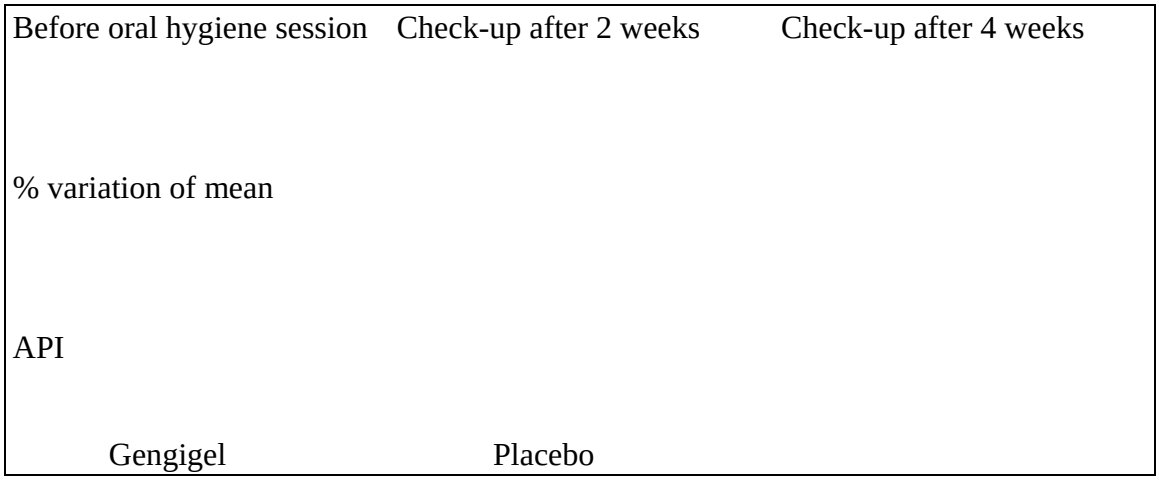

Figure 3: % variation in approximal plaque index (API) means compared with basal value. The differences between the means were not significant (NS) in the inter-group comparison between GENGIGEL® and the placebo.

TREND OF SYMPTOMS

The patients in both groups presented a gradual, statistically significant (P<0.001) improvement in symptoms at both follow-up visits compared with the basal values. Statistically significant differences clinically in favour of GENGIGEL® (p<0.001) were found in the inter-group comparison at both follow-up visits for all symptoms, namely reddening and swelling of the marginal mucosa and the interdental papillae (Table 1).

SULCUS BLEEDING INDEX (SBI)

The SBI index (Table 1 and Fig. 4) in both groups presented a significant reduction (P<0.001) compared with the basal value at both follow-up visits. In the inter-group comparison between GENGIGEL® and the placebo, a statistically significant difference (P<0.001) clinically in favour of GENGIGEL® was found after 2 and 4 weeks.

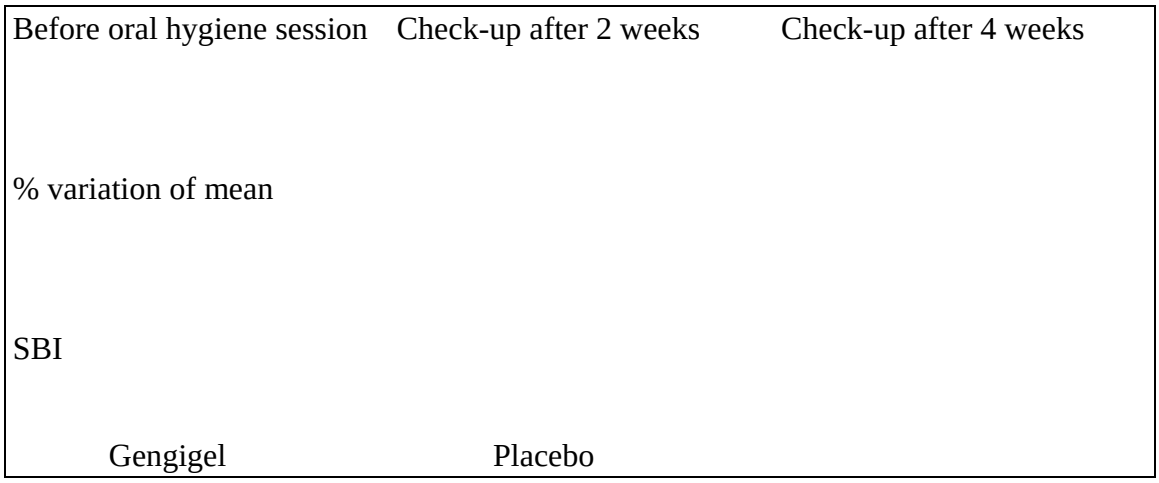

Figure 4: % variation in sulcus bleeding index (SBI) means compared with basal value, and significance of differences between the means in the inter-group comparison between GENGIGEL® and the placebo.

DISCUSSION

Our patients presented over 95% compliance with the prescription; this level is certainly associated with the practicality of GENGIGEL® and its excellent acceptability, including acceptability of its sensory characteristics.

The efficacy of GENGIGEL®, confirmed in this trial by the trend of the SBI index and the individual symptom scores (reddening and swelling of the marginal mucosa and the interdental papillae), is consistent with the known activity (1, 2, 3, 6) of HMV hyaluronic acid, ie. its anti-hyaluronidase, anti-oedematigenous, tissue repair and protective effect.

GENGIGEL® aided the gingivitis healing process after the oral hygiene session even in patients whose oral hygiene condition could not be considered "ideal" during the trial, although it definitely improved as a result of the instructions given by the dentist.

Regular use of GENGIGEL® as a complement to oral hygiene, especially when such hygiene is not ideal, can therefore produce benefits in terms of a lower tendency to relapse, ie. a lower risk of the gradual loss of attachment associated with the generally cyclical nature of plaque-generated gingivitis (4).

CONCLUSIONS

As a result of the “natural” activity of HMW hyaluronic acid (which has an anti-hyaluronidase, tissue repair, protective and anti-oedematigenous effect), GENGIGEL® proved able to promote rapid remission of symptoms after the professional session when used twice a day for four weeks as a complement to oral hygiene by our patients.

The demonstrable effects of GENGIGEL® can effectively protect the marginal gingiva against the consequences of the inevitable re-formation of plaque accumulations in patients who, though they use toothbrush and toothpaste regularly, are unable to maintain an “ideal” oral hygiene condition after professional sessions, which in these cases are necessarily periodic.

In view of the pathogenetic mechanism of periodontal disease (or pyorrhoea) which is now unanimously acknowledged, GENGIGEL®, due to the special “natural” activity of HMW hyaluronic acid, can be usefully employed to prevent damage caused by imperfect oral hygiene and the consequent relapsing episodes of gingivitis, not only to the marginal mucosa, but also to the deeper periodontal structures, which can suffer gradual loss of attachment.

The excellent tolerability of GENGIGEL®, due to its “natural” formulation which contains no cariogenic sugars (xylitol is used as sweetener), mean that it has no contra-indications, even for long-term use. The excellent acceptability of GENGIGEL® in terms of practicality and sensory characteristics is likely to promote good compliance by patients with the prescription, even over long periods.

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KEYWORDS

Oral hygiene,

sodium hyaluronate,

gingivitis,

double-blind clinical trial versus placebo.

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GENGIGEL®

(hyaluronic acid)

LONG-ACTING GUM PROTECTING AND FLUID BALANCING AGENT

Treatment of states of hyper-reactivity of the gingival mucosa, including post-operative hyper-reactivity

GENGIGEL® is an orthostomatological gel containing high molecular weight (HMW) hyaluronic acid (in the form of sodium hyaluronate), obtained by a biotechnology method.

Hyaluronic acid is a "natural" substance in that it is a physiological constituent of connective tissue (especially in the gingival mucosa), where it performs an anti-oedema and tissue repair action as a result of the macroaggregating effect of the substance.

Under basal conditions, HMW hyaluronic acid is distributed in a selective, specific manner; it is particularly concentrated in the outermost layers of the gingival epithelium, where it contributes to the barrier function and the tensile strength of the periodontal ligament. In periodontal disease it increases considerably (by up to some 200% compared with the basal values), thus demonstrating its specific role in regulating cell turnover and optimising local regeneration capacities.

Subsequently, after release of the hyaluronidases and proteases produced by bacterial plaque, periodontal hyaluronic acid is depolymerised, extensively altering the architecture of the gingival connective tissue.

The hyaluronic acid deficiency that arises under these conditions prevents the molecule from:

- deactivating bacterial hyaluronidases
- normalising the macroaggregation of connective tissue proteoglycans
- bonding with free water, thus performing an anti-oedema effect.

GENGIGEL® is therefore an innovatory product, which performs a long-acting fluid balancing and repair effect on the periodontal membrane.

The effects of HMW hyaluronic acid on the mucosa are enhanced by the specific formulation of *GENGIGEL*®, which guarantees the maximum adhesion and thus allows the active constituent (which would otherwise be eliminated by constant salivary drainage) to remain in situ; its effects are also rendered safe by 2,4-dichlorobenzene methanol, a known substance with a potent antiseptic effect.

GENGIGEL® is extremely safe; as it presents no contraindications or side effects, it can be used without restriction even by children, pregnant women and the elderly. The product can also be used in cases in which the use of anti-inflammatories is contraindicated. By virtue of the properties of xylitol, a natural sweetener which does not promote tooth decay or cause significant variations in the blood sugar level, the product is also suitable for diabetics.

Indications: States of hyper-reactivity of the gingival mucosa, including post-operative hyper-reactivity.

Directions for use: After correct oral hygiene apply the product to the gingival tissue with the fingers, massaging gently to aid absorption. It is advisable to repeat the treatment twice a day or more for 3-4 weeks, continuing until all symptoms have disappeared.

Warnings: Confirmed individual hypersensitivity to the constituents of the formulation.

Packaging: Tube containing 20 ml.

GENGIGEL®: 20 ml pack (16,600 lire). On sale in pharmacies only.