A comparison in postoperative healing of sites receiving non-surgical debridement augmented with and without a hyaluronan 0.8% gel

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Abstract

Hyaluronic acid forms the basis of the extracellular matrix in which the cell growth takes place. A commercial preparation of hyaluronic acid called Hyaluronan (Genigel) has recently been introduced for oral use to promote healing in inflamed sites and sites aected by periodontal disease. 52 patients with moderate to severe periodontal disease who were medically and socially able to receive a single application of Haluronan gel immediately after thorough root surface debridement. Sites to receive the Hyaluronan gel or a placebo gel were selected on a randomised basis for each patient.

Aim: The aim of the study was to determine if any beneficial treatment advantage derived from a single application of Hyaluronan after nonsurgical therapy.

Materials and Methods 52 patients were randomly selected from patients aged 18-65 who attended for treatment for chronic periodontal disease. For inclusion in the study all patients had BPE scores of 3 or 4. Patients were randomly allocated into two groups, a Hyaluronan-based gel and a placebo gel. The selected site was cleaned with a rubber cup and prophylaxis, and a single application of the active gel or placebo gel was applied. The active gel and placebo groups were selected on a randomised basis for each patient.

Results have demonstrated highly significant improvements in the clinical variables of bleeding on probing and periodontal pocketing in the sites that received the Hyaluronan compared to the placebo sites that had not received the active gel. It was concluded that highly signicant improvements in healing after nonsurgical therapeutic debridement can be achieved by a single topical application of Hyaluronan gel immediately after root surface debridement. This observation is borne out by further trials, the potential for achieving enhanced healing after treatment may have considerable clinical significance.

Introduction

Chronic Adult Periodontitis affects over 2/3 of all patients in the age group 45 years and over (Agerholm D 2001), and is also the second most common cause of tooth loss in the U.K. (McCaul LK et al 2001). Treatment of these patients has characteristically involved flap surgery and root planing: to provide a smooth root surface for reattachment, supplemented with intensive oral hygiene instruction, to prevent contamination of the healing area during the healing and reattachment phase. Reattachment has been shown not to occur, and some periodontal pockets seem to be resistant to healing in spite of vigorous mechanical debridement. More recently, this approach to treatment has been reappraised, so that instead of aiming for smooth root surface treatment, treatment aims to disinfect and decontaminate the root surface cementum of aetected sites. Topical agents are increasingly being used as adjuncts to manual root surface debridement in an attempt to promote healing.

Although Chlorhexidine irrigation is almost ubiquitous in general dental practise for the suppression of oral surgical, periodontal therapeutic debridement, a recent review has concluded that there is no benefit from this over scaling and root planning alone (Hanes P et al 2001). Locally delivered Chlorhexidine in the form of controlled release re sorbable “chips” has been shown to have a significant adjunctive e ects (Killoy W 1988), but controlled release Deoxycholic acid was shown in a comparative study of topical antibacterials with Chlorhexidine (Salvi E et al 2002), to be the preparation of choice. These devices are only once -a -time at the site of placement and are relatively costly. However, increasing evidence indicates that, while plaque is the primary a ectional agent in establishing periodontal disease, the host reaction to the bacterial challenge is crucial to the initiation and progression of periodontal diseases. More recent work has therefore focused on the management of the host response, rather than the microbial challenge from bacterial plaque biofilm.

“Periostal” (Alliance Pharma UK Ltd) is a subantimicrobial dose Deoxycholic acid preparation. It derives its benefits from the well-documented anti-inflammatory properties of the tetracycline group of antibiotics and several studies have concluded that this preparation achieves significant attachment gains and probing depth reductions over and above those achieved by scaling and root planning alone (Abel et al 2005). However, it has the major disadvantage of being a systemic preparation, with long treatment times, and may need to be repeated at regular intervals. More recently a topically applied anti infective agent based on Hyaluronic acid (Genigel: Oraldent UK) has been launched. Hyaluronic acid (HA) is a linear polymer de -rived from two repeating disaccharide units (D-Glucuronic acid and N acetylgalosamine), and is a natural constituent of the body’s glycosaminoglycan (GAG) population. Its synthetic form is referred to as Hyaluronic acid, and is available in gel or liquid preparations for topical oral use. It has many properties that make it a potentially ideal molecule for assisting wound healing by inducing early beneficial granulation tissue forma -tion, inhibiting destructive inflammation during the healing phase, promoting ep -ithelial turnover and also con -nective tissue angiogenesis. (Ichikawa et al 2002, Moseley et al 2002, Chen et al 1999). In ad -dition, it has been demonstrated that HA has antibacterial proper- ties in vitro (Pirnazar et al 1999).

Clinical studies have shown that topical application of Hyaluronan promotes healing of both leg ulcers (Ortonne 1996), and the nasal mucosa after surgery (Soldati et al 1999). It has also been shown to reduce the incidence of high-grade radio- epithelitis in patients who have undergone radiotherapy for head and neck cancer (Liguori et al 1997).

Hyaluronan is a hygroscopic macromolecule and in solution, has a positive charge. These properties are likely to be rele vant in controlling tissue hydra -tion during changes to the tissue such as the inflammatory process or response to tissue injury. Hyaluronic acid also contrib- u tes to local foci of tissue hydra -tion, which is important dur ing cell proliferation and migra -tion. These local foci of tissue hydration weaken cell attach -ment to facilitate cell migration and division. In inflammation, Hyaluronan’s diffusion permits a modulating effect through free radical scavenging (Presi et al 1994) as well as the exclusion of tissue de -grading enzymes such as metalloproteases (Fraser et al 1996).

All these properties plus the re lease of cytokines when Hyaluronan binds to its specific re ceptor CD 44 explain why Hyaluro nan plays such a key role in the healing process. At a macroscopic level, this agent is tasteless, odourless and colourless. It is easy to apply, does not stain teeth and is not inactivated by Sodium Laurel Sulphate. It has no known adverse patient reactions or drug interactions. As Hyaluronan is presented in gel form, it can be cheaply and easily delivered to all areas under -going therapy. When used in combination with non-surgical periodontal therapy, a more effective outcome is achieved.

Aim: The aim of this study was to determine the clinical benefts of a Hyaluronan-based gel (Genigel Prof ) used as an adjunc to non-surgical periodontal therapy.

Methods and materials

52 patients were randomly selected from patients aged 18-65 who attended for treatment for chronic periodontal disease. For inclusion in the study all patients had BPE scores of 3 or 4 in at least 2 quadrants. On selection for the study patients received a full mouth assessment of bleeding on probing and pocket depth measurements recorded in millimetres, using a six point charting. Patients were excluded from the study if their medical status or prescribed medication compromised their immune system, if they only had moderate periodontal disease requiring non surgical treatment only, or if they had too few remaining teeth to allow a comparative analysis of test and control sites.

Table 1: Comparison of clinical variables at the selected sites from baseline to the three months post treatment assessment.

<table>
<thead>
<tr>
<th>TIME</th>
<th>N</th>
<th>MEAN</th>
<th>SD</th>
<th>P VALUE</th>
</tr>
</thead>
<tbody>
<tr>
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<td>52</td>
<td>1.9945</td>
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<td></td>
<td>5m Post-op</td>
<td>52</td>
<td>2.0199</td>
<td>0.6137</td>
</tr>
<tr>
<td>TEST</td>
<td>Baseline</td>
<td>52</td>
<td>2.0199</td>
<td>0.6137</td>
</tr>
<tr>
<td></td>
<td>5m Post-op</td>
<td>52</td>
<td>2.0720</td>
<td>0.4648</td>
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</table>

Table 2: Comparison of mean and median e ef of test and control sites from baseline to the three months post treatment assessment.

<table>
<thead>
<tr>
<th>TIME</th>
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<th>MEAN</th>
<th>SD</th>
<th>P VALUE</th>
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<td>0.5858</td>
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<tr>
<td></td>
<td>5m Post-op</td>
<td>52</td>
<td>3.060</td>
<td>0.5858</td>
</tr>
<tr>
<td>TEST</td>
<td>Baseline</td>
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<td>3.628</td>
<td>0.6186</td>
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<tr>
<td></td>
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<td>3.589</td>
<td>0.6186</td>
</tr>
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Table 3: Comparison of mean and median pocket depth measurements in the test and control sites from baseline to the three months post treatment assessment.

<table>
<thead>
<tr>
<th>TIME</th>
<th>N</th>
<th>MEAN</th>
<th>SD</th>
<th>P VALUE</th>
</tr>
</thead>
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<td>0.266</td>
</tr>
<tr>
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<td>5m Post-op</td>
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<td>3.484</td>
<td>0.266</td>
</tr>
<tr>
<td>TEST</td>
<td>Baseline</td>
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<td>3.188</td>
<td>0.357</td>
</tr>
<tr>
<td></td>
<td>5m Post-op</td>
<td>35</td>
<td>3.188</td>
<td>0.357</td>
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</table>

Table 4: Comparison of mean and median pocket depth measurements between the test and control sites during the study.

<table>
<thead>
<tr>
<th>DRUG</th>
<th>N</th>
<th>MEAN</th>
<th>SD</th>
<th>P VALUE</th>
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<td>0.3186</td>
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<tr>
<td></td>
<td>5m Post-op</td>
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<tr>
<td>TEST</td>
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<td>0.2749</td>
</tr>
<tr>
<td></td>
<td>5m Post-op</td>
<td>52</td>
<td>3.828</td>
<td>0.2749</td>
</tr>
</tbody>
</table>

Table 5: Comparison of mean and median pocket depth measurements between the test and control sites during the study.

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All of the clinicians were calibrated against a standard predetermined protocol for the study, to ensure a high level of intra- and inter-examiner reproducibility. This was achieved by means of a preliminary pilot study in which five patients, who were not included in the study, were subjected to repeated measurements of the clinical variables used in the study by all of the clinicians. Both intra and inter-examiner reproducibility was found to be high.

Root surface debridement was carried out in all pockets equal or greater than 4 mm and the healing of these sites was used in the statistical analysis. Debridement was undertaken in two quadrants at a time. Patients were randomly selected to receive a post debridement application of the active gel or the placebo, in the treated quadrants. Wherever possible the left and right quadrants were used as adjunctive gel/non-adjunctive gel comparisons, but where this was not possible (due to too few teeth being present), the upper and lower quadrants were compared. 0.8% Hyaluronan gel was applied into the pockets in those sites that had been randomly assigned to receive it, using a prefilled syringe after completion of the mechanical debridement. The other sites received an application of an inert placebo gel.

At both baseline and at the three months follow-up assessment appointments, bleeding on probing and pocket depths were measured and annotated for each subject. These variables were then consolidated into individual and then group mean values which were then subjected to simple (Student’s t-test) and linear ANOVA using the SAS statistical software package.

Results

It can be seen from table 1 that highly significant improvements occurred in the group bleeding scores in both placebo and test sites from baseline to the three-month review appointment. Similarly table 3 shows highly significant improvements in periodontal pocketing in both the placebo and test groups from baseline to three months after treatment.

In table 2 it can be seen that the mean improvement in bleeding scores in the placebo group was 24.6%, while in the test group it was over double at 59.05%. This is a highly significant incremental improvement (p<0.0005). Similarly table 4 illustrates the improvements in pocket depth measurements. In the placebo group pockets improved by an average of 18.45%, whereas in the test group it was nearly double that level of improvement at 52.59%. This is reflected in a highly significant p-value of p=0.0027.

While the group on the test drug (Hyaluronan) was shown to have a significant benefit over the time period of the study, the results of ANOVA illustrated in table 5 show that the individually significant results are substated when time/drug interactions are accounted for in the analysis.

Figures 1 and 2 graphically demonstrate the compara-tive results in terms of the variables of bleeding and pocketing at baseline and at the three-month assessment appointment. From these illustrations it is clear that at baseline the mean values for both the test and placebo group were virtually equivalent, whereas marked dividends are evident in both variables at the three-month appointment.

Discussion

Hyaluronan has been identified in all periodontal tissues, being particularly concentrated in the non-mineralised tissues such as gingival and periodontal ligament. It is also present in low concentrations in mineralised tissues such as cementum and alveolar bone. Hyaluronan has many structural and physiological functions within tissues and is a key component in the series of stages associated with the wound healing process in both mineralised and non-mineralised tissues (i.e. inflammation, granulation tissue formation, epithelium formation and tissue remodelling) (Culp et al 1979).

As a consequence of its non-toxicity, biocompatibility and numerous biochemical and physiological properties, the use of exogenous hyaluronan applied topically to inflamed periodontal sites, would appear to offer beneficial effects in modulating and accelerating the host response. Several double blind studies have demonstrated the beneficial effect of Hyaluronan 0.2% gel in the treatment of gingivitis. Jentsch et al (2003) showed that 0.2% gel produced a significant improvement in both clinical and para-clinical variables in plaque induced gingivitis.
Deminerelised white spot lesions occur frequently after orthodontic treatment. Some teeth are more prone to deminerelisation, typically the maxillary lateral incisors and the mandibular canine teeth. The disto-gingival area of the labial enamel surface is the area most commonly affected (Fig. 1). In the first few weeks after removal of the fixed appliances, there is a reduction in white spot lesion size and appearance, possibly due to the action of saliva (Fig. 2).

Various treatment methods have been proposed to assist the process of remineralisation. It is important to note that fluoride should not be used in high concentration, as it tends to prevent deminerelisation and can lead to further unsightly staining. Low concentrations of fluoride, however, may assist remineralisation, such as those found in casein calcium phosphate materials. Additionally, stimulation of salivary flow by chewing sugar-free gum is helpful.

This article will describe a revolutionary new approach to the cosmetic treatment of white spot lesions (Fig. 5). With Icon, a microinvasive technology from German manufacturer DMG, deminerelised enamel can be filled and reinforced without drilling or anaesthesia (Figs. 4 & 5).

One of the reasons that earlier approaches to the treatment of white spot lesions have fallen short is that fluoride therapy is not always efficacious in the advanced stages, and the use of restorative fillings usually sacrifices significant amounts of healthy tooth structure.

Instead of adopting a wait and see approach, Icon has been
shown to arrest the progress of early enamel lesions up to the first third of dentine in one simple procedure (Fig. 6), without unnecessary loss of healthy tooth structure.

In the procedure described here, the surface area of the white-spot lesion is eroded with a 15 % HCl gel, which opens the pore system of the lesion. This is then dried with ethanol, followed by the application of Icon onto the lesion with the application aid. The extremely high penetration coefficient enables it to penetrate into the lesion pores. Excess material is then removed, and the material is light-cured. The total treatment time should be about 15 minutes (Fig. 7).

The cosmetic treatment of cariogenic white spots in one visit can be very appealing, especially to young patients and their parents (Figs. 8a & b). No drilling or anaesthesia is required and those patients who have already demonstrated poor compliance with their brushing can be treated earlier.

I would recommend that clinicians try the Icon product when attempting to remineralise white spot lesions post-orthodontic treatment. This is not just minimally invasive dentistry; it is micro-invasive dentistry.

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givitis compared to placebo. Pa-
gnacco et al (1997) and Pistorius
et al (2005) in separate double
blind studies demonstrated the
beneficial effect of Hy-
alaronan gel in producing significant im-
provements in the measurement
variables of inflammation in gin-
givitis.
A study by Yi Xu et al (2004)
concluded that there was no clin-
ical improvement was achieved by the
adjunctive use of Hyaluro-
onan 0.2% gel compared to me-
chanical debridement. However
in this study Hyaluronan 0.2%
gel was applied only once a week
for six weeks, a total of seven ap-
plications over a six week period,
compared to the recommended
application level of three times
daily for at least 4-8 weeks. The
absence of observed clinical im-
provements, contrary to other
published studies, may indicate
that the Hyaluronan levels used
in this study were well below the
optimum levels required to
achieve a significant clinical im-
provement.
Mesa Aguado et al (2001) in a
double study on patients with pe-
riodontal disease concluded that
Hyaluronan gel was effective in
controlling inflammation and
 gingival bleeding and a re-
duction in the depth of gingival pack-
es was observed along with a
significant reduction in epithelial
and lymphocytic cell proliferation.
This study has demonstrated that
the use of Hyaluronan gel statisti-
cally improves patient outcome (reflected by highly sig-
nificant improvements in bleed-
ing indices and pocket probing
depths) when used as an adjunct to
non-surgical periodontal therapy.
The bleeding index improved by 24.6% in the placebo group, whereas the treatment group displayed a reduction of 59.05%. This equates to a twofold improvement in outcome in the treatment group. Pocket probing depth also demonstrated a highly significantly (P=0.0027) incremental improvement in the treatment group. The test group therefore experienced a 75.75% better treatment outcome in comparison to the base-line healing rate (placebo group). These results markedly dem-
strate the additional benefits afforded by the use of Hyaluro-
onan 0.8% gel.

Conclusions
This study confirms results, which indicate that exogenous Hyaluronan gel has a beneficial effect in the growth, develop-
ment and repair of tissues in pe-
riodontal disease. In this study it was shown that even a single subgingival appli-
cation of Hyaluronan gel after non-surgical debridement results in highly significant im-
provements in treatment out-
comes as assessed by reductions in bloodind and pocket depth
measurements.
It is therefore concluded that the adjunctive use of Hyaluro-
onan after thorough mechanical debridement potentially has major clinical benefits in terms of improved healing after non-
surgical therapy. However fur-
ther work needs to be done to
confirm the results of this study
and to assess the long term heal-
ing of the tissues in sites in which
the Hyaluronan was applied. If you wish to contact any of
the authors of this article see be-
low for contact details. Address:
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London, W11 3RF, United King-
dom.
E-mail: pndg@periodontal.co.uk
Tel: 020 8202 8360
Fax: 020 8202 4231

Figure 1: To demonstrate the additional benefit in terms of reduced bleeding achieved by application of
the Hyaluronan gel after non-surgical debridement

Figure 2: To demonstrate the additional benefit in terms of reduced pocket depths achieved by
application of the Hyaluronan gel after non-surgical debridement

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