Clinical article

A comparison in postoperative healing of sites receiving non-surgical debridement augmented with and without a single application of 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 (Gengigel) has recently been developed for intra-oral use to promote healing in inflamed sites and sites affected by periodontal disease. 52 patients with moderate to severe periodontal disease who were medically healthy were selected 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 outcomes derived from a single application of Hyaluronan after nonsurgical therapy.

Materials and Methods 52 patients were selected who had BPE scores of 3 or greater in at least 2 quadrants were selected. Root surface debridement was carried out in all pockets equal or greater than 4 mm. Patients were randomly selected to receive a post debridement topical application of the active gel or a placebo in the treated quadrants. At baseline and 3 months postoperatively, assessment of bleeding on probing and pocket depth were completed. Individual and group mean values were subjected to Student's t-test and linear ANOVA using the SAS statistical software package.

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 significant improvements in healing after non-surgical therapy can be achieved by a single topical application of Hyaluronan immediately after root surface debridement. If this observation is borne out by further trials, the potential for achieving enhanced healing after treatment has considerable clinical significance.

Introduction

Chronic Adult Periodontitis affects over 2/3 of all patients in the UK aged greater than 45 years (Agerholm D 2001), and is also the second most common cause of tooth loss in the UK (McCaul LK et al 2001). Treatment of these patients has characteristically involved non-surgical scaling and root-planing to provide a smooth root surface for reattachment, supplemented with intensive oral hygiene instruction, to prevent contamination of the treated site 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 now aims to disinfect and detoxify the root surface cementum of affected 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 supplementation of non-surgical periodontal therapy, a recent review has concluded that there is no benefit of this over scaling and root planing alone (Hanes P et al 2003). Locally delivered Chlorhexidine in the form of controlled release resorbable "chips" has been shown to have a significant adjunctive effect (Killoy W 1998), but controlled release Doxycycline 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 effective at the site of placement and are relatively costly. However, increasing evidence indicates that, while plaque is the primary aetiological 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.

"Periostat" (Alliance Pharma UK) is a sub antimicrobial dose Doxycycline preparation. It derives its benefit from the well-documented anti-inflammatory properties of the tetracycline group of antibiotics and several studies have concluded that this product achieves significant attachment gains and probing depth reductions over and above those achieved by scaling and root planning alone (Abdel 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-inflammatory product based on Hyaluronic acid (Gengigel: Oraldent UK) has been launched. Hyaluronic acid (HA) is a linear polymer derived from two repeating disaccharide subunits (D-Glucuronic acid and N-acetylglucosamine), and is a natural constituent of the body's glycosaminoglycan (GAG) population. Its synthetic form is referred to as Hyaluronan, 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 formation, inhibiting destructive inflammation during the healing phase, promoting epithelial turnover and also connective tissue angiogenesis.(Ichikawa et al 2002, Moseley et al 2002,J Chen et al 1999). In addition, it has been demonstrated that HA has antibacterial properties in vitro (Pirnazar et al 1999).

	TIME	N	MEAN	SD	P VALUE
PLACEBO	Baseline	52	1.9945	0.7012	p=0.0003
	3m Post-op	52	1.5030	0.6149	
TEST	Baseline	52	2.0199	0.6137	P<0.0005
	3m Post-op	52	0.8270	0.4648	

Table 1: To demonstrate bleeding on probing in the test and control sites from baseline to the three month post treatment assessment.

	MEAN CHANGE	MEAN DIFFS.	PERCENTAGE
PLACEBO	1.9945 - 1.5030	0.4915	24.6%
TEST	2.0199- 0.8270	1.1929	59.05%
SIGNIFICANCE		P<0.0005	

Table 2: To compare the reduction in bleeding on probing between the test and control sites during the study.

	TIME	N	MEAN	SD	P VALUE
PLACEBO	Baseline	52	3.906	0.9338	p=0.0005
	3m Post-op	52	3.186	1.0885	
TEST	Baseline	52	3.828	0.7842	P< 0.0005
	3m Post-op	52	2.588	0.8759	

Table 3: To demonstrate pocket depth measurements in the test and control sites from baseline to the three month post treatment assessment.

	MEAN CHANGE	MEAN DIFFS.	PERCENTAGE
PLACEBO	3.906 - 3.186	0.72	18.43%
TEST	3.828 - 2.588	1.24	32.39%
SIGNIFICANCE		p= 0.0027	

Table 4: To compare the reduction in pocket depths between the test and control sites during the study.

VARIABLE	MEAN SQUARE	F VALUE	SIGNIFICANCE
DRUG	5.502	18.099	p<0.0005
TIME	35.884	135.942	p<0.0005
DRUG x TIME	6.394	73.342	p<0.0005

Table 5: Summarised results of ANOVA showing the effect of Time x Drug Interactions

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 also has been shown to reduce the incidence of high-grade radioepithelitis in patients who have undergone radiotherapy for head and neck cancer (Liguori et al 1997).

Hyaluronan is a hygroscopic macromolecule and in solutions it is highly osmotic. These properties are likely to be relevant in controlling tissue hydration during changes to the tissue such as the inflammatory process or response to tissue injury. Hyaluronan synthesis contributes to local foci of tissue hydration, which is important during cell proliferation and migration. These local foci of tissue hydration weaken cell attachment to the extra cellular matrix allowing temporary detachment to facilitate cell migration and division. In inflammation Hyaluronan has a moderating effect through free radical scavenging (Presti et al 1994) as well as the exclusion of tissue degrading enzymes such as metallproteinases (Fraser et al 1996). All these properties plus the release of cytokines when Hyaluronan binds to its specific receptor CD 44 explain why Hyaluronan plays such a key role in the healing process.

Hyaluronan gel 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 re-

actions or drug interactions. As Hyaluronan is presented in gel form, it can be cheaply and easily delivered to all areas undergoing 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 benefits of a Hyaluronan-based gel (Gengigel Prof) used as an adjunct 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 greater 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.

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 18.43%, whereas in the test group it was nearly double that level of improvement at 32.39%. 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 substantiated when time/drug interactions are accounted for in the analysis.

Figures 1 and 2 graphically demonstrate the comparative 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

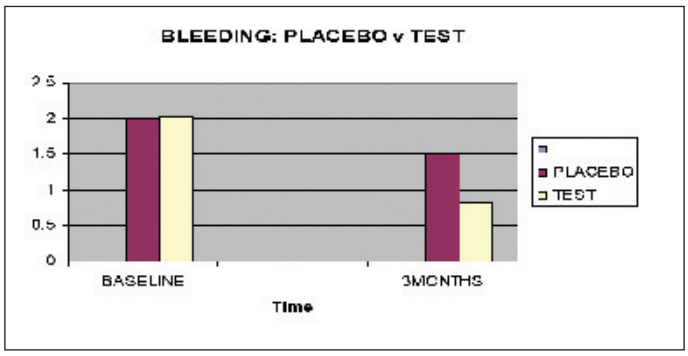

Figure 1: To demonstrate the additional benefit in terms of reduced bleeding achieved by application of the Hyaluronan gel after root surface debridement

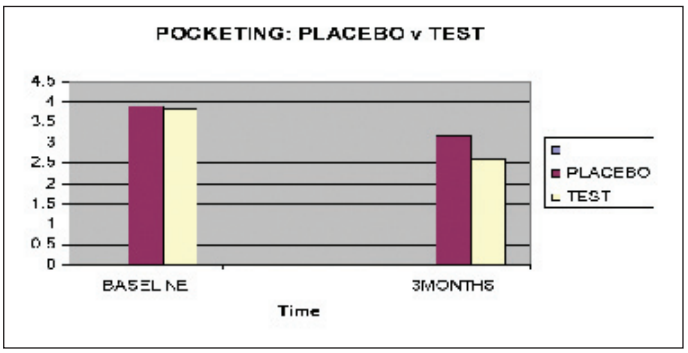

Figure 2: To demonstrate the additional benefit in terms of reduced pocket depths achieved by application of the Hyaluronan gel after root surface debridement

mean values for both the test and placebo group were virtually equivalent, whereas marked differences are evident in both variables at the three-month assessment 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 al1 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 compared to placebo.

Pagnacco et al (1997) and Pistorius et al (2005) in separate double blind studies demonstrated the beneficial effect of Hyaluronan gel in producing significant improvements in the measurement variables of inflammation in gingivitis.

A study by Yi Xu et al (2004) concluded that there was no clinical improvement was achieved by the adjunctive use of Hyaluronan 0.2% gel compared to mechanical debridement. However in this study Hyaluronan 0.2% gel was applied only once a week for six weeks, a total of seven applications 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 improvements, 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 improvement.

Mesa Aguado et al (2001) in a double study on patients with periodontal disease concluded that Hyaluronan gel was effective in controlling inflammation and gingival bleeding and a reduction in the depth of gingival pockets was observed along with a significant reduction in epithelial and lymphocyte cell proliferation.

This study has demonstrated that the use of Hyaluronan gel statistically improves patient outcome (reflected by highly significant improvements in bleeding 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 improvment in the treatment group. The test group therefore experienced a 75.75% better treatment outcome in comparison to the baseline healing rate (placebo group). These results markedly demonstrate the additional benefits afforded by the use of Hyaluronan 0.8% gel.

Conclusions

This study confirms results, which indicate that exogenous Hyaluronan gel has a beneficial effect in the growth, development and repair of tissues in periodontal disease.

In this study it was shown that even a single subgingival application of Hyaluronan gel after non-surgical debridement results in highly significant improvements in treatment outcomes as assessed by reductions in bleeding and pocket depth measurements.

It is therefore concluded that the adjunctive use of Hyaluronan after thorough mechanical debridement potentially has major clinical benefits in terms of improved healing after non-surgical therapy. However further work needs to be done to confirm the results of this study and to assess the long term healing of the tissues in sites in which the Hyaluronan was applied.

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