Local Delivery of Hyaluronan as an Adjunct to Scaling and Root Planing in the Treatment of Chronic Periodontitis

Annsofi Johannsen,* Monica Tellefsen,† Ulf Wikesjö,‡ and Gunnar Johannsen†

Background: The aim of the present study was to evaluate the adjunctive effect of the local application of a hyaluronan gel to scaling and root planing in the treatment of chronic periodontitis.

Methods: Twelve patients with chronic periodontitis were recruited to participate in a study with a split-mouth design and provided informed consent. Plaque formation and bleeding on probing were evaluated pretreatment (baseline) and at 1, 4, and 12 weeks post-treatment. Probing depths and attachment levels were evaluated at baseline and at 12 weeks. The patients received full-mouth scaling and root planing. A hyaluronan gel was administered subgingivally in the test sites at baseline and after 1 week. Significant differences between test and control were evaluated using the paired *t* test, repeated-measures analysis of variance (Wilks lambda), and a non-parametric Wilcoxon signed-rank test.

Results: A significant reduction in bleeding on probing scores and probing depths was observed in both groups at 12 weeks ($P < 0.05$). Significantly lower bleeding on probing scores were observed in the hyaluronan group compared to control at 12 weeks ($P < 0.05$). Mean probing depth reductions between baseline and 12 weeks were 1.0 ± 0.3 mm and 0.8 ± 0.2 mm for the hyaluronan and control groups, respectively. The difference between the groups was statistically significant ($P < 0.05$).

Conclusion: The local application of hyaluronan gel in conjunction with scaling and root planing may have a beneficial effect on periodontal health in patients with chronic periodontitis. *J Periodontol 2009;80:1493-1497.*

KEY WORDS

Dental plaque; hyaluronan; periodontitis.

* Dental Hygiene Program and Department of Periodontology, Institute of Odontology, Karolinska Institute, Huddinge, Sweden.
† Department of Periodontology, Danakliniken, Mörby Centrum, Danderyd, Stockholm, Sweden.
‡ Laboratory for Applied Periodontal and Craniofacial Regeneration, Departments of Periodontics and Oral Biology, School of Dentistry, Medical College of Georgia, Augusta, GA.

Scaling and root planing (SRP) is an effective therapy for reducing gingival inflammation and probing depths (PDs) in patients with chronic periodontal disease.[1,2] Nevertheless, a multitude of adjunctive therapies has been tried and tested to amplify the beneficial effects of SRP.[3,4] For example, the local delivery of chlorhexidine in a bioabsorbable chip produced added benefits to SRP.[5,6] Similar improvements were reported following the adjunctive use of locally administered microencapsulated minocycline.[7,8] Most studies evaluating the effects of adjunctive antimicrobials reported positive outcomes. However, observed improvements are usually incremental; thus, the question remains whether they are clinically meaningful.[3,4]

Hyaluronan, a non-sulfated glycosaminoglycan, is widely distributed throughout connective tissue and epithelial and neural tissues. It is a critical component of the extracellular matrix and contributes significantly to tissue hydrodynamics and cell migration and proliferation. Hyaluronan is also produced by fibroblasts in the presence of endotoxin; it plays an important anti-inflammatory role through the inhibition of tissue destruction and facilitates healing.[9,10] The use of exogenous hyaluronan and hyaluronan-based biomaterials in the treatment of inflammatory processes has been established in several settings. Hyaluronan was used in the treatment of

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osteoarthritis of the knee[11] and in combination with cataract surgery.[12] A hyaluronan-containing cream was used prophylactically to reduce radioepithelitis following radiation therapy.[13] Intra-articularly injected hyaluronate alleviated clinical characteristics of rheumatoid arthritis.[14] Moreover, hyaluronan was shown to generate bacteriostatic effects in vitro.[15]

Only a few studies have examined the effect of hyaluronan on gingival health. Jentsch et al.[16] and Pistorius et al.[17] demonstrated the beneficial effects of topical hyaluronan preparations in the treatment of gingivitis. Less is known about the effect of topical hyaluronan on periodontitis. The aim of the present study was to evaluate the effect of a hyaluronan gel used in adjunct with SRP in the treatment of chronic periodontitis.

MATERIALS AND METHODS

Patients

Twelve patients, aged 42 to 63 years (seven men, aged 54 ± 8 years, and five women aged 56 ± 7 years), were recruited to participate in this split-mouth design study. Two were smokers, and one used snuff. All patients were referred to a specialist clinic, Danakliniken, for the treatment of chronic periodontitis and were treated between January and September 2008.

Inclusion criteria were ≥20 teeth and at least five interproximal sites with PD >5 mm. The teeth chosen for treatment were canines and premolars bilaterally, and two interproximal sites on each tooth were required to have PDs ≥5 mm.

The patients were generally healthy and exhibited no known allergies. Furthermore, they did not receive antibiotic therapy within the last 6 months or receive previous periodontal treatment. This study was approved by the Ethics Committee at Huddinge University Hospital, Huddinge, Sweden. The subjects gave their written informed consent to participate in the study.

Procedures

Contralateral pairs of premolar and canine teeth in the maxilla (teeth #4 through #6 versus teeth #11 through #13) or the mandible (teeth #20 through #22 versus teeth #27 through #29) were randomized to receive the test treatment (adjunctive hyaluronan gel) or to serve as SRP controls. The jaw quadrants were treated in sequence; the control sites were always treated first to reduce potential crossover effects from the contralateral test sites. The control sites were treated and evaluated prior to treatment of the test sites.

The observation interval for each jaw quadrant was 3 months. All sites were included in the dataset.

The following assessments were made at baseline: plaque index (modified PI),[18] bleeding on probing (BOP),[19] PD, and clinical attachment level (CAL). PDs were recorded to the nearest millimeter using a standard periodontal probe[§] graded at 2-mm intervals, with a tip diameter of 0.5 mm. All teeth were evaluated at six sites: mesio-buccal, mesio-lingual, mid-buccal, disto-buccal, disto-lingual, and mid-lingual. CAL was recorded from the cemento-enamel junction. BOP was recorded as a positive score if bleeding occurred within 60 seconds after gentle intracrevicular probing. One experienced examiner (MT) performed all measurements.

All patients received SRP of the control jaw quadrants at baseline using hand instruments. PI and BOP were recorded at 1 and 4 weeks, as well as at 12 weeks post-treatment when PD and CAL were recorded. Next, contralateral experimental jaw quadrants received the identical protocol with the addition of the subgingival administration of 0.2 ml 0.8% hyaluronan gel[‖] into all selected sites following SRP. The hyaluronan gel was reapplied at 1 week post-treatment. No oral hygiene instructions were provided; the patients were encouraged to use their routine oral hygiene habits.

Statistical Analyses

All analyses were made using software.[¶] In Tables 1 and 2, the data are shown as percentages, and the non-parametric Wilcoxon signed-rank test was used to test hypotheses about equal ranks between the groups. The non-parametric Friedman test was used to test hypotheses about equal ranks over time. In Tables 3 and 4, a repeated-measures analysis of variance was used to test the hypotheses about equal means longitudinally, and paired *t* tests were used to compare groups cross-sectionally. The level of significance was set at 0.05 for all tests.[1]

RESULTS

The PI scores at baseline and at the various observation intervals are shown in Table 1. There was a significant reduction between baseline and 12 weeks for the test ($P<0.01$) and control ($P<0.01$) groups, but there were no significant differences between the groups.

BOP scores at baseline and subsequent recordings are presented in Table 2. Both groups showed significantly reduced BOP scores at 12 weeks ($P<0.01$). Comparing the groups using a non-parametric Wilcoxon signed-rank test revealed statistically significantly lower BOP scores in the test group compared to the control group at 12 weeks ($P<0.05$).

PDs are presented in Table 3. The PD reduction between baseline and 12 weeks was statistically significantly greater for the test group than the control group (1.0 ± 0.3 mm and 0.8 ± 0.2 mm, respectively; $P<0.05$).

§ PCP-UNC, Hu-Friedy, Chicago, IL.
‖ Gengigel, Ricerfarma, Milan, Italy.
¶ SPSS 11.5, Chicago, IL.

Table 1.

Median Dental Plaque Accumulation (% [interquartile range]) at Teeth Receiving SRP With or Without Adjunctive Application of a Hyaluronan Gel at Baseline and 1, 4, and 12 Weeks Post-Treatment

Treatment Modalities	Baseline	1 Week	4 Weeks	12 Weeks	*P* Value
SRP	48.0 (49.2)	21.0 (15.0)	16.0 (23.0)	25.0 (14.8)	<0.01
SRP + hyaluronan gel	58.0 (45.8)	16.0 (16.4)	16.0 (17.0)	20.5 (19.0)	<0.01
P value	0.78	0.40	0.53	0.08	

Table 2.

Median BOP (% [interquartile range]) at Teeth Receiving SRP With or Without Adjunctive Application of a Hyaluronan Gel at Baseline and 1, 4, and 12 Weeks Post-Treatment

Treatment Modalities	Baseline	1 Week	4 Weeks	12 Weeks	*P* Value
SRP	58.0 (26.0)	22.0 (36.0)	16.0 (23.0)	25.0 (14.8)	0.01
SRP + hyaluronan gel	74.5 (45.7)	19.0 (25.7)	16.0 (10.0)	22.0 (28.5)	0.01
P value	0.16	0.84	0.76	0.05	

Table 3.

Mean PD (mm [95% confidence interval]) at Teeth Receiving SRP With or Without Hyaluronan Gel at Baseline and 12 Weeks Post-Treatment

Treatment Modalities	Baseline	12 Weeks	*P* Value
SRP	4.2 (3.6 to 4.7)	3.4 (2.9 to 3.8)	0.001
SRP + hyaluronan gel	4.2 (3.7 to 4.7)	3.2 (2.6 to 3.7)	0.001
P value	0.92	0.14	

Table 4.

Mean CAL (mm [95% confidence interval]) at Teeth Receiving SRP With or Without Hyaluronan Gel at Baseline and 12 Weeks Post-Treatment

Treatment Modalities	Baseline	12 Weeks	*P* Value
SRP	4.5 (4.2 to 4.7)	4.4 (4.1 to 4.6)	0.55
SRP + hyaluronan gel	4.4 (4.1 to 4.8)	4.4 (4.0 to 4.7)	0.39
P value	0.90	0.36	

CAL measurements are shown in Table 4. No statistically significant differences were found for the two groups.

DISCUSSION

In the present study, the adjunctive application of hyaluronan gel generated possible beneficial effects on periodontal health; the hyaluronan/SRP protocol resulted in statistically significantly greater reductions in BOP scores and PD compared to the SRP control. These observations were recorded in the absence of remarkable differences in oral hygiene standards between the groups.

Hyaluronan was shown to generate bacteriostatic effects in vitro, in particular on *Aggregatibacter actinomycetemcomitans* (previously *Actinobacillus actinomycetemcomitans*), *Prevotella oris*, *Staphylococcus aureus*, and *Propionibacterium acnes* strains.[15] The present study did not demonstrate any effect of subgingival hyaluronan application on dental plaque formation; a significant reduction in PI from baseline, from ~50% to 20%, was observed for both groups. This was despite the fact that specific oral hygiene instruction was not provided. In fact, the patients were encouraged to use their routine oral hygiene habits. Reduced plaque formation likely resulted from improved gingival health following SRP in combination with improved oral hygiene routines commonly observed in study subjects, irrespective of intentional oral hygiene training.[20,21]

A statistically significant reduction in BOP scores following local subgingival application of the hyaluronan gel was observed in the present study. This observation is in concert with previous reports[16,17] of improved gingival health after the supragingival application of various hyaluronan formulations in subjects with gingivitis. A five-times-daily topical hyaluronan spray over 1 week[17] or twice-daily topical application of hyaluronan gel adjunctive to conventional oral hygiene over 3 weeks[16] significantly reduced gingivitis in these subjects. However, other investigators did not show a beneficial effect of hyaluronan on periodontal health. Xu et al.,[22] also investigating the effect of a subgingivally administrated hyaluronan gel in combination with SRP, found no

differences between the hyaluronan and control groups relative to BOP and PD. The hyaluronan gel was administered six times: at baseline and then every week up to week 6. Differences in hyaluronan formulations and treatment protocols, observation intervals, disease severity, and measurements may explain variations in the outcomes between that study and the present study. Also, the use of a sequential treatment protocol in the present study, to abolish potential crossover effects of the hyaluronan gel on the control sites, may have played a role.

Hyaluronan formulations were evaluated in surgical settings in support of periodontal regeneration (guided tissue regeneration) and after the nonsurgical local application adjunctive to SRP in intrabony periodontal defects.[23] Control sites received identical protocols, except for topical hyaluronan. There were no noteworthy differences in clinical parameters, including PDs, between the hyaluronan and control groups at the 12-month follow-up. The present study showed limited PD reductions between baseline and 12 weeks that were statistically significantly greater for the hyaluronan sites than for the control sites, indicating a clinical benefit of the hyaluronan protocol. CALs did change remarkably, which should not be expected based on the initially moderately deep PDs.[24]

CONCLUSIONS

Patients in the present study had not received previous treatment for periodontitis, nor was oral hygiene reinforced before or during the study. The hyaluronan gel was professionally administered, eliminating any possibility that patient compliance influenced the results, which must be considered if patients apply hyaluronan themselves as a spray or a gel. Moreover, to minimize potential crossover effects, treatments were sequenced in a split-mouth design protocol rather than in parallel. The treatments were limited to bilateral canine and premolar teeth exhibiting similar disease patterns. Collectively, these factors may account for the observed beneficial effects of the local application of hyaluronan gel on periodontal health. Further studies are required to investigate the long-term effect of this combination therapy and to investigate variations in administration protocols to optimize the results.

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Correspondence: Dr. Annsofi Johannsen, Dental Hygienist Program and Department of Periodontology, Institute of Odontology, Karolinska Institute, P.O. Box 4064, SE-141 04 Huddinge, Sweden. Fax: 46-8-7467915; e-mail: annsofi.johannsen@ki.se.

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