DOI: 10.7860/JCDR/2014/8848.5237

Original Article

Dentistry Section

Hyaluronic Acid as an Adjunct to Scaling and Root Planing in Chronic Periodontitis. A Randomized Clinical Trail

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ABSTRACT

Aim: Aim of the present study was to evaluate the adjunctive effect of local application of hyaluronon gel following scaling and root planing (SRP) in chronic periodontitis patients.

Materials and Methods: In this randomized split mouth study 33 subjects with chronic periodontitis were evaluated after full mouth SRP. In the test sites hyaluronon gel was applied immediately after SRP and one week post therapy, the control sites were treated with SRP alone. Bleeding on probing (BOP), probing pocket depth (PPD), and clinical attachment level (CAL) were recorded at baseline, 4 wk and 12 wk.

Results: Significant reduction in BOP scores was observed in both the groups at 12weeks ($p<0.001$). The hyaluronon group showed a greater reduction in BOP ($p<0.001$). In the hyaluronon group the mean PPD at baseline was 6.33±0.09 which reduced to 2.49±0.51 at 12 weeks which was statistically significant ($p<0.001$). In the control group the mean PPD at baseline was 6.09±1.26 which reduced to 4.36±1.29 at 12 weeks which was statistically significant ($p<0.001$). The CAL measurements showed a significant difference between the groups ($p<0.001$) at 12 wk post therapy.

Conclusion: Hyaluronic Acid (HA) has a beneficial effect on periodontal health in patients with chronic Periodontitis. HA appears to be a suitable candidate as an adjunct to SRP in chronic periodontitis patients.

Keywords: Chronic periodontitis, Clinical trial, Hyaluronic acid, Root planing

INRTODUCTION

Scaling and root planing are well documented as effective methods in treatment of periodontal diseases [1]. However, key questions facing periodontitis and general dentists is whether SRP accompanied by use of an adjunctive antimicrobial agent improves patient outcome over time more than SRP alone in chronic periodontitis cases [2]. Mechanical debridement alone may fail to remove pathogenic organisms because of their location in sub epithelial connective tissue and crevicular epithelial cells [3-8].

A number of studies have documented the clinical efficacy of SRP in combination with systemically or locally delivered antimicrobial agents [9-11].

Practitioners have traditionally chosen the antimicrobial agents based more on personal experience than on evidence from microbiological studies and rigorous clinical trials. Systemic antibiotics which are currently used in periodontics have lost their antimicrobial abilities because of the development of resistance [12].

In a systematic review conducted by Bonito Arthur J et al., [2], it was found that among the locally administered adjunctive antimicrobials the most positive results occurred from tetracycline, minocycline, metronidazole and chlorhexidine. Hyaluronic Acid (HA) is a recent addition to the local chemotherapeutic agents. HA was discovered in bovine vitreous humor by Meyer and Palmer [13]. HA is widely sequerested in the extracellular matrix and it plays an active role in regulating cell behaviour including random motility, chemotaxis, invasion, proliferation and metabolic reactions. HA is secreted by many cells including fibroblasts [14,15].

HA is recognized by specific cell receptor CD44 acting as selective and protective quote around cell membrane. CD 44 can exist in numerous isoforms. HA binding properties of CD44 are determined by the isoform and the cell type on which it is expressed [16]. HA participates in tissue repair and wound healing and is used topically as anti inflammatory and anti-oedematous agent [17]. The anti-inflammatory effect may be due to action of exogenous hyaluronon as a scavenger by draining prostaglandins, metalloproteinases and other bioactive molecules [18].

The wide use of HA in inflammatory conditions of knee and TMJ has led to the study of its topical application in the treatment of periodontal disease [19].

HA has been studied as a metabolite or a diagnostic marker of inflammation in gingival crevicular fluid (GCF) [20]. HA has shown good results in patients with plaque and gingivitis [21]. High molecular weight HA has been used as a scaffold in periodontal tissue regeneration [22]. Vanden Bogaerde evaluated the clinical efficacy of esterified HA in the treatment of infrabony defects and found that there was significant reduction in probing depths and gain in clinical attachement level. A few studies have been reported where HA has been used as an adjunct to SRP in non-surgical periodontal treatment. In view of the above, the present study was designed to investigate the effect of SRP with HA in patients with Chronic Periodontitis [23].

MATERIALS AND METHODS

After approval of the study by the institutional review board (IRB) of St. Joseph Dental college Eluru (A.P) India, 33 selected volunteers (15 males and 18 females) provided written informed consent to their participation in the randomized non-masked split mouth clinical trial, in the Department of Periodontics from August to December 2011.

Systemically healthy individuals with moderate to severe chronic periodontitis with ≥5 sites of PPD ≥5mm having a minimum of 20 teeth were included in the study. Individuals were excluded if they had taken antibiotics 6 months before the study or if they had received periodontal treatment in the previous year. Pregnancy, nursing, smoking, hypertension, chronic diseases such as diabetes mellitus or rheumatoid arthritis were the other criteria for exclusion.

Sixty Six sites from 33 patients were selected for the study and the selected sites were randomly divided into Group A (test/ experimental group) and Group B (control group) The clinical parameters recorded included, gingival index (GI), plaque index (PI)

Group		Baseline	4 weeks	BL-4Wk			12weeks	BL-12Wk		
				Mean Diff	t value ^	p-value		Mean Diff	t value ^	p-value
Controls		1.00 ± 0.00	0.52±0.51	0.48 ± 0.51	5.49	0.00 **	0.48±0.51	0.52±0.51	5.83	0.00 **
Exp.		1.00 ±0.00	0.09 ± 0.29	0.91	12.89	0.00 **	0.06±0.24	0.94±0.24	22.27	0.00 **
Controls v/s Exp.	t value ^^	0.00	4.16	4.16	--	--	4.33	4.34	--	--
	p-value	1.00, NS	0.00 **	0.00 **			0.00 **	0.00 **		

[Table/Fig-1]: Intra and Inter group comparison of bleeding index
*^ Intra-group comparisons : Paired t test, ^^ Inter-group comparisons: Unpaired t test, ** P < 0.001, HS*

Group		Baseline	4 weeks	BL-4Wk			12weeks	BL-12Wk		
				Mean Diff	t-value ^	p-value		Mean Diff	t-value ^	p-value
Controls		6.09±1.26	4.09±1.38	2.00±0.83	13.86	0.00 **	4.36±1.29	1.73±1.04	9.55	0.00 **
Exp.		6.33±0.99	3.21±0.65	3.12±0.89	0.00 **	0.00 **	2.49±0.51	3.85±1.06	20.77	0.00 **
Controls v/s Exp.	t value ^^	0.87	3.31	5.29	--	--	7.76	8.19	--	--
	p-value	0.39, NS	0.002 *	0.00 **			0.00 **	0.00 **		

[Table/Fig-2]: Intra and inter group comparison of probing pocket depth
*^ Intra-group comparisons : Paired t test, ^^ Inter-group comparisons: Unpaired t test, ** P < 0.001, HS*

Group		Baseline	4 weeks	BL-4Wk			12weeks	BL-12Wk		
				Mean Diff	t-value ^	p-value		Mean Diff	t-value ^	p-value
Controls		9.12±1.67	7.76±1.80	1.36±0.74	10.55	0.00 **	7.48±1.51	1.63±0.55	17.13	0.00 **
Exp.		10.18±2.08	7.24±1.25	2.94±1.41	11.95	0.00 **	6.91±1.16	3.27±1.64	11.43	0.00 **
Controls v/s Exp.	t value ^^	2.28	1.35	5.67	--	--	1.72	5.42	--	--
	p-value	0.03 *	0.008, HS	0.00 **			0.00, HS	0.00 **		

[Table/Fig-3]: Intra and Inter group comparison of clinical attachment level
*^ Intra-group comparisons : Paired t test, ^^ Inter-group comparisons: Unpaired t test, ** P < 0.001, HS*

Variable	Baseline	4 weeks	BL-4Wk			12 weeks	BL-12 Wk		
			Mean Diff	t-value ^	p-value		Mean Diff	t-value ^	p-value
GI	1.31 ± 0.16	0.77 ± 0.16	0.54	27.66	0.00 **	0.78 ± 0.15	0.53	14.41	0.00 **
PI	2.61 ± 0.37	1.03 ± 0.30	1.57	20.35	0.00 **	0.85 ± 0.33	1.76	20.92	0.00 **

[Table/Fig-4]: Mean and standard deviation of gingival index and plaque index scores
*^ Paired t test, ** P < 0.001, HS*

[24], bleeding on probing (BOP) [25], probing pocket depth (PPD), clinical attachment level (CAL) at three appointments: before SRP, four weeks and 12 weeks after SRP, using UNC-15 probe and rounded off to the nearest millimeter. The clinical measurements and treatment was performed by a single examiner

Therapy and follow up treatment

All patients received full mouth SRP in the control jaw quadrant at baseline in one or two sessions carried out within 24 h using hand instruments. Identical protocol was followed in the contra-lateral experimental quadrant with the addition of 0.2%hyaluronon gel (Gengigel®) marketed by Ricerfarma pharmaceuticals, Milan, Italy into the selected sites following SRP.

The hyaluronon gel was reapplied 1week post treatment by the periodontist himself, oral hygiene instructions were given to all patients and the patients were followed up for a period of three months.

STATISTICAL ANALYSIS

Mean and standard deviation (SD) of all the clinical parameters were calculated. Statistical analysis of the clinical data was done using SPSS software version 15. Intra group comparisons was done using paired t-test while inter group comparisons was done using unpaired t-test.

RESULTS

Compared to baseline BOP reduced significantly in both the groups at 12 wk post therapy. When inter group comparison was done using unpaired t-test, the test group showed a significant difference in BOP ($p < 0.001$) at 4 and 12 wk postoperatively [Table/Fig-1].

Significant improvements were detected for PPD and CAL in the test and control groups. Analysis of difference between the two groups revealed significant PPD improvement and CAL gain in test group compared to control group [Table/Fig-2,3].

The mean GI and PI scores reduced significantly at 4 and 12 weeks post therapy [Table/Fig-4].

DISCUSSION

SRP was once considered to bring about positive changes in the subgingival microflora. However, studies have shown that the subgingival sites get recolonized with potential periodontal pathogens three weeks after treatment. This would support the need for frequent recall visits for patients who may be periodontally at risk and unable to maintain a proper standard of oral hygiene as suggested by Nyman and co-workers [26].

A meta analysis results of the studies that have investigated the effect of scaling and root planing in periodontal probing depth and attachment loss showed that periodontal probing depth and gain of attachment level did not improve significantly following SRP in patients with shallow initial probing depths, however a reduction of 2mm was found in deep initial periodontal probing depths, similarly there was about 0.5mm gain in attachment for medium initial periodontal probing depths and slightly more than 1mm gain for attachment for deep initial periodontal probing depths, however a consistent improvement in PPD and gain of attachment has been demonstrated when SRP is combined with local antibiotic therapy. It seems that both providers and patients have choice to make whether or not to use combined therapies. Patient preferences

for one type of periodontal therapy over another, and or the self perceived skill or style of a provider will determine which alternative to choose for particular patients [27].

Pistorius et al., studied the effect of topical application of HA in gingivitis patients and found that HA reduces gingival bleeding and acted as a cofactor in the reduction of inflammation [28].

Engstrom et al., investigated the anti-inflammatory and regenerative effect of HA in periodontal defects in surgical and non surgical groups. They observed that the difference in bone height between the test and control sites was found to be less than 1mm in the surgical group 12 months post therapy. No statistical difference was found clinically or on radiographs in the non surgical groups. Mean probing depth reduced in both the groups, The authors concluded that Hyaluronon in contact with bone and soft tissue had no influence on immune system [29].

A statistically significant reduction in BOP scores following local subgingival application of the hyaluronon gel was observed in the present study, our observation is in accordance with previous reports of improved gingival health following application of various hyaluronon formulations in subjects with gingivitis. Jentsch et al in their study found that adjunctive application of hyaluronon significantly reduced gingivitis [30].

Contrary to our results Xu et al., found no difference between hyaluronon and control group relative to BOP and PPD [31]. Sushma et al., also reported no additional benefit in periodontal parameters following subgingival application of 0.2% HA gel as an adjunct to scaling and root planning in chronic periodontitis patients [32].

In the present study both the treatment groups showed a significant reduction in PPD, however in the test group where hyaluronon was used as an adjunct to SRP, reduction was found to be highly statistically significant. This findings are in accordance with Sigrun Eric et al., who analysed the effect of additional application of HA gel during SRP and found that the probing depth measurements improved significantly in the test group, however no difference was found between the groups with respect to CAL. The authors concluded that the observed PD reduction could be attributed to the antibacterial effects of high molecular weight HA on periodontal pathogens [33].

In a randomised clinical study by Francesco et al., it was found that the treatment of infrabony defects with HA offered an additional benefit in terms of PD reduction and CAL gain compared to treatment with open flap debridement alone.They concluded that HA appears to effectively support periodontal wound healing and it can be adapted to different anatomical morphologies [34].

In the present study a significant CAL gain was also observed at 12weeks post therapy in the test group with p-value of 0.001.

There was a significant reduction in the GI and PI scores in the present study. This could be attributed to, scaling and root planning and oral hygiene instructions and also motivation of the patient following therapy.

HA is a candidate for use in the restoration of periodontal integrity due to its complex interactions with the extracellular matrix and its components [35]. HA plays an important role in post-inflammatory tissue regeneration, facilitating cell migration and differentiation during tissue formation and repair [36]. At present it is not possible to identify with certainty those patients who may possess some form of hyper-inflammatory trait. The concept of periodontal hyper-responder together with other risk factors could explain increased susceptibility to periodontal disease. The hyper-responder concept was originally proposed in the context of responsiveness of monocytes to LPS challenge, suggesting that patients with disease possess an individual hyper-responsive monocyte trait, characterized by elevated levels of inflammatory mediators released from monocytes in response to bacterial challenge [37]. It is likely that there are many reasons contributing to disease variations between individuals such as variations in immune response, pathogenesis and the plaque biofilm resulting in an uneven disease experience in the population.

Different mechanisms have been proposed to explain the effect of HA on the inflammatory process. HA gel reduces cell proliferation in gingival epithelial cells, fibroblasts and lymphocytes arrests the inflammatory process and improves periodontal lesions in patients with chronic Periodontitis [38]. The anti-inflammatory effect of hyaluronon may be due to the action of exogenous hyaluronon as a scavenger by draining prostaglandins, metalloproteinases and other bioactive molecules [39].

The sequential treatment protocol in the present study could have produced the beneficial effect on periodontal health. Our findings suggest that more intensive and additional application of HA gel may produce long term beneficial effect though we cannot say how long the added benefits of HA with SRP is going to last, nonetheless the proven clinical variables suggest the beneficial effect of HA gel with SRP at all time periods.

CONCLUSION

The present study showed that adjunctive application of HA produced positive effect in patients with chronic periodontitis. Professionally administered hyaluronon has eliminated possibility of patient compliance influencing the results. In addition split mouth design protocol minimises the cross over effects compared to parallel design. Further studies are needed to investigate the long term effect and to verify the mode of action of HA in periodontitis patients.

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FINANCIAL OR OTHER COMPETING INTERESTS: None.

Date of Submission: **Feb 08, 2014**
Date of Peer Review: **Aug 21, 2014**
Date of Acceptance: **Sep 03, 2014**
Date of Publishing: **Dec 05, 2014**