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ADJUNCTIVE USE OF HYALURONIC ACID WITH SCALING & ROOT PLANING IN TREATMENT OF CHRONIC PERIODONTITIS PATIENTS WITH DIABETES MELLITUS TYPE 2: A RANDOMIZED CONTROLLED TRIAL

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ABSTRACT

Objective: The present study aimed to assess the adjunctive use of Hyaluronic acid with scaling & root planing (SRP) in patients with chronic periodontitis & diabetes mellitus type 2.

Subjects &Methods: Thirty subjects with chronic periodontitis & diabetes mellitus type 2 were included in this randomized clinical trial. These subjects were randomly allocated into test & control equal groups. The test group comprised fifteen patients who received SRP with subgingival application of Hyaluronic acid as an adjunct. The control group included fifteen patients who received SRP alone. Plaque index (PI), gingival index (GI), probing depth (PD) & clinical attachment level (CAL) were measured & documented at baseline, 6 weeks & 12 weeks intervals.

Results: A statistically significant clinical improvement in all clinical parameters was shown in the test & control groups after SRP, 6 weeks & 12 weeks follow up intervals ($p \leq 0.05$). Statistically significant better results were observed in the test group, compared to control group, in all periodontal parameters, except PI, at 6 weeks and 12 weeks ($P \leq 0.05$).

Conclusion: Adjunctive use of Hyaluronic acid with SRP in the treatment of chronic periodontitis patients with diabetes mellitus type 2 offers superior clinical results compared to SRP alone.

KEYWORDS: Hyaluronic acid, chronic periodontitis, scaling & root planning, diabetes mellitus type 2.

INTRODUCTION

Diabetes mellitus (DM) is an endocrinal chronic disorder that results from defect in release or in functions of insulin, or combined defects in insulin release & functions. DM is primarily divided into type 1 & type 2 [1,2]. DM type 2, previously recognized as adult onset DM, is the most common

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type accounting for approximately 85-90% of all diabetics [1-3].

The interplay between periodontitis & DM had been tremendously studied & bidirectional relationship was well established between type 2 DM & periodontitis[4]. Moreover, chronic periodontitis prevalence and severity were found to be higher among diabetic patients than among non-diabetics[5-7]. In fact, periodontitis is known as the 6th complication in DM[8].

The main goal of treatment of periodontitis is to stop progression of the disease whereas the paramount goal is the regeneration of the lost periodontal tissues caused by periodontitis[9-11]. Successful non-surgical periodontal therapy ultimately leads to repair. Unfortunately, repair entails healing of the damaged parts by tissues not completely replacing the same structure &/or function of the lost ones. In contrast, regeneration leads to the reconstitution of the damaged periodontal supporting tissues [10-12]. Thus, several biomaterials & chemotherapeutics have been proposed & investigated in many trials, with scaling & root planing (SRP), aiming to enhance regeneration of the damaged periodontal tissues [13-16].

Hyaluronic acid is an endogenous well-known glycosaminoglycan present naturally in the extracellular matrix of mammalian connective tissue[17]. It is secreted by fibroblast & other connective tissue cells [18] and is found in all periodontal tissues. Specifically, Hyaluronic acid is found to be more abundant in non-mineralized tissues compared to mineralized tissues [19]. Noteworthy, Hyaluronic acid is well recognized for its anti-inflammatory [20], anti-edematous [21], bacteriostatic, [22] & osteo-inductive properties [23]. Several trials had clarified the important action of hyaluronic acid during wound healing in early stages of inflammation [24-26]. Indeed, exogenous hyaluronic acid has been successfully used in several medical specialties including ophthalmology, rheumatology and dermatology to accelerate the process of wound healing [21, 27-29]. In dental practice, especially in periodontology, hyaluronic acid topical application has shown promising beneficial results in plaque-induced gingivitis [30, 31]. However, studies investigating the adjunct use of hyaluronic acid for periodontitis treatment are few and their results are still controversial [32-35]. No previous studies investigating the adjunctive use of hyaluronic acid for periodontitis treatment in diabetic patients were done before. Hence, this current study aimed at investigating the clinical effects of the adjunctive use of hyaluronic acid with SRP for treating periodontitis patients with DM type 2.

PATIENTS AND METHODS

Study design & patients selection

Thirty patients (16 males & 14 females with age range 38-56 years) presenting with chronic periodontitis & controlled DM type 2 joined this randomized clinical trial. A computer program was used to randomly divide included patients into two equal test & control groups according to treatment modality that will be carried out. Study group received SRP & subgingival hyaluronic acid application as an adjunct. Control group received SRP only. The allocation ratio was 1:1.

Patients' selection was carried out in the Outpatient Clinic of Oral Medicine & Periodontology department, Faculty of Dentistry, Cairo University between March 2017 and June 2017. Full medical history was collected from all patients following the modified Cornell Medical Index[36] detailed questionnaire. The study protocol was accepted by the Institutional Research Ethics Committee & was clarified to all patients who agreed to participate in this study & signed a written consent.

Inclusion Criteria

This study included patients having DM type 2 for at least one year before enrollment. Diagnosis of these patients was based on the diagnostic

standards set by American Diabetes Association[37]. All included patients were controlled diabetics with glycated hemoglobin levels (HbA1c) ranging from 6% to 7% & they were under therapy with oral hypoglycemic drugs &/or insulin.

Chronic periodontitis was diagnosed in these patients according to the World Workshop [38] radiographic & clinical characteristics. Each patient had a minimum of 20 teeth and not less than four sites having clinical attachment level (CAL) ≥ 3 mm & probing depth (PD) ≥ 4 mm.

Exclusion Criteria

Patients having any systemic disorder other than DM type 2, pregnant & lactating females, former & current smokers, patients who have received antibiotics & periodontal therapy in the past six months were excluded from this investigation.

Periodontal Examination & Measurements

Clinical examination of periodontal parameters was carried out for included patients by one calibrated examiner (GM). For each patient, periodontal parameters were documented in six sites for each tooth; mid-buccal, mid-lingual, mesio-buccal, mesio-lingual, disto-buccal & disto-lingual. Plaque index (PI)[39], gingival index (GI)[40], PD & CAL utilizing William's graduated periodontal probe, at baseline before starting non-surgical periodontal therapy and later during follow up at 6 weeks & 12 weeks intervals. Diagnosis of chronic periodontitis was confirmed by full mouth periapical radiographs[41].

Periodontal Therapy

All patients of test & control groups received detailed instructions for oral hygiene measures & brushing technique as well as regular interdental brush usage at 1st visit and reinforced at each recall visit. In addition, all patients received full-mouth supra- & sub-gingival SRP with the use of ultrasonic device & periodontal universal & Gracey curettes under local anesthesia.

In addition to SRP, patients in the test group received adjunct subgingival application of hyaluronic acid (Hyadent BG, BioScience GmbH, Ransbach-Baumbach, Germany) in all selected periodontal pockets.

Follow up & reassessment of all periodontal parameters were carried out at 6 weeks & 12 weeks intervals for all patients. Treatment was provided by a single periodontist (IR) to both test & control groups and all clinical parameters were taken before & after treatment by another periodontist (GM).

The primary outcome of this trial is the mean changes in CAL. Secondary outcomes included PI, GI and PD mean changes between both studied groups.

Sample size calculation

G power analysis program [42] was utilized to calculate the sample size. The sample size was calculated based on the primary outcome of the study which is the mean changes of CAL for both studied groups. A total of 30 patients divided into 2 groups of 15 each was needed for detection of significant difference ($P \leq 0.05$) at 80% power test.

Randomization

A computer randomization program was used to randomly assign the included patients to receive either SRP & subgingival hyaluronic acid application as an adjunct or to receive SRP only, with allocation ratio 1:1. The computer-generated randomization list was then concealed & kept with one of the authors (BM) in charge of randomization. Allocation concealment was accomplished by central randomization. The operator contacted by phone the person in charge of randomization, who had the randomization list, to allocate the patient to either SRP & hyaluronic acid application or to SRP only.

STATISTICAL ANALYSIS

Age, PI, GI, PD and CAL mean & standard deviation values were calculated for both test & control groups. For comparison of PI, GI, PD & CAL at different intervals within each group, paired Student t-test was applied. For comparison of PI, GI, PD & CAL at different intervals between the test & control groups, unpaired Student t-test was utilized. All data were statistically analyzed using SPSS 17 software (SPSS Inc., Chicago, IL, USA). P value ≤ 0.05 is statistically significant.

RESULTS

Table 1 shows the demographic data of all included patients in the test & control groups. All periodontal parameters of test & control groups at baseline, 4 weeks & 6 weeks intervals are shown in table 2. Intra-group comparisons showed improvement in PI, GI, PD & CAL for both groups from baseline to 12 weeks follow up & this improvement is statistically significant (P≤0.05). Inter-group comparisons revealed no statistical difference in PI, GI, PD & CAL between the two groups at baseline (p>0.05). At 6 & 12 weeks intervals, PI did not show statistical significant difference in the test group compared to control group (p>0.05). GI, PD & CAL showed statistical significant difference at 6 & 12 weeks intervals among the test group compared to controls (P≤0.05). In comparison to controlgroup (SRP only), test group (SRP+Hyaluronic acid) showed statistically significant better results in all periodontal parameters, except PI, at 6 & 12 weeks intervals (P≤0.05).

TABLE (1) Demographic data of SRP+Hyaluronic acid group (test group) & SRP group (control group)

Patient groups	Number	Age (years) (mean ± SD)	Sex (M:F)
SRP+Hyaluronic acid	15	46.37 ± 3.95	8:7
SRP	15	47.28 ± 4.13	9:6

TABLE (2) Comparison of periodontal parameters of the test group (SRP+Hyaluronic acid) and control group (SRP) at different intervals; baseline, 6 weeks & 12 weeks (Data are represented as mean ± SD)

Periodontal parameters	Interval	SRP+Hyaluronic acid	SRP	p value
PI	**Baseline**	1.92 ± 0.48	1.86 ± 0.41	0.7156#
	6 weeks	1.18 ± 0.24	1.27 ± 0.26	0.3330#
	12 weeks	0.91 ± 0.27	1.02 ± 0.29	0.2915#
GI	**Baseline**	1.88 ± 0.43	1.91 ± 0.44	0.8516#
	6 weeks	1.16 ± 0.29	1.39 ± 0.32	0.0485*
	12 weeks	0.85 ± 0.28	1.06 ± 0.27	0.0457*
PD (mm)	**Baseline**	3.49 ± 0.43	3.56 ± 0.49	0.6807#
	6 weeks	2.48 ± 0.31	2.79 ± 0.33	0.0130*
	12 weeks	2.39 ± 0.38	2.68 ± 0.36	0.0407*
CAL (mm)	**Baseline**	4.35 ± 0.56	4.29 ± 0.53	0.7653#
	6 weeks	3.07 ± 0.59	3.48 ± 0.49	0.0477*
	12 weeks	3.03 ± 0.47	3.46 ± 0.51	0.0232*

 # Not statistically significant p>0.05 *statistically significant p≤0.05 (Unpaired Student t-test)

DISCUSSION

Till now, SRP remains the gold standard & the cornerstone for successful periodontal therapy for chronic periodontitis patients & DM type 2[43,44]. Nonetheless, several diverse adjunctive treatments have been proposed & investigated in a trial to increase the beneficial outcomes of SRP[45,46]. In the last few years, Hyaluronic acid has received great interest & has been proposed as an adjunct chemotherapeutic to SRP owing to its anti-inflammatory, bacteriostatic & wound healing promoting properties[47]. Wound healing in diabetic patients is a well-known major problem[48]. To our knowledge, the current investigation studied, for the first time, the use of hyaluronic acid as an adjunct to SRP for chronic periodontitis & DM type 2 patients compared to SRP alone.

Results of this trial revealed statistically significant improvement in all periodontal measurements in test & control groups with time (from baseline to 6 weeks & 12 weeks follow up). In addition, GI, PD & CAL mean changes showed more favorable results in SRP & Hyaluronic acid test group & these results were statistical significant. Results of this trial suggest that hyaluronic acid as adjunct to SRP has superior beneficial effects over SRP alone in chronic periodontitis & DM type 2 patients. Results of this trial are in agreement with *Rajan et al*.[49] & *Shah et al*.[50] who reported clinical improvement in PD & CAL with the use of Hyaluronic acid in conjunction with SRP in chronic periodontitis patients. Furthermore & in line with our results, *Koshal et al*.[51] concluded highly significant improvement in clinical periodontal parameters, in chronic periodontitis patients, with Hyaluronic acid & SRP compared to placebo & SRP. *Johannsen et al*.[35] reported no statistical significant difference in PI as well as a statistically significant decrease in bleeding on probing scores & PD with the adjunctive use of hyaluronic acid with SRP compared to SRP alone & this is partially in accordance with results observed in our study. However, they found no statistical significant difference in CAL with the adjunctive use of Hyaluronic acid & this is inconsistent with our results. Similarly, *Eik et al*.[32] showed statistically significant improvement in PD with the adjunctive use of Hyaluronic acid with SRP & this is in concert with our results. However, in contrast to our result, they reported no statistical significant difference in CAL[32]. In addition, *Xu et al*.[34] reported no significant improvement in all periodontal parameters with adjunctive use of Hyaluronic acid with SRP compared to SRP alone, this is in contrast to our results. Similarly, *Gontiya & Galgali*[52] declared that the adjunctive use of Hyaluronic acid in patients with chronic periodontitis showed no statistical significant changes in PD & CAL. Only a significant improvement in GI was reported in their study[52]. Discrepancies in results of all these previous studies may be attributed to different Hyaluronic acid preparations & concentrations used with different therapeutic strategies, different severity of chronic periodontitis and follow-up intervals as well as small sample sizes.

Favorable superior results of using hyaluronic acid as adjunct to SRP showed here in our study may be accredited to the unique biological & physiochemical properties of Hyaluronic acid [21, 53, 54]. Hyaluronic acid possesses viscoelastic properties that enable it to act as a barrier preventing penetration of periodontal bacterial pathogens[55]. In fact, bacteriostatic properties of Hyaluronic acid have been reported by *Pirnazar et al*.[56]. Anti-inflammatory property of Hyaluronic acid is credited to its role in scavenging metalloproteinases, bio-active molecules & prostaglandins[20]. Most importantly, Hyaluronic acid has pivotal actions in several functions of cells including cells recognition, proliferation, activation & migration, all of which are responsible for its wound healing properties[57]. During early stages of healing, hyaluronic acid interacts with fibrin clot providing a structural framework that modulates the infiltration of keratinocytes, fibroblasts, osteoblasts & cementoblasts into the wound site stimulating them to release a variety of pro-inflammatory cytokines[58].

Moreover, Hyaluronic acid induces activation of polymorph nuclear leukocytes & macrophages leading to their migration & adhesion to the wound site, ultimately resulting in phagocytosis & bacterial killing[59,60]. Furthermore, Hyaluronic acid has paramount function in formation of extracellular matrix & organization of granulation tissue. This will allow gingival epithelium' basal layer re-attach to basal lamina [56]. Taken together, diverse functions of hyaluronic acid may orchestrate concomitantly leading to enhancement in periodontal parameters seen in results of this trial & highlight the beneficial role of Hyaluronic acid with SRP for treating chronic periodontitis & DM type 2 patients.

As stated earlier, periodontitis is the 6th complication of diabetes[6,8]. In fact, diabetes' complications were found to impair quality of life in diabetics[61]. Thus, successful treatment of periodontitis will ultimately lead to improvement of diabetic patients' quality of life. Indeed, *Mizuno et al*.[62] reported improvement of quality of life scores after non-surgical periodontal treatment in chronic periodontitis patients with diabetes type 2. Furthermore, in their randomized controlled clinical trial, *Mauri-Obradors et al*.[44] concluded that non-surgical periodontal treatment improves significantly HbA1c levels in chronic periodontitis diabetics[44]. Similar results were obtained from other studies [63-65] that reported reduction in HbA1c levels by about 0.4%-0.8% following SRP. Taken all together, results of this study suggest using Hyaluronic acid with SRP in chronic periodontitis & type 2 DM patients.

CONCLUSION

Within limitations of this trial, the authors concluded that adjunct use of Hyaluronic acid with SRP improves significantly all clinical parameters in chronic periodontitis & DM type 2 patients. Further trials, with large sample sizes, are recommended to clarify the longstanding therapeutic results of hyaluronic acid in regeneration of periodontal tissues.

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