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ORIGINAL ARTICLE

Clinical comparison of oral administration and viscosupplementation of hyaluronic acid (HA) in early knee osteoarthritis

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Abstract
Purpose Osteoarthritis (OA) is a progressive, chronic and degenerative joint disease characterized by a loss of articular cartilage. Treatment of OA is largely palliative based on nonsteroidal anti-inflammatory drugs, opioids and injections of steroids. Regarding conservative treatment, intra-articular injections of hyaluronic acid (HA) can play a role in early symptomatic knee OA.
Materials and methods Between August 2015 and September 2015, sixty patients (32 males and 28 females) between 40 and 70 years old were randomly allocated into two groups: Half were treated with three weekly intra-articular injections of hyaluronic acid 1.6 % (group A), while the others were treated with Syalox 300 Plus® (hyaluronic acid 300 mg + Boswellia serrata extract 100 mg) 1 tab/die for 20 days and afterward Syalox 150® (hyaluronic acid 150 mg) 1 tab/die for other 20 days (group B). All patients were evaluated clinically with American Knee Society Score (AKSS) and visual analogue scale (VAS) for the pain before the treatment and after 3 months.
Results AKSS of the patients in both groups was significantly increased by the treatment, and VAS score was significantly reduced. In both groups, two subgroups were created with patients older than 60 years and patients younger than 60 years. Better results are reported in younger patients of group A and older subjects in group B.
Conclusions Despite several limitations, the results of the study have shown that HA injection and oral administration may have beneficial therapeutic effects on patients with early osteoarthritis. Different outcomes in younger and older subject suggested a combined therapy first with local infiltrations and then with oral composition.

Keywords Early knee osteoarthritis · Hyaluronic acid · Viscosupplementation

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Introduction

Osteoarthritis (OA) is a progressive, chronic and degenerative joint disease characterized by a loss of articular cartilage. OA is a multifactorial disease: Obesity, aging, genetics and joint trauma increase the risk of development of this condition. Aging in developed country societies leads to a significative rise in the costs related to the disease; in particular, in the USA, patients suffering from knee OA were 43 million in 1997 and the prevision for 2020 is more than 60 million. The prevalence is higher in women, and over 50 years old, the incidence is 45 % higher than in men [1].

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Table 1 Patients treated with intra-articular injections of hyaluronic acid 1.6 %

Group A							
	KSS pre	KSS post	DIFF	%	SD pre	SD post	Age avg
AKSS							
>60	146.636364	166.363636	19.7272727	13.4531928	20.5244865	25.893137	65.7272727
<60	146.210526	174.947368	28.7368421	19.6544276	18.6773153	20.8925124	52.1578947
TOT	146.366667	171.8	25.4333333	17.3764518			57.1333333
	VAS pre	VAS post	DIFF	%	SD pre	SD post	
VAS							
>60	7.18181818	5.09090909	2.09090909	29.1139241	0.8738629	2.16585066	
<60	6.84210526	3.63157895	3.21052632	46.9230769	1.11868762	2.26594416	
TOT	6.96666667	4.16666667	−2.8	−40.191388			
gr lib		58		*p*			
tVAS		6.0698135		1.0453E−07		1.0453E−07	
tAKSS		4.69155176		1.6957E−05		1.6957E−05	

Pain and joint tenderness are most frequent symptoms [2] in association with stiffness, swelling and decrease in range of motion. Common signs of OA are subchondral bone sclerosis, joint space narrowing, osteophytes, subchondral cysts and synovitis.

Conventional radiography is the gold-standard imaging technique, and the Kellgren and Lawrence [3] scoring system is a widely accepted scheme for defining the severity of OA based on the presence of osteophytes.

Treatment of OA is largely palliative, characterized by the use of nonsteroidal anti-inflammatory drugs (NSAIDs), opioids and injections of steroids. Prosthetic replacement is the only procedure that allows satisfactory long-term results [4].

Regarding conservative treatment, intra-articular injections of hyaluronic acid (HA) can play a role in early symptomatic knee OA.

HA is a polymer of disaccharides present in the synovial fluid, composed of D-glucuronic acid and N-acetylglucosamine [5]. Injected into joint, it may have a slow but considerably longer effect on pain compared with steroids [6].

Some studies reported a certain effect on knee OA pain also with HA ingestion [7–10], but there is lack of evidence due to the shortness of the follow-up and the heterogeneity of the compared groups.

On the basis of these considerations, we conducted a study about the clinical effects in the administration of injected and oral HA.

Materials and methods

Between August 2015 and September 2015, sixty patients (32 males and 28 females) between 40 and 70 years old were selected for this study. The subjects included were affected by knee degenerative OA grade I or grade II according to Kellgren and Lawrence classification. Exclusion criteria were rheumatoid arthritis or other inflammatory joint disease, secondary OA, and problems with liver, kidney, or their motor or nerve systems.

Patients were randomly allocated into two groups: Half were treated with three weekly intra-articular injections of hyaluronic acid 1.6 % (group A), while the others were treated with Syalox 300 Plus® (hyaluronic acid 300 mg + Boswellia serrata extract 100 mg) 1 tab/die for 20 days and afterward Syalox 150® (hyaluronic acid 150 mg) 1 tab/die for other 20 days (group B).

All patients were evaluated clinically with American Knee Society Score (AKSS) and visual analogue scale (VAS) for the pain before the treatment and after 3 months.

Results

Background of the subjects in both groups is shown in Tables 1 and 2. No significant difference was found between the two groups with respect to age, AKSS and pain VAS score before the treatment.

All patients completed the study, and no adverse events were observed in both groups during the study.

AKSS of the patients in both groups was significantly increased by the treatment. The percentage difference from the baseline for the two groups was 17.38 and 10.66, respectively.

Pain VAS score of the patients in group A was significantly reduced by the treatment. The percentage difference from the baseline in the pain VAS score in group A was −40.19. The pain VAS score in group B was also

Table 2 Patients treated with Syalox 300 Plus® and afterward Syalox 150® per OS

Group B							
	KSS pre	KSS post	DIFF	%	SD pre	SD post	Age avg
AKSS							
>60	145.285714	163.714286	18.4285714	12.6843658	16.596703	20.3486101	66.5714286
<60	148.1875	161.25	13.0625	8.81484606	15.984237	15.3470953	53.375
TOT	146.833333	162.4	15.5666667	10.6015891			59.5333333
	VAS pre	VAS post	DIFF	%	SD pre	SD post	
VAS							
>60	7.21428571	4.92857143	−2.2857143	−31.683168	1.18831305	2.20014985	
<60	13.875	5.875	−8	−57.657658	1.21106014	1.70782513	
TOT	7.1	5.43333333	1.66666667	23.4741784			
gr lib			58			*p*	
t VAS			3.96053662			0.00020699	
t VAS ex			0.00020699				
tAKSS			3.58128704			0.00069997	

significantly reduced by the treatment with a percentage change from baseline of −23.79.

Sub analysis

In both groups two subgroups were created with patients older than 60 years and patients younger than 60 years.

In group A, the percentage difference from baseline in AKSS and pain VAS score was 19.45 and −46.92, respectively, in the younger group, while it was 13.45 and −29.11, respectively, in the older group.

In group B, the percentage change from baseline in AKSS and pain VAS score was 8.82 and −16.19, respectively, in patients younger than 60 years. In patients older than 60 years, the percentage difference was 12.68 in AKSS and −31.68 in pain VAS score (Tables 1, 2).

Discussion

In both groups, we observe a mean improvement in pain (VAS scale) and AKSS after 3 months. In the literature, it was reported that intra-articular HA improves synovial fluid elasticity and viscosity [11]. It decreases the release of pain producing neuropeptides and proinflammatory mediators released by synovial cells [12]. Anti-inflammatory effects such as IL-1 suppression are detected in studies in vitro [13, 14]. Otherwise, a recent systematic review based on the analysis of pain relief and functional improvement concluded against the routine use of HA injection [15]. The benefits of these therapy compared with a placebo (intra-articular saline solution) were not clinically relevant. However, some limitations are present in that review: HA formulation, dosages, formulation, population and timing of injection were different in trials considered. Another critic focus was the timing of assessment after the therapy [15].

Our research finds out encouraging results at 3-month follow-up after viscosupplementation in patients with initial signs of OA, in particular in younger patients.

Also patients treated with oral HA have shown good results, slightly lower than those treated with injection therapy. This proves that orally administered HA is absorbed and distributed to the joints. Animal experiments claim that oral administration allowed absorption and distribution to various tissues such as skin, bone and synovial joints [16, 17]. Moreover, a substantial part of HA should not be degraded, preserving biological activities, and would be maintained in tissues for prolonged periods [18, 19].

All these studies had shown the beneficial effects of oral HA over a short period of therapy. Considering that OA is a progressive disease and its symptoms fluctuate with time from years to decades [35 in Tashiro], long-time follow-up studies are needed. Tashiro et al. treated sixty patients with 12-month oral therapy and reported alleviation of knee OA symptoms in particular in relatively young patients at the early time points (2nd and 4th months). In authors' opinion, these results are probably due to differences in cell metabolism or in the pathology of OA between the younger end older subjects, but this is only a supposition [20].

On the basis of this study, we decided to divide all the subjects by age and we observed that proportionally younger patients aged 60 years or less show better results

with HA injection. Otherwise, older subjects seem to respond better to the oral administration. The scientific explanation of these outcomes is not clear but might be ascribed to the change in composition of synovial fluid and the presence of Boswellia serrata in the oral therapy. Better results of HA injection in young patients are probably ascribed to biological differences in the molecular reaction of immune system at this chronic disease.

Acetyl-keto-beta-boswellic acid (AKBA) contains Boswellia resin and is an inhibitor of the lipoxygenase pathway and is suggested to have anti-inflammatory properties [21, 22]. Nine clinical trials that examined pain relief and improvement in function after Boswellia extract administration are reported in the literature. Almost all have shown some benefits for OA although the studies analyzed small numbers of patients, were conducted over short periods only, and did not meet all rigorous criteria [23–26].

Conclusions

Despite several limitations, the results of the study have shown that HA injection and oral administration may have beneficial therapeutic effects on patients with early osteoarthritis. Different outcomes in younger and older subject suggest a combined therapy first with local infiltrations and then with oral composition. The effect and the use of HA remain controversial in the latest literature reviews, and long-term, prospective randomized trials are necessary for clarify its therapeutic role. However, HA supplementation in addition to anti-inflammatory agents such as AKBA could be a valid attempt to decrease the use of NSAIDs in early OA.

Compliance with ethical standards

Conflict of interest None.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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