

## VISCOSUPPLEMENTS WITH LOW MOLECULAR WEIGHT AND HIGH MOLECULAR WEIGHT IN THE TREATMENT OF KNEE OSTEOARTHRITIS

Arianit Bajraktari<sup>1</sup>, Rina Hoxha<sup>3</sup>, Ismet H. Bajraktari<sup>1,2</sup>, Avni Kryeziu<sup>2</sup> and Halit Bajraktari<sup>\*2</sup>

<sup>1</sup>Specialist Private Practice of Internal Medicine – Rheumatology – Prorheuma-Prishtina.

<sup>2</sup>Alma Mater Europea Campus College Rezonanca.

<sup>3</sup>National Institute for Public Health.

<sup>4</sup>Specialist of Internal Medicine.



\*Corresponding Author: Halit Bajraktari

Alma Mater Europea Campus College Rezonanca.

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### SUMMARY

In the prospective-randomized study we have followed up action of paraenteral – intraarticular therapy with hyaluronic acid of small molecular weight and high molecular weight among the patients with knee Osteoarthritis. In the study were included 259 patients – 70 males and 189 females separated in 2 group. Patients belong to various group ages with the mean age of 54.2 year old. Osteoarthritis belongs to the II – III radiological scale according to Kellgren – Lawrence classification. Results are following: after the third week of treatment, among 83.3% of patients treated with the high molecular weight (HMW) ampoule, we have observed subsided pain according the Likert Scale and increase in the movement amplitude, whereas this percentage among the patients treated with the low molecular weight (LMW) ampoule was 64.6 %. During the first month of treatment this percentage was 23.8 % for treatment with LMW ampoule, respectively 7.7% for treatment with HMW ampoule. After the third month of treatment improvements were achieved in 8.8% of patients treated with LMW ampoule, respectively in 2.6% of those treated with HMW ampoule. After 24 weeks 22.2% of patients treated with HMW ampoule needed re-treatment, 74% of them needed re-treatment after 38 weeks, whereas 3.8% of patients needed re-treatment after more than 1 year. During the treatment with LMW ampoules, re-treatment was necessary after 24 weeks among 65.2% of cases, another 33.4% of cases needed re-treatment after 36 weeks, while re-treatment after 1 year was needed for 1.4% of cases. The best results are achieved in intra-articular application of the high molecular weight hyaluronic acid. Viscosupplementation is a simple and low-cost method, with no side effects and is applicable when other treatment methods are exhausted.

**KEYWORDS:** Osteoarthritis, Viscosupplementation, Hyaluronic acid.

### INTRODUCTION

Viscosupplements are pharmaceutical products that are used as replacement of synovial liquid on the joints affected by osteoarthritis. Viscosupplements have wide spectrum of application, particularly in the knee osteoarthritis. In the beginning they were produced from hyaluronic acid extracted and cleaned from rooster's tissue, whereas today viscosupplements are produced with biologic engineering technology. There are positive evaluations on their impact, but also doubts about their clinical benefits in osteoarthritis and rationale of treatment with these products.

Viscosupplements are intra-articular medications without counter-indications, with no systemic effects, and as such are applicable in cases where we cannot apply NSAIDs, analgesics, corticosteroids, etc. In the clinical practice of

internal medicine and rheumatology very often we encounter patients who along with osteoarthritis suffer from other chronic ailments, such as renal insufficiency, cardiac insufficiency, liver insufficiency, chronic gastritis, gastroduodenal ulcer, and other disorders of gastro-intestinal system, and in these cases analgesics, NSAIDs, oral chondro-protectors and local corticosteroids cannot be applied and therefore medications of first choice are viscosupplements.

Osteoarthritis (OA) is a degenerative disease of the joints characterized by damaging and loss of the part of articular cartilage, subchondral sclerosis, bone hypertrophy under the damaged cartilage, and osteophytes formation in the articular edged.<sup>[1]</sup>

OA is the most common disease of joints and the main cause of inability to work. Around 80% of population worldwide over the age of 60 has radiological signs of OA, and 60% of patients over this group age require medical treatment.<sup>[2]</sup>

OA most frequently presents in knees, coxo-femoral joints, fingers of hands, apophyseal joints of vertebral column. In general all joints may be affected by OA.<sup>[3]</sup>

In all joints, excluding the hip joint, OA are more frequent among women than men.<sup>[4]</sup>

OA in most of cases are primary (with unknown cause), while in rare cases the cause is known thus are classified as secondary. Causes of OA are unknown however its many initial and developing mechanisms are fully known. There are for sure numerous factors that supplement each other. To name some of them: heredity, obesity, previous damages, vocation, metabolic disorders, lack of alimentary components, etc.<sup>[5,6]</sup>

The main cause for OA development is deranged balance between regeneration and decomposition of joint cartilage. In the beginning collagen fibers tear apart, proteoglycan amount decreases, cartilage turns edematous due to increase of fluid volume in perihondrocytal space. In this phase we notice the increase of level of the enzymes that break down cartilage tissue fibers as well as the decrease of levels of chondroitin sulfate and hyaluronic acid. In later stages after several years, smooth surface of cartilage is compromised, fissures and scratches occur, also a part of cartilage can cut off from the joint's cartilage. The bone tissue suffers damage of surface and deficient supply with nutrients, vascularization increases, articular surface develops sclerotization and as a compensatory mechanism tends to increase articular surface by developing osteophytes on the lateral sides of joints. Impact of immune factors must be mentioned too.<sup>[7]</sup>

Treatment of OA is complex. It is pharmacological and non-pharmacological. NSAIDs, oral chondro-protectors, local glucocorticoids, physical therapy and visco supplementation are used for this purpose. In advanced OA surgical treatment is preferred: arthroscopy, osteotomy unilateral or total condylar endo-prosthetics. In the field of biologic engineering there has been attempts of chondrocytes implantation which would produce hyaline cartilage that subsequently would cover the micro-lesions of cartilage, but outcomes of these results are still pending.<sup>[8]</sup>

#### **Viscosupplements and Viscosupplementation**

Articular cavities contain synovial fluid which is composed of high amounts of hyaluronate (hyaluronic acid) in concentrations 2.5 – 4 mg/ml with molecular weight (MW, 4 – 6 mill Dalton).

Normally in one knee joint is found approximately 2 – 3.5 ml synovial fluid with 4 – 8 mg of hyaluronate. Such a high concentration of hyaluronate is of vital importance for the proper function of joint. Hyaluronate is being synthesized in the joint tissue by three types of cells: Type A cells (Hyalocytes), and type B cells (Fibroblasts) of synovial membrane, as well as chondrocytes.

In OA we see depletion of these cells, reduced production of hyaluronate, reduced fluid viscosity, increased amount of fluid with low molecular weight, and decreased amount of fluid with high molecular weight.<sup>[9]</sup>

Viscosupplementation is the intra-articular application of a viscos-elastic matter which contains hyaluronate. Pharmacies in Kosova are supplied with small molecular weight viscosupplements (Hyalart, Hyalgan, Ostenil, Supartz, GO-ON, Yaral, Suplasyn) that are applied intra-articularly 5 weeks into one joint, whereas brands of high molecular weight viscosupplements are few (Ortho visc and Syn visc). These are applied only in 3 intra-articular doses, once a week.

Viscosupplementation gives improved results on the viscosity of joints, improves elasticity of synovial fluid, and maintains joint's homeostasis. Chondroprotective action is result of hyaluronate's viscosupplementation in the damaged joint, whereas analgesia is the result of inhibiting the inflammatory mediators. Therapeutic effects are evident in most of cases after three weeks, in some case after one month and in very rare cases after three months. Articular pain subsides, movement amplitudes expand, contractures diminish, crepitations are more rare and therapeutic effect last in most of cases 6 – 12 months, while in some cases 12 – 18 months. Treatment must be repeated after this time period.

#### **AIM AND OBJECTIVE**

Purpose of the study is to present the treatment of knee OA with low molecular weight and high molecular weight viscosupplements.

Analyze differences in clinical – therapeutic response of these two types of viscosupplements. Analyze effectiveness of therapeutic action and duration of effects for both type of viscosupplements.

#### **MATERIAL AND METHODS**

During the period 2012 – 2015 have been treated a total of 259 patients with knee OA, among them 70 males and 189 females belonging to group age 29 – 85 year old. These patients were selected out of a total 724 patients with knee OA, but who had also other rheumatic conditions. 181 patients of this group have been treated with low molecular weight (LMW) viscosupplement, whereas 78 patients were treated with high molecular weight (HMW) viscosupplement.

The study is prospective, randomized, transverse type (cross-sectional).

Diagnose was ascertained based on the anamnesis, objective examination, radiological scale II – III according to Kellgren – Lawrence classification, and laboratorial examinations.<sup>[10]</sup>

Joints' movement amplitude is evaluated before and after treatment, whereas for the pain evaluation is used the Likert Scale (0 – 4). Patients were treated with low molecular weight hyaluronic acid ampoules, 1 ampoule on each knee joint once a week during 5 consecutive

weeks, as well as with high molecular weight hyaluronic acid ampoules, 1 ampoule on each knee joint during three consecutive weeks. During and after application of therapy we have followed up the intensity of pain, expansion of movement amplitudes, and articular stability, Regular check-up and clinical evaluation during therapeutic application was performed every week, after 1 month,3 months,6 months,9 months and 1 year after the last application.

## RESULT

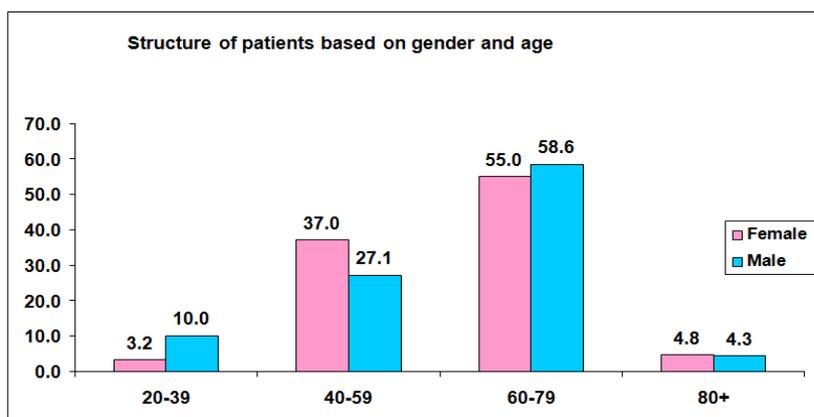
Most of the patients live in village (57.6%) others come from cities (42.4%).

**Table 1: Patients according to gender and age.**

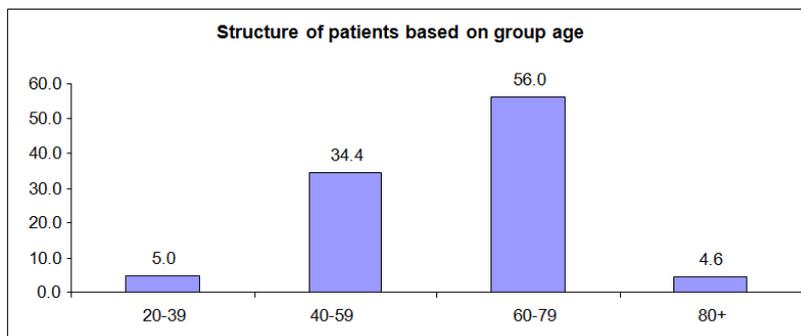
Gender	N	%	$\chi^2$ -test
Females	189	73.0	$\chi^2=54.7$ ; ShL=1; p<0.00001
Males	70	27.0	
Total	259	100.0	-

**Table 2: Structure of patients with knee OA according to gender and group age.**

Group age	Gender				Total	
	Female		Male		N	%
	N	%	N	%		
20-39	6	3.2	7	10.0	13	5.0
40-59	70	37.0	19	27.1	89	34.4
60-79	104	55.0	41	58.6	145	56.0
80+	9	4.8	3	4.3	12	4.6
Total Patients	189	100.0	70	100.0	259	100.0
Mean Age $\pm$ SD	61.9 $\pm$ 11.7		60.8 $\pm$ 13.2		61.6 $\pm$ 12.1	



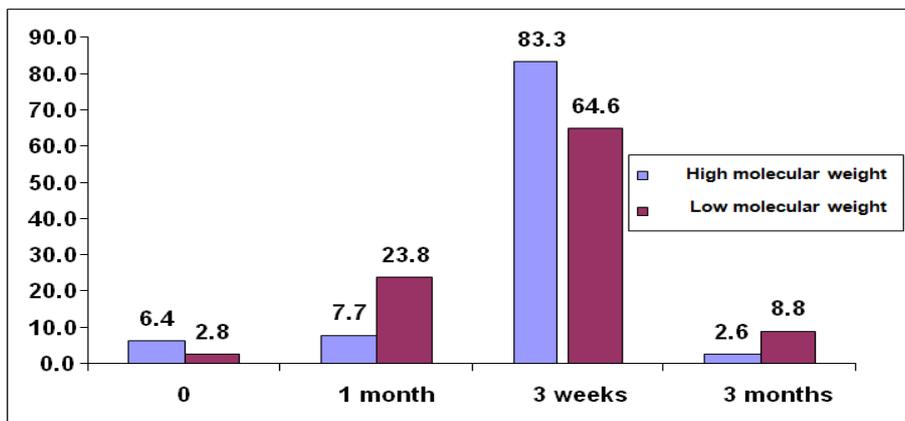
**GRAPH 1**



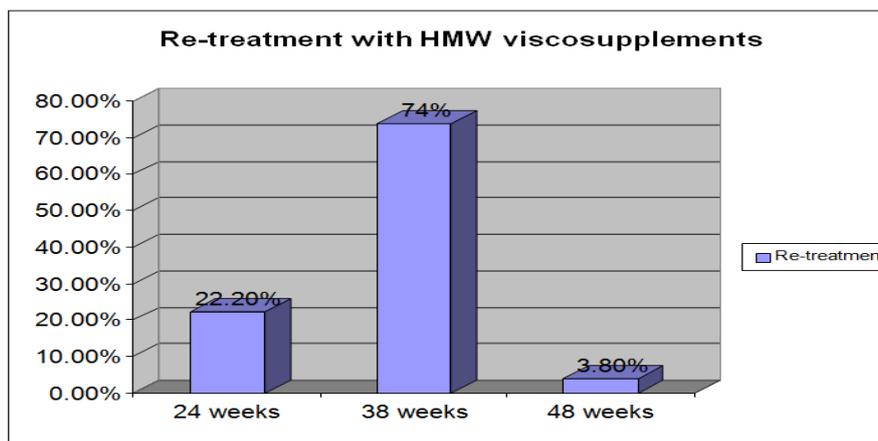
GRAPH 2

Table 3: Effectiveness of viscosupplementation in knee OA.

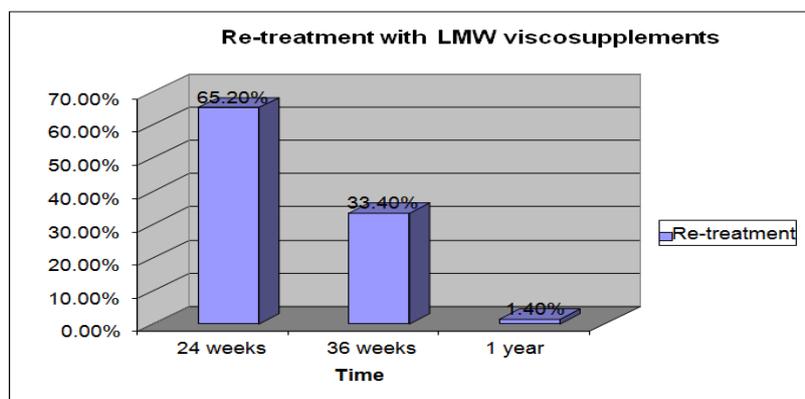
Time of Reaction	Viscosupplement				Total	
	High molecular Weight		Low molecular Weight			
	N	%	N	%	N	%
0	5	6.4	5	2.8	8	3.1
1 month	6	7.7	43	23.8	49	18.9
3 weeks	65	83.3	117	64.6	182	70.3
3 months	2	2.6	16	8.8	18	6.9
<b>Total</b>	<b>78</b>	<b>100.0</b>	<b>181</b>	<b>100.0</b>	<b>259</b>	<b>100.0</b>



Graph 3: Reaction time in therapy.



GRAPH 4



GRAPH 5

## DISCUSSION

OA is object of studying due to its destructive feature against joint and its cartilage. OA play a significant role in causing damage to health and generate high costs for a patient and society in general.

Viscosupplementation as a method for the joint treatment, regeneration and lubrication has been an object of studying since beginning of its application in 1980-81 due to its efficiency, tolerability and impact in maintaining joint's homeostasis.

Most of accomplished studies indicate the long term positive impact of viscosupplementation, such as improvement of movement amplitudes, diminishing of pain, regeneration and lubrication of joint.

Author Lubowitc in his work offers important information on diminished pain in the knee and improved joint function after intraarticular application of hyaluronic acid.<sup>[11]</sup>

Monticone et al. have studied a total of 115 references and have selected 8 studies out of them whereby they have compared patients treated with hyaluronic acid, patients treated with physical therapy, as well as patients who were having pain in the knee and limited capacity of knee. The study has analyzed reaction of patients' and has indicated that patients treated with hyaluronic acid therapy were having improved quality of life.<sup>[12]</sup>

Author Shah et al. have explored changes on T1rho in the RM sequence among patients after viscosupplementation and have noticed improved parameters, but also unchanged parameters who didn't respond positively on the viscosupplementation.<sup>[13]</sup> Author Migliori proposed viscosupplementation to be included in the treatment of other joints affected by OA in order to diminish pain, improve lubrication and improve the quality of life.<sup>[14]</sup>

Author Gigante has studied the role of intraarticular hyaluronates in the treatment of knee OA and have concluded that application of this therapy have yielded

significant results in diminishing the pain, and in the increase of movement amplitudes.<sup>[15]</sup>

Author Navarro et al. in their joint project called "Amelia" have investigated efficacy of viscosupplementation compared with placebo therapy in a 40 month period and have concluded significant changes.<sup>[16]</sup>

Most of accomplished studies indicate the long term positive impact of viscosupplementation, such as improvement of movement amplitudes, diminishing of pain, regeneration and lubrication of joint, etc.<sup>[17-28]</sup>

Japanese authors (Muneaki Ishijima et al.) have carried out comparative studies on viscosupplements along with NSAIDs and have presented important data on the action of both these pharmaceutical agents in the treatment of osteoarthritis.<sup>[29]</sup>

Also the action and therapeutic impact of buffer phosphate salts in the knee osteoarthritis has been studied. Several authors indicate limited results of viscosupplementation's clinical efficiency.

Results from our study indicate positive conclusions which are based on the increase of movement amplitudes, subsided pain, improved articular stability, as well as the long term action and tolerance of medication. Most of patients have experienced significant improvements since the third week of treatment, and others have had significant improvements after 1 respectively 3 months.

Impact of medication has always lasted longer than 6 months. Patients didn't experience hematological or biochemical changes. Also urinary and gastrointestinal tract were not affected.

## CONCLUSION

Viscosupplementation therapy in the treatment of OA is an efficient and long-term therapy, with less side effects in comparison to other types of treatment.

Viscosupplementation is a modulation therapy in the treatment of osteoarthritis, and particularly in knee osteoarthritis.

Always when possible we should apply the high molecular weight viscosupplements due to their clinical impact, duration of activity, fewer number of applications, and smaller chances for complication.

Viscosupplements are clinically very well tolerated and incur a low-cost treatment.

These medications can be applied in patients who take therapy for other conditions (cardiovascular, respiratory, gastrointestinal and other diseases).

Viscosupplements subside intensity of pain, increase the amplitudes of movements and after the treatment a limited number of patients need a re-treatment.

The results of our study are in concordance with the results of studies published so far, even though our expectations were higher.

Viscosupplements are many times more efficient than oral chondroprotectors.

This therapy may be applied in cases when other therapeutic modes in the treatment of osteoarthritis are contraindicated, as well as prior the fixation of knee endoprosthesis.

Viscosupplements are recommended by EULAR in the treatment of OA.<sup>[30]</sup>

#### CONFLICT OF INTERESTS: NONE DECLARED LITERATURE

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