

## **Efficacy and safety of intra-articular use of hyaluronic acid (Suplasyn) in the treatment of knee osteoarthritis**

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Osteoarthritis (OA) is one of the leading causes of disability in the elderly. Changes in the lubricating properties of synovial fluid lead to significant pain and functional disability. Viscosupplementation based on the injection of hyaluronic acid (HA) into the knee joint represents an important part of current therapeutic regimen of pain in knee OA. Intra-articular HA and hylan have proven to be an effective, safe, and tolerable treatment for symptomatic knee OA. In an effort to limit cardiovascular, gastrointestinal, and renal safety concerns related to COX-2 selective and non-selective Nonsteroidal antiinflammatory drugs (NSAIDs) and maximize HA efficacy, it is even proposed using HA earlier in the treatment paradigm for knee OA and also as part of a comprehensive treatment strategy. Our study reconfirmed efficacy and safety of intra-articular use of hyaluronic acid (Suplasyn) in the treatment of knee osteoarthritis.

*Key words:* hyaluronic acid, knee osteoarthritis, hyaluronate.

### **Introduction**

Osteoarthritis (OA) is currently one of the life-style diseases. Due to an increase in average life span, more individuals are at high risk of having the condition [9]. Basic problems of these patients include pain and decreased quality of life.

OA involves destruction of the articular cartilage. Damage on the collagen network and an increased production of proteoglycans by chondrocytes cause inflammation and thickening of the cartilage. The course of the disease involves a decreased content of water and proteoglycans, metalloproteinase activation, an increase of pro-inflammatory cytokine activity, subchondral degenerative bone cysts (or “geodes”) and development of subchondral sclerosis. Osteophytes (bone projections) are formed on the bone-cartilage border. Joint capsule and ligaments become harder and lose elasticity [4].

Main symptoms of osteoarthritis include primarily pain and inflammation of the affected joints. Sometimes, there is restricted mobility of the affected joint, muscular atrophy and, in more advanced cases, irreversible stiffness of the joints affected. The disease leads to the increase of disability and hinders the autonomy in the patient's life.

Osteoarthritis has a significant economic impact

due to its high incidence and a significant disability in work capacity, which due to the treatment costs, affects significantly the patients budget.

OA may affect multiple joints; most commonly (in order of frequency): spine, knee, hip, shoulder and hand joints.

Etiology of osteoarthritis has not been completely known. However, the chronic inflammation due to excessive metabolic activity of the affected joint seems to be the basis of the pathological process.

Current treatment is mostly focused on reducing the symptoms intensity: reduction of inflammation and pain relief using non-steroid anti-inflammatory drugs, other analgesics and steroids.

Besides the pharmacological treatment, physiotherapy including physical therapy and surgical treatment are applied. Recently, Intra-articular injections of hyaluronic acid (HA) have become one of the most popular therapies. HA is a natural component of the synovial fluid responsible for its elastic properties; thus, it is essential for the regular function of articular surfaces [5]. Symptoms of knee OA are primarily related to inflammation of the synovial membrane and other articular structures, as well as in the synovial fluid, where hyaluronate level decreases. Administration of HA in injections effi-

ciently supplements its deficit and prevents its depolymerisation, a process that facilitates leukocyte migration into the synovial fluid. The restoration of rheological properties of the synovial fluid reduces the development of inflammation through the inhibition of leukocyte migration from synovial membrane capillaries into the synovial fluid.

However, mechanism of action of the hyaluronic acid is not completely understood. Modifications in physicochemical properties of synovial fluid after HA administration cannot explain long-term reduction of symptoms, considering HA short half life. [6]. Probably HA also has some biological effect on the inflammatory cells and stimulates HA production by synovial cells. Administration of hyaluronic acid, as proven by many authors, reduces the symptoms and development of the pathological process, as well as improves patients development in daily activities [10].

### Material and methods

An observational study was carried out from 30th Jan. 2007 to 30th June 2008. Overall, 4519 patients (59% females, 41% males) diagnosed with osteoarthritis, with a mean age of 54.2 years (SD 13.2). Affection of the right knee was present in 39.4% of OA patients; the left knee affection represented a 39.3%, and in 21.2% both knees were affected. The study was conducted by orthopaedic, rheumatology and internal medicine specialist doctors. Each patient received a mean of three intra-articular injections of Suplasyn (20 mg of sterile hyaluronic acid) and followed for a 30 day period. During the study, measures of intensity of symptoms were checked before and after treatment, including pain at rest and pain during walking (using VAS score). Changes in pain intensity (basic scored characteristic for OA degree) and symptoms like morning stiffness, after rest stiffness, pain after ascending stairs and walking on the surface level were evaluated. Evaluation also included changes in the range of motion of the knee joint based on evaluation of extension and flexion restrictions. According to their disability degree, patients were classified into five groups: regular mobility, slightly impaired mobility, moderately impaired mobility, severely impaired mobility and extremely impaired mobility. The study also evaluated the use of orthopaedic appliances (elbow crutches, orthoses). Besides all these parameters, doctors and patients opinions on efficacy and safety of Suplasyn were recorded. Each case of adverse reaction was registered. The analysis involved all the patients enrolled to the study (n = 4519).

The data gathered was presented using descriptive statistics. Quantitative variables were expressed with sample size, minimum, maximum and median values, arithmetic mean and standard deviation (SD). For qualitative variables, absolute numbers and relative numbers for particular classes were provided. Questionnaires with missing data were provided. To make a comparison of selected variables between diagnostic and follow visits, t-Student, Wilcoxon and McNemar tests were followed respectively.

### Results

Patients scored the pain level at rest and during walking (Tables 1 and 2) before treatment as 3.4 (SD 2.2) and 5.0 (SD 2.1), respectively. After treatment the scores for pain level at rest and during walking decreased to 1.5 (SD 1.5) and to 2.2 (SD 1.7), respectively.

Table 1. Pain at rest (VAS)

	Number of patients	Min	Max	Median	Mean	SD
Diagnostic visit	4505	0	10	3	3.4	2.2
Follow-up visit	4505	0	9	1	1.5	1.5

No data: 14; p<0.001

Table 2. Pain during walking (VAS)

	Number of patients	Min	Max	Median	Mean	SD
Diagnostic visit	4505	0	10	5	5.0	2.1
Follow-up visit	4505	0	9	2	2.2	1.7

No data: 14; p<0.001

Mean scores of the morning stiffness intensity (Table 3) before and after treatment were 3.5 (SD 2.2) and 1.8 (SD 1.6), respectively. Score of stiffness at rest (Table 4) also decreased from 3.0 (SD 2.2) to 1.5 (SD 1.5). The treatment also showed some improvement in walking on surface level and walking up and down stairs; results are presented in Tables 5 and 6.

Table 3. Morning stiffness

	Number of patients	Min	Max	Median	Mean	SD
Diagnostic visit	4507	0	10	3	3.5	2.2
Follow-up visit	4507	0	9	2	1.8	1.6

No data: 12; p<0.001

Table 4. Stiffness after rest

	Number of patients	Min	Max	Median	Mean	SD
Diagnostic visit	4507	0	10	3	3.0	2.2
Follow-up visit	4507	0	9	1	1.5	1.5

No data: 16; p<0.001

Table 5. Walking on flat surface

	Number of patients	Min	Max	Median	Mean	SD
Diagnostic visit	4487	0	10	3	3.6	2.1
Follow-up visit	4487	0	9	1	1.7	1.5

No data: 32; p<0.001

Table 6. Walking up and down stairs

	Number of patients	Min	Max	Median	Mean	SD
Diagnostic visit	4494	0	10	5	5.1	2.1
Follow-up visit	4494	0	10	2	2.4	1.7

No data: 25;  $p < 0.001$

Ability to extend and range of flexion after treatment changed significantly compared to the baseline. The total number of patients assigned to particular groups is presented in Figure 1 and Figure 2. After treatment, use of orthopaedic appliances decreased (Fig. 3).

Fig. 1. Ability to extend.

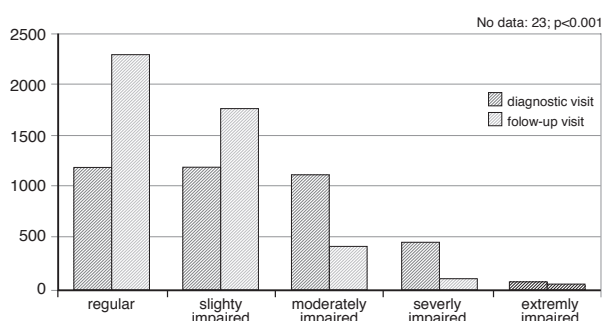


Fig. 2. Range of flexion.

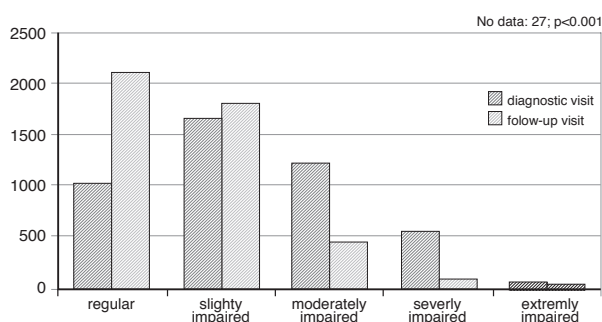
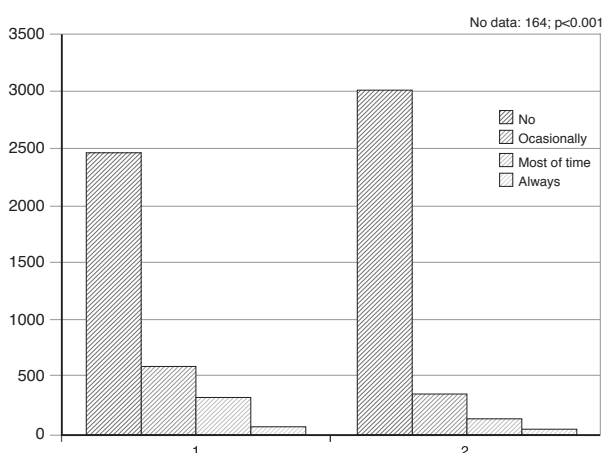


Fig. 3. Use of orthopaedic appliances.



According to the 59.1% of doctors, mean patient condition improved significantly, and 34.4% of them scored it as moderate. Patients scored improvement in a similar pattern, and the proportions were 59.9% and 32.6%, respectively. Treatment tolerance was evaluated as very good and good in 68.8% and 29.6% of patients, respectively. Adverse effects, such as edema, exudate, pruritus, redness and pain occurred in 1.6% of the patients; association with some of these effects with the injection itself cannot be excluded. No serious adverse effects were reported.

## Discussion

Numerous previous multicentre trials confirmed the efficacy of hyaluronic acid in knee osteoarthritis treatment [6,7,8], including the American College of Rheumatology (ACR) and European League against Rheumatism (EULAR) [1,11].

This study results confirms the benefits from the administration of hyaluronic acid (Suplasyn) in the treatment of knee osteoarthritis. Short and long term pain relief and mobility improvement are great important to patients because a significant improvement in quality of life. Despite short half-life of hyaluronic acid, its confirmed long term action [6], produce some improvement on patient's quality of life for longer periods.

The study confirms beneficial effect of HA. The functionality of the affected knee after treatment with Suplasyn improved, with the resolution of pain at rest and during walking. Extension ability and flexion range were improved. Patients reported less frequently complains on morning stiffness and stiffness after rest. Also, problems with daily activity, such as walking on flat surface and walking up and down stairs were reduced.

A very important feature of the product is its extremely low rate of adverse effects. Good tolerance of HA also was confirmed in numerous studies [1,6]. Very good and good tolerance of the treatment was noted in 68.8% and 29.6% of the patients, respectively. Adverse effects, such as edema, exudate, pruritus, redness and pain occurred in 1.6% of the patients. However, association with some of these effects with the injection itself cannot be excluded. No severe adverse effects were reported.

Considering low rate of adverse effects, HA seems to be particularly indicated in the osteoarthritis treatment in individuals with bad tolerance to NSAIDs (such as elderly patients) or for whom NSAIDs are contraindicated (e.g. patients with peptic ulcer) [7].

## Conclusion

The study confirmed high efficacy and good tolerance of Suplasyn in the treatment of knee osteoarthritis. Due to adverse reactions related to the treatment with NSAIDs, treatment with hyaluronic acid is increasingly considered as the therapy of choice in patients suffering from osteoarthritis [8].

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