

POLYNUCLEOTIDES VERSUS SODIUM HYALURONATE IN THE LOCAL TREATMENT OF KNEE OSTEOARTHRITIS

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Abstract: We conducted a randomized, double-blind clinical trial to assess the efficacy of intra-articular injections of polynucleotides versus hyaluronan in patients with symptomatic knee osteoarthritis. The 30 patients enrolled were randomized in two groups and received 3 intra-articular knee injections at 1 week intervals with either polynucleotides (CondrotideTM, n=15) or hyaluronan (Synocrom®, n=15). The patients were followed for 3 months after the end of treatment, with clinical evaluation before administering the first injection and then at 4, 8 and 16 weeks afterward. We used the Visual Analog Scale for pain assessment and calculated the Knee Osteoarthritis Outcome Score and Knee Society Scores (knee and functional). We found a statistically significant decrease of pain levels in both groups, with Knee Society Scores showing a statistically significant improvement only in the polynucleotide group. We concluded that the use of polynucleotide injections in the treatment of knee arthritis is a viable option in symptomatic cases.

Cuvinte cheie:
polinucleotide, gonartroză, hialuronat de sodiu, intra-articular

Rezumat: În acest studiu clinic randomizat, dublu-orb, am evaluat comparativ eficacitatea injecțiilor intra-articulare cu polinucleotide și hialuronat de sodiu la pacienți cu gonartroză decompensată algic. Am randomizat 30 de pacienți în 2 loturi de câte 15, care au beneficiat de 3 infiltrații intra-articulare la nivelul genunchiului, la intervale de 1 săptămână, cu polinucleotide (CondrotideTM - n= 15) sau hialuronat de sodiu (Synocrom® - n= 15). Perioada de urmărire a fost de 3 luni după finalizarea tratamentului. Pentru evaluare am folosit Scala Analog Vizuală pentru durere, scorul Knee Osteoarthritis Outcome Score și scorurile de genunchi și funcțional Knee Society Score înaintea administrării primei infiltrații, și apoi la 4, 8 și 16 săptămâni. Nivelul durerii s-a îmbunătățit statistic semnificativ la ambele loturi, în timp ce valorile scorurilor KSS au prezentat o îmbunătățire semnificativă doar la lotul tratat cu polinucleotide. Am concluzionat că injecțiile intra-articulare cu polinucleotide reprezintă o alternativă viabilă în tratamentul gonartrozei.

INTRODUCTION

Epidemiologic studies have shown that osteoarthritis is the most common joint disease worldwide (1,2) with approximately 1/3 of adults having radiological signs of arthritis. It has also been estimated that 25 to 30% of people over the age of 45 are affected by osteoarthritis.(3)

There are several forms of the disease, but knee osteoarthritis is the most frequently diagnosed, having been observed in approximately 6% of the population.(4)

Although the mechanism of development and progression in osteoarthritis is not yet fully known or understood, currently available data seem to indicate that both mechanical and biological factors might be involved.(5)

The main feature of arthritis is articular cartilage degeneration with physico-chemical changes in the synovial fluid and subsequent macroscopic changes of the affected joint. Unfortunately, there is still no cure for arthritis at the moment, and the principal aims of the available therapeutic options are generally symptom relief (especially pain) and a possible slowing of the disease's progression. Depending on the severity of arthritis, there are several treatment options, from non-pharmacologic therapy, through pharmacotherapy and ending in surgery – minimally invasive or major surgery.

Intra-articular injections of hyaluronic acid are commonly used in the treatment of the initial stages of osteoarthritis – the principle involved is the presumed improvement of the viscoelastic properties of the synovial fluid, which is supposed to protect the cartilage from the mechanical stress and may alleviate pain, but recent meta-analyses have questioned the efficacy of these treatment options.(6)

A possible explanation could be found in the way in which these substances act – that is by providing joint lubrication, but without addressing other important factors in the pathogenesis of osteoarthritis (biochemical, metabolic or inflammatory factors).

Polynucleotides were developed in an attempt to provide nutrients to restore articular cartilage homeostasis and the physiology of the intra-articular environment, in addition to offering mechanical protection for the cartilage. These are polymer molecules that are able to bind large amounts of water and thus form a tri-dimensional gel.

Besides moisturizing the articular surfaces, polynucleotides also release oligonucleotide molecules that retain water and have the same viscoelastic properties as the polynucleotides – this way their effect lasts longer.

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PURPOSE

The purpose of our randomized, double-blind study was to evaluate and compare the efficacy of intra-articular injections of hyaluronan and polynucleotides in patients with painful knee osteoarthritis.

METHODS

The current study was conducted between 2011 and 2012 in the Clinic of Orthopaedics and Traumatology of the Mureş County Hospital. We included 30 patients aged 18 to 71, who were diagnosed with knee osteoarthritis.

Inclusion criteria were: (1) persistent knee pain – at least 2 months duration, (2) a diagnosis of knee osteoarthritis based on the clinical/ clinical and radiologic criteria of the American College of Rheumatology (7), and (3) early and medium stages of knee osteoarthritis based on the radiological classification of Kellgren and Lawrence.(8) The following exclusion criteria were defined: alcohol and/or drug abuse, pregnancy or lactation, fractures or serious injuries of the studied knee, rheumatoid arthritis, blood disorders, hypersensitivity to the studied substances (hyaluronic acid, polynucleotides), hyaluronic acid or corticosteroids intra-articular injections in the previous 3 months, systemic treatment with anticoagulants or anti-inflammatory steroids in the preceding month.

The study was approved by the Ethics Committees of the University of Medicine and Pharmacy and the Clinic of Orthopaedics and Traumatology of Tîrgu-Mureş, and all patients signed an informed consent. The 30 enrolled patients were randomized at the time of enrolment into 2 groups of 15 patients each, who received 3 intra-articular injections in the affected knee with either polynucleotides (group I/ Condrotide™ group, n = 15) or sodium hyaluronate (group II/ Synocrom® group, n = 15). Injections were administered at 1 week intervals. We used the following substances:

- Condrotide™ – a gel of long chain natural, highly purified polynucleotides, with a concentration of 20 mg/ ml, in prefilled syringes of 2 ml each.
- Synocrom® – sodium hyaluronate produced by bio-fermentation, with a molecular weight of 1.6 million Da and a concentration of 10 mg/ ml, in prefilled syringes of 2 ml each.

Infiltration and evaluation were performed by separate investigators in order to maintain the study's double-blind character. During the study period patients were prohibited to take oral or parenteral corticosteroids, but the use of anti-inflammatory drugs (NSAIDs) was permitted as needed, and NSAIDs use was reported in patient files.

The study had a follow-up period of 3 months after the completion of treatment. All clinical parameters were evaluated at 4 different times as follows: before the first infiltration (denoted as T0), and at the scheduled control visits at 4, 8 and 16 weeks (T4, T8 and T16). During these visits any adverse effects of treatment were noted, along with NSAIDs consumption in the previous period. Our clinical evaluation was subjective and objective – we used the Visual Analog Scale (VAS), Knee Injury and Osteoarthritis Outcome Score (KOOS) and the Knee Society Scores (KSS) – knee and functional scores. All questionnaires were completed prior to the first infiltration and at the 3 subsequent visits.

The primary endpoint was the change in pain levels at rest, and secondary endpoints were the changes in the values of the subjective and objective scores (KOOS, KSS) and consumption of NSAIDs. We also assessed the safety profile of the used substances – this was done by noting the occurrence of adverse effects.

All statistic calculations were performed using Graph Pad Software, San Diego, California, USA. In the first stage the values of the VAS and the subjective and objective scores (KOOS, KSS) were tested for compliance (Kolmogorov-Smirnov test, D'Agostino test) – testing for normality. We then applied parametric statistical tests – the Student test for independent samples comparing two values, and the ANOVA test to compare more than three samples of values. All tests were performed with p defined as 0.05, and statistical significance was obtained for p values < 0.05.

RESULTS

We did not lose any patients to follow-up. The two groups of patients were similar in terms of demographic characteristics (table no. 1).

Based on the results obtained with the VAS, we observed a statistically significant decrease in pain in both groups of patients, from 6.7 ± 1.03 cm (T0) to 2.7 ± 0.8 cm (T16) in group I (treated with polynucleotides) and from 5.1 ± 1.8 cm (T0) to 2.8 ± 1.3 cm (T16) in group II (treated with sodium hyaluronate) (table no. 2), but we noticed a more pronounced improvement of algic symptoms in patients from group I.

Table no. 1. Patient demographics of the two groups included in the study presented as median and range (BMI = Body Mass Index)

Parameter	Group I (polynucleotide)	Group II (sodium hyaluronate)
Number of patients	15	15
Age (years)	62 (31 – 71)	60 (18 – 68)
Sex (female/ male)	8 F/ 7 B	9F/ 6B
Height (cm)	161 (152 – 175)	165 (150 – 180)
Weight (kg)	72 (64 – 89)	68 (60 – 105)
BMI (kg/ m ²)	27,7 (23,6 – 33,2)	29,1 (24,2 – 36,1)

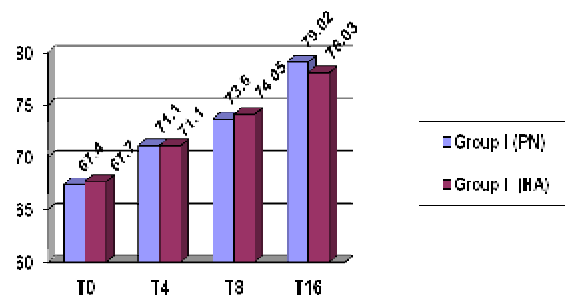
Table no. 2. Pain levels at rest measured by VAS

Evaluation	Group I*	Group II*	P value**
T0	6,7±1,03	5,1±1,8	0,006
T4	4,7±1,2	4,1±1,8	0,31
T8	3,5±0,9	3,1±1,3	0,33
T16	2,7±0,8	2,8±1,3	0,75

* Data are presented as mean ± SD; ** Student test

KOOS score values also showed improvement in both groups between T0 and T16. By plotting the differences between T16 and T0 KOOS values we can see a greater increase in the score's value for the group treated with polynucleotides (11.62) compared to the group treated with hyaluronate (10.33) (figure no. 1).

Figure no. 1. Mean values of the KOOS score in the two compared groups



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Regarding the two KSS scores, the knee score showed a statistically significant improvement only in the patients from group I ($p = 0.01$, ANOVA) (figure no. 2). The KSS functional score values also increased and were statistically significantly higher in the group treated with polynucleotides ($p = 0.002$, ANOVA) compared with group II, that only showed a slight increase ($p = 0.26$) (figure no. 3).

Figure no. 2. KSS knee score values in the two groups (the box plot diagrams have had the mean values of the KSS score inserted)

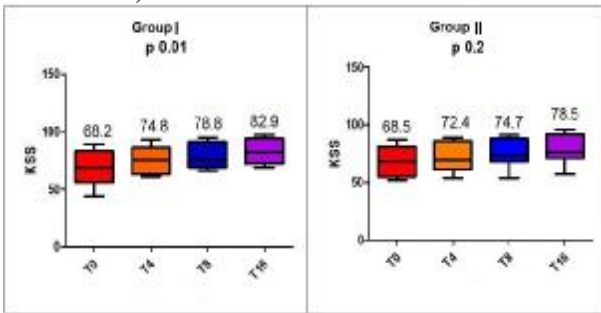


Figure no. 3. KSS functional score values in the two groups (the box plot diagrams have had the mean values of the KSS score inserted)

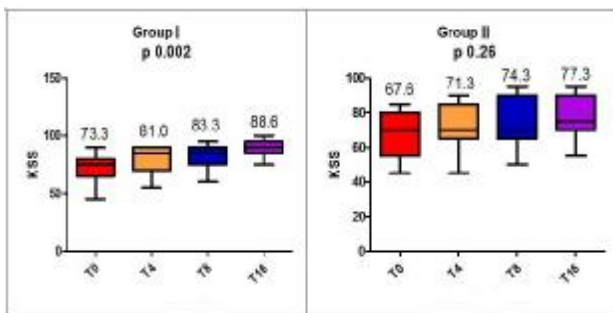
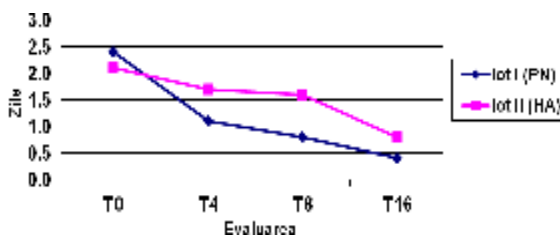


Figure no. 4. NSAIDs consumption in the two groups of patients during the study period



We did not encounter any significant adverse effects of the used substances. We only noted a slight joint pain immediately after the injection in 3 patients (2 from group I and 1 from group II), but this was alleviated in a few hours post-infiltration. There were no cases of intra-articular infection.

DISCUSSIONS

Osteoarthritis is a common chronic condition that could potentially become the 4th leading cause of disability worldwide by 2020 (9,10) due to the population's increased life expectancy. Unfortunately, arthritis remains a disease that is still considered "incurable", despite various treatment methods available.

In the early stages of knee osteoarthritis, physicians have several pharmacological therapeutic options (intra-articular injections of hyaluronic acid and corticosteroids, oral or topical NSAIDs, chondroprotective supplements - glucosamine, chondroitin -, and so on). Most of these options have shown favourable results in studies, but some authors reported only minor benefits of pharmacological treatments versus placebo.(6,11,12)

One of the latest innovations in the pharmacological treatment of early to medium stages of osteoarthritis is the use of intra-articular injections of polynucleotide molecules from natural sources that release oligonucleotides intra-articularly through cleavage. Several studies have shown that enzymatic degradation derivatives of polynucleotide chains (single nucleotides, nucleosides, nitrogenous bases) are normally present in the extracellular environment and are useful substances for cell metabolism.(13,14) By administering polynucleotides in intra-articular injections, the synovial fluid is enriched with nucleotides, purine and pyrimidine bases, which support cellular metabolism. In a study similar to ours, Vanelli et al.(15) compared the efficacy of intra-articular injections of polynucleotides with that of hyaluronic acid in patients suffering from osteoarthritis, noting similar results in both groups of patients over a follow-up period of 16 weeks.

CONCLUSIONS

We observed significant pain reduction in osteoarthritis patients treated by intra-articular injections of polynucleotides and hyaluronan, with improvement of the values of the used clinical scores (KOOS, KSS). In the case of polynucleotides, the symptomatic and functional improvements were superior to those obtained by treatment with sodium hyaluronate. Therefore, intra-articular polynucleotide injections are a viable alternative in the treatment of early and medium stage knee osteoarthritis.

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