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INTRAARTICULAR KNEE JOINT INJECTION: HYALURONIC ACID VS POLYNUCLEOTIDES

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SUMMARY

This study is a retrospective work of ambulatorial injections in patients suffering from Class II osteoarthritis (OA) of the knee. The research was conducted from January 2012 to July 2012 in a private clinic in Benevento, Hospital Val D'Elsa, Poggibonsi, Siena. A total of 60 patients were treated with intraarticular knee injections. Group A, composed of 30 patients (15 male and 15 female), was treated with injections of low molecular weight Hyaluronic Acid and Group B, composed of 30 patients (15 male and 15 female) was treated with injections of Ploynucleotide. At the six month follow-up, Group B showed a statistically significant difference ($p<0.05$) of the Visual Analogue Scale (VAS); the Knee injury and Osteoarthritis Outcome Score for Group B also showed a statistically significant difference ($p<0.05$). The results obtained suggest that polynucleotides can be considered as a valid alternative to hyaluronic acid for the treatment of symptomatic osteoarthritis of the knee.

Introduction

Osteoarthritis (OA) is a chronic joint disease characterized by degeneration of the articular cartilage, changes in the physico-chemical properties of the synovial fluid and macroscopical modifications of the joint. Scientific and clinical data gathered to date have linked the onset and progression of osteoarthritis to both mechanical and biological factors (1). Among the various kinds of arthritic diseases, OA is the most frequent: it is estimated that 25–30% of people over 45 years old are affected by it(2). Estimates of incidence and prevalence of OA of the knee vary considerably among 29 studies from 14 countries and 4 ethnic groups (incidence: 10 to 2230 per 100,000 people per year, prevalence: 0.5% to 36%)(3).

Today, many different therapies are available for the treatment of OA and other osteochondral defects, ranging from non-pharmacologic therapy (arthroscopic and arthroprosthesis) to pharmacological approaches (viscosupplementation, oral supplements or topical treatments, weight loss), but a flawless treatment has yet to be found. Patients with Classes I and II of knee OA can be treated with non-pharmacologic therapy but patients with severe symptomatic OA, whose pain does not respond to medical therapy and who have progressive limitation in ADL, should be referred to an orthopaedic surgeon for evaluation. Surgical options include traditional arthroscopic debridement, total joint arthroplasty and innovative techniques such as autologous chondrocytes implantation (ACI) (4) or cartilage repair using mesenchymal stem cells(5). Intraarticular Hyaluronic Acid

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(HA) supplementation is a simple and widespread way to treat minor and moderate degree osteoarthritic joints(6). Currently, Polynucleotides are being used to treat OA of the knee which should both provide a mechanical protection of the cartilage surface as well as restore the chondrocytes' homeostasis by reinstating the physiological articular microenvironment and supplying nutrients(7).

Material and Methods

This study is a retrospective work of clinical injections in patients that suffered from Class II osteoarthritis (OA) of the knee. This is not a double randomized blind trial. The research was conducted from January 2012 to July 2012 in a private clinic in Benevento, Hospital Val D'Elsa, Poggibonsi, Siena. A total of 60 patients (Table 1) were treated with intraarticular knee injection. Group A, composed of 30 patients (15 male and 15 female), was treated with injections of low molecular density Hyaluronic Acid and Group B, composed of 30 patients (15 male and 15 female), was treated with injections of Ploynucleotide. The average patient age in Group A was 70.4 (ranging from 55-75) and in Group B 70.6 (ranging from 55-78). Patients in group A were taller on average at 163.4 cm (ranging from 147-189cm), weighed an average of 72.6kg (ranging from 45-86kg) with an average Body Mass Index (BMI) of 24.6 (ranging from 21.2-27.3), while patients in group B averaged a height of 166.2cm (ranging from 148-187), weighed an average of 74.2kg (ranging from 48-96kg) with an average BMI of 25.7 (ranging from 22.4-29.2) (Table 1).

The first visit for all patients was in the clinic. All patients used 1 pill (90mg) per day of Etoricobix for 7 days and, after that period, continued use as needed for pain and inflammation relief. After the initial visit at the clinic, all patients began physiokinesis therapy according to Cole et al(8). Physiokinesis therapy was not performed in the same center for all patients. Follow-up was conducted at one, three, and sixth month intervals to evalute the pain and function of the knee. We decided to give the injections at the first orthopedic visit, and subsequently one, three, and six months after the first injection to try to eliminate a possible "placebo effect"(24). For each of the injections, we used a low molecular weight Hyaluronic Acid of 16 mg/2 ml or Polynucleotide of 20 mg/ml. The injections were well tolerated by the patients. Patients were given exhaustive descriptions of the two types of viscosupplementation and asked to decide which to use based on the cost of therapy and their physical condition. Pain levels were measured using a 0-10 cm Visual Analogue Scale (VAS). The secondary evaluation criteria included Knee Osteoarthritis Outcome Score (KOOS).

Criteria for exclusion included alcohol or drug abuse, breastfeeding, hypersensibility to study products, ongoing or suspended (for less than 3 months) hyaluronic acid or steroid infiltration therapy, ongoing or suspended (for less than 1 month) systemic treatment with anticoagulants and steroids, previous bone fractures or severe traumas of the interested knee, presence of rheumatoidarthritis and of relevant haematological pathologies, and people with a BMI>30. The follow-up to our retrospective study was 6 months after the first injection. The data were imported in an

Population/ Treatment	Hyaluronic Acid	Polynucleotide
Number of patients	30	30
Males/ Females	15/15	15/15
Average age of patients	70.4	70.6
Age range of patients	55-75	55-78
Class of Gonathrosis	II	II
Average height(cm)	163,4	166,2
Height (range in cm)	147-189	148-187
Average weight(Kg)	72.6	74.2
Weight (range in Kg)	45-86	48-96
Average BMI	24.6	25.7
BMI range	21.2-27.3	22.4-29.2
Antinflamatory used	etoricoxib	etoricoxib
Kinesis Therapy	all	all

Table 1: Description of the study's population.

electronic spreadsheet (Excel, Microsoft Office) for further processing and statistical analysis.

Results

Group A started with an average VAS of 8.6 and Group B with 8.8. There was no statistically significant difference (p> 0.05) between the groups. After the first month, Group A VAS was 7,9 and Group B 8.0, again with no statistically significant difference (p> 0.05). After the third month, Group A VAS was 6.7 and Group B 6.7 with no statistically significant difference (p> 0.05). After the sixth month, Group A VAS was 6.3 and Group B 4.8, this time there was a statistically significant difference (p<0.05) for Group B(Table 2).

Group A started with an average KOOS of 65.3 and Group B 64.7. After the first month, KOOS of Group A was 70.0 and Group B 69.6 with no statistically significant difference (p> 0.05). After the third month, KOOS of Group A was 86.8 and Group B 87.3, again with no statistically significant difference (p> 0.05). After the sixth month, KOOS of Group A was 94.5 and Group B 97.2 with a statistically significant difference (p<0.05) for Group B (Table 3).

Time of Injection	Average VAS of Hyaluronic Acid's Group	Average VAS of Polynucleotide's Group
0	8,6	8,8
Ist Month	7,9	8
IIIrd Month	6,7	6,7
VIth Month	6,3	4,8

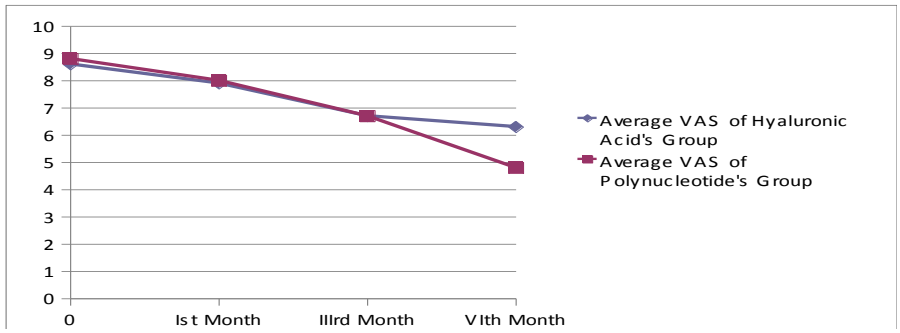

Table 2: The difference of VAS in the Group A and Group B at the six month follow-up. At the sixth month follow-up, VAS of Group A was 6,3 and Group B 4,8 with a statistically significant difference (p<0.05) for Group B.

Time from start of Kinesis Therapy	Average KOOS of Hyaluronic Acid's Group	Average KOOS of Polynucleotide's Group
0	65,3	64,7
Ist Month	70	69,6
IIIrd Month	86,8	87,3
VIth Month	94,5	97,2

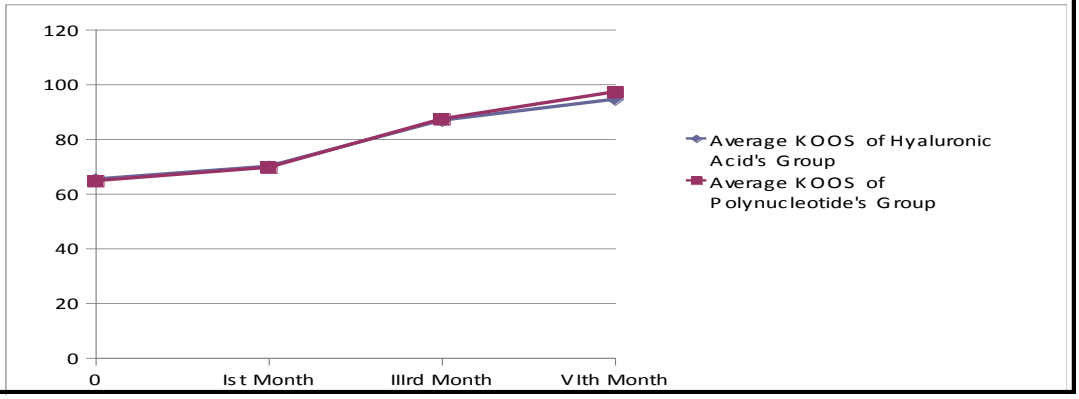

Table 3: The difference of KOOS in Group A and Group B at the six month follow-up. At the sixth month follow-up, VAS of Group A was 6,3 and Group B 4,8 with a statistically significant difference (p<0.05) for Group B.

No adverse effects related to the use of the two drugs or miscellaneous complications were reported in either group.

Discussion

OA is a widespread chronic disease. By the year 2020, osteoarthritis will become the fourth leading cause of disability worldwide. Today, it accounts for nearly 3% of total years of people living with disability globally (9). Several pharmacological approaches are used for the treatment of OA, like intraarticular hyaluronan or corticosteroid, NSAIDs, oral supplements (e.g., glucosamine or chondroitin) (10) and topical treatments (e.g., capsaicin) (11). For some of these therapies, a considerable amount of clinical data is available, often claiming a substantial efficacy in dealing with osteoarthritis symptomatology. The progressive stages in knee OA are characterized by synovial inflammation, cartilage erosion, soft tissue fibrosis, subchondral bone sclerosis and increased bone resorption, as well as pain and stiffness in the affected joints (32,33,34). Getting hyaluronic acid (HA) injected into joints is one treatment that may ease the pain and stiffness of osteoarthritis (32). Hyaluronic acid joint injections are quick and relatively painless. In addition to potential symptomatic relief, Smith et al (13) have reported ample evidence for statistically significant disease-modifying effects of intraarticular HA injection in both animal models and human OA. First Mensitieri et al (14), and then Altman et al (16), have reported in their papers that HA can block inflammation and chondrocyte apoptosis, and that it effectively prevented cartilage degeneration in rat and rabbit OA models. In 2002, Barret et al (17) reported that in a canine anterior cruciate ligament transection model, HA inhibited the formation of a fibroblast-like cell layer on the articular surface, reduced cartilage lesions and significantly improved both gross joint morphology and histopathology. According to a paper by Plaas et al (32) published in 2011, in both canine and ovine OA models, subintimal fibrosis and hypervascularity of the synovium was reduced after intraarticular HA injection (18,19). Clinical relevance of such observations is underscored by reports of human OA in which HA has been found to reconstitute the superficial cartilage layer (20), reduce synovial inflammation and edema (21), reduce the number and aggregation of lining synoviocytes (22), as well as reduce the progression of joint space narrowing in patients with high joint space width upon entry into the study (23). Although the cellular mechanisms of biological action of HA on both animal and human models of knee OA are poorly understood, the polymers of HA can reduce the swelling, inflammation, and hyperplasia of the synovium (32) in the knee joint.

Polynucleotides are polymeric molecules which are able to bind a large amount of

Time from start of Use of Etoricoxib	Average Pills for month in Hyaluronic Acid Group	Average Pills for monthin Polynucleotide Group
0	18,3	17,7
Ist Month	17,9	17,5
IIIrd Month	12,6	11,9
VIth Month	10,4	8,7

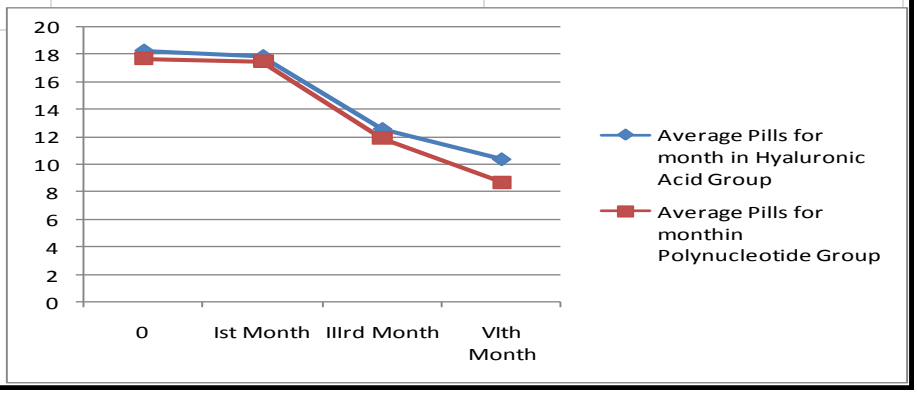

Table 4: Over the course of 6 months, group A took an average of 10.4 tablets per month of Etoricoxib (ranging from 5-22), while group B consumed an average of 8.7 including Etoricoxib (ranging from 7-18).

water and to re-organize their structure by orienting and coordinating water molecules to form a 3-D gel. These polymeric molecules, when infiltrated intraarticularly, can deeply moisturize articular surfaces. They undergo enzymatic cleavage and progressively release in the articular cavity both water molecules and smaller-sized oligonucleotides that retain their moisturizing and viscoelastic properties thereby maintaining the effect longer. Polynucleotides (PN) are extracted from natural sources (fish sperm). It is already known in literature (7,12,25-28) that the derivatives of enzyme degradation of polynucleotide chains (simple nucleotides, nucleosides, nitrogen bases) are physiologically present in the extra-cellular environment and are useful substrates for cells. Intra-articular infiltration progressively enriches the synovial fluid of PN and thus of nucleotides, purine and pyrimidine bases that cells can use to promote their metabolism.
From the first visit and injection at the clinic, our attitude was cautious towards the use of viscosupplementation. Injection of therapy was correlated with adequate treatment of Etoricoxib(31) and monitoring the physiotherapic treatment(29-30), modifying it according to the needs and demands of the patient. Overall efficacy of polynucleotides, both in terms of pain reduction and KOOS results, was comparable to hyaluronic acid until the sixth month. In VAS and KOOS results, we can see there was a statistically significant difference ($p<0.05$). We assumed this statistically significant difference was that the derivatives of enzyme degradation of polynucleotide chains (simple nucleotides, nucleosides, nitrogen bases) were physiologically present in the extra-cellular environment and useful substrates for cells. Intra-articular infiltration progressively enriches the synovial fluid with PN and thus with nucleotides; purine and pyrimidine bases that cells can use to promote their metabolism(12). The population we studied, although made up of people mostly 80 years old, has a population of active people with with arthritis below Class II. This supports the role and use of viscosupplementation in elderly people treated infiltratively as a means to improve the level of activity and quality of life over time, attempting to counter or reduce the progressive deterioration of cartilage. We have noticed that patients who have been subjected to treatment with polynucleotides consumed on average a lower amount of anti-inflammatory medications per month (Table 4). Over the course of 6 months, group A took an average of 10.4 tablets per month of Etoricoxib (ranging from 5-22), while group B consumed an average of 8.7 tablets per month including Etoricoxib (ranging from 7-18). We did not recruit patients in our study with BMI> 30 because, in our view, that would have distorted the study because obesity is also one of the main causes of knee osteoarthritis in elderly patients where weight loss is erratic and difficult to attain quickly. Physiokinetic exercises are a useful adjunct to treatment and have been shown to reduce pain and disability(29,30). On average, group B was heavier than group A, but without a statistically significant difference. From this information, we cannot determine whether or not the polynucleotides have a better effect on pain compared to hyaluronic acid in patients who tend to be overweight.
The principal limitation of this study is represented by the lack of a double blind randomized trial. This study was also limited by the good quality of life of all participants in the study and their diagnosis of second class OA.

Conclusions

The results obtained suggest that polynucleotides can be considered as a valid alternative to hyaluronic acid for the treatment of symptomatic osteoarthritis of Knee. Polynucleotides work better with COX-2 and physiokynesis.

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