

Research article

In the Aging Knee: Which Mitigation and Intervention Strategies do we apply in the Intra-articular Knee Joint Injection? The comparison of the effects of 5 drugs and review of the literature.

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Abstract

This study is a retrospective work of ambulatorial injections in patients suffering from Class II and Class III osteoarthritis (OA) of the knee. The research is reported from a former study conducted from January 2012 to July 2012 and new data from January 2013 to June 2014 compiled at private clinic in Benevento, Hospital Alta Val D'Elsa, Poggibonsi Siena, AOUS Siena, AO Rummo, Benevento. A total of 177 patients were treated with intraarticular knee injections. 30 patients in group A were treated with injections of Low Molecular Weight Hyaluronic Acid, and 30 patients in group B were treated with injections of Polynucleotides. Group C is composed of 36 patients treated with High Molecular Weight Hyaluronic Acid, Group D is composed of 31 patients treated with Platelet Rich Plasma, and Group E is composed of 50 patients treated with Triamcinolone Hexacetonide. At the six month follow-up, Groups B,C,D, and E showed a statistically significant difference [from baseline] ($p < 0.05$) on the Visual Analogue Scale, and there was also a significant difference ($p < 0.05$) for the the Knee Injury and Osteoarthritis Outcome Score for groups A,B,C and D. The results obtained suggest that these four drugs can be considered as valid treatments to cure symptomatic osteoarthritis of the knee.

Key Words: Aging Knee, Intra-articular Knee, Low Molecular Weight Hyaluronic Acid, Polynucleotides, High Molecular Weight Hyaluronic Acid, Platelet Rich Plasma, Triamcinolone Hexacetonide.

Introduction

Osteoarthritis (OA) is a chronic joint disease characterized by degeneration of the articular cartilage, changes in the physio-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, and weight loss). However, a flawless treatment has yet to be found. Patients with Class I or II of knee OA and some of Class III Knee OA can be treated with non-pharmacologic therapy. 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 orthopedic 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 low molecular weight Hyaluronic Acid (HA) supplementation is a simple and widespread way to treat minor and moderate osteoarthritic joints[6]. Currently, Polynucleotides are being used to treat OA of the knee. Polynucleotide treatment should provide both mechanical protection of the cartilage surface as well as restore chondrocyte homeostasis by reinstating the physiological articular micro-environment and supplying nutrients[7]. High molecular weight Hyaluronic Acid (HHA) has been used in attempts to treat osteoarthritis of the knee via joint injection. It has not been proven, however, to generate significant benefit and has potentially severe adverse effects[8]. Intra-articular platelet-rich plasma (PRP) injection has emerged as a promising treatment for knee osteoarthritis. Studies to date, including multiple randomized controlled trials, have shown that PRP is a safe and effective treatment option for knee osteoarthritis. Intra-articular PRP is similar in efficacy to hyaluronic acid, and seems to be more effective than hyaluronic acid in younger, active patients with low-grade osteoarthritis. Treatment benefits seem to decline after 6-9 months. There are numerous PRP treatment variables that may be of importance, and the optimal PRP protocol remains unclear. Future investigations should control and analyze the effects of these variables in PRP treatment. High-quality randomized controlled trials are needed to optimize PRP treatment methods and better define the role of PRP in osteoarthritis management in the knee and potentially in other joints [9]. Since the 1960s, knee injections of steroids have become widely available for the symptomatic management of pain and movement limitations associated with arthritis. Triamcinolone hexacetonide offers an advantage over triamcinolone acetone and should be the intra-articular steroid of choice (2B+ level)[10].

Material and Methods

This study is a retrospective work of clinical injections and an integration of Meccariello et al's past work published in Euro-Mediterranean Biomedical Journal[11] in patients who suffered from Class II osteoarthritis (OA) of the knee, Class III OA (Triamcinolone hexacetonide), and patients who refused knee arthroprosthesis. 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 and from January 2013 to June 2014 in AOUS Policlinico le Scotte Siena, AOG Rummo Benevento. A total of 177 patients (**Tab.1**) were treated with intra-articular knee injection with different drugs. Group A[11], composed of 30 patients (15 male and 15 female), was treated with injections of low molecular density Hyaluronic Acid and Group B[11], composed of 30 patients (15 male and 15 female), was treated with injections of Polynucleotide. The average patient age in group A was 70.4 (ranging from 55-75) and 70.6 in group B (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). 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[11] (ranging from 22.4-29.2) (**Tab.1**).

Group C included 36 patients (13 male and 23 female), who were treated with one injection of High molecular weight hyaluronic acid. The average patient age in Group C was 71.3 (ranging from 52-82). Patients in Group C were taller on average at 165.3 cm (ranging from 150-188cm), weighed an average of 72.3kg (ranging from 45-96kg) with an average Body Mass Index (BMI) of 25.9 (ranging from 21.7-29.5) (**Tab.1**).

Group D included 31 patients (16 male and 15 female), who were treated with injections of Platelet Rich Plasma (PRP). The average patient age in Group D was 72.5 (ranging from 50-80). Patients in group D were taller on average at 168.2 cm (ranging from 152-192cm), weighed an average of 71.5kg (ranging from 43-99kg) with an average Body Mass Index (BMI) of 26.3 (ranging from 20.3-28.9) (**Tab.1**).

Group E included 50 patients (28 male and 22 female) who were treated with one injection of Triamcinolone hexacetonide 40mg. The average patient age in Group E was 77.6 (ranging from 60-85). Patients in group E were taller on average at 161.4 cm (ranging from 143-178cm), weighed an average of 77.3kg (ranging from 42-102kg) with an average Body Mass Index (BMI) of 26.8 (ranging from 22.3-29.7) (**Tab.1**).

The first visit for all patients was in the clinic. All patients took 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 physiotherapy according to Cole et al.[12]. Physiotherapy was not performed in the same center for all patients. Follow-up was conducted at one, three, and sixth month intervals to evaluate the pain and function of the knee[11], except for the group treated with high molecular weight hyaluronic acid that received a single injection 2 weeks after the first visit. For the PRP group, we conducted a single patient preparation using a variety of commercially available anti-inflammatory and chondroprotective [drugs] to be taken daily for three months before the start of treatment with PRP injections. 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"[13]. For each of the injections, we used a low molecular weight hyaluronic acid of 16 mg/2 ml, Polynucleotide of 20 mg/ml, high molecular weight hyaluronic acid of 6.000 kdalton or from 1.000.000 to 2.000.000, platelet x µl in 4cc per syringe, or Triamcinolone hexacetonide 40mg. The injections were well tolerated by the patients. Patients were given exhaustive descriptions of the five 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) and the number of Etoricobix pills used per month.

Criteria for exclusion included alcohol or drug abuse, breastfeeding, hypersensitivity to study products, previous bone fractures or severe traumas of the interested knee, presence of rheumatoidarthritis, relevant haematological pathologies, cardiac problems, high blood pressure, 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 electronic spreadsheet (Excel, Microsoft Office) for further processing and statistical analysis.

Results

Group A started with an average VAS of 8.6, Group B with 8.8, Group C with 8.7, Group D 8.6 with and Group E with 9.3. There was no significant difference ($p > 0.05$) between the groups. After the first month, Group A VAS was 7.9, Group B with 8.0, Group C with 8.0, Group D with 8.1, and Group E with 8.4 with no significant difference ($p > 0.05$) between groups. After the third month, Group A VAS was 6.7, Group B with 6.7, Group C with 6.6, Group D with 6.5 and Group E with 6.3. and there was a significant difference ($p > 0.05$) between groups. After the sixth month, Group A VAS was 6.3, Group B with 4.8, Group C with 4.7, Group D with 4.5,

and Group E with 5.1, and there was a statistically significant difference ($p < 0.05$) for Group B, Group C, Group D and Group E (**Tab.2**).

Group A started with an average KOOS of 65.3, Group B with 64.7, Group C with 65.6, Group D with 65.8 and Group E with 52.3. After the first month, KOOS of Group A was 70.0, Group B with 69.6, Group C with 71.3, Group D 70.9 with and Group E with 58.2, and there was a statistically significant difference ($p < 0.05$) for Group A, Group B, Group C and Group D. After the third month, KOOS of Group A was 86.8, Group B with 87.3, Group C with 86.6, Group D with 86.7, and Group E with 62.42, again with a statistically significant difference ($p < 0.05$) for Group A, Group B, Group C and Group D. After the sixth month, KOOS of Group A was 94.5, Group B with 97.2, Group C with 94.7, Group D with 97.7, and Group E with 72.3, again with a statistically significant difference ($p < 0.05$) for Group A, Group B, Group C and Group D (**Tab.3**).

Group A started with an average of 18.3 Etoricoxib pills used per person each month, Group B used 17.7 per month, Group C used 20.3 per month, Group D used 20.7 per month and Group E used 16.3 per month. After the first month, the number Etoricoxib pills used per person was 17.9 per month in group A, Group B used 17.5 per month, Group C used 17.3 per month, Group D used 18.3 per month, and Group E used 16.3 per month. After the third month, the number of Etoricoxib pills used per person in Group A was 12.6 per month, Group B used 11.9 per month, Group C used 12.3 per month, Group D used 16.3 per month, and Group E used 15.7 per month. After the sixth month, the number of Etoricoxib pills used per person in Group A was 10.4 per month, Group B used 8.7 per month, Group C used 9.4 per month, Group D used 14.3 per month, and Group E used 15.7 per month (**Tab.4**).

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 the total years of people living with disability globally [11,14]. Several pharmacological approaches are used for the treatment of OA such as intra-articular hyaluronan or corticosteroid, NSAIDs, oral supplements (e.g., glucosamine or chondroitin) [11,15] and topical treatments (e.g., capsaicin) [11,16]. 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, increased bone resorption, as well as pain and stiffness in the affected joints [11,17,18,19]. Receiving a hyaluronic acid (HA) injection into the joints is one treatment that may ease the pain and stiffness of osteoarthritis [11,17]. Hyaluronic acid joint injections are quick and relatively painless. In addition to potential symptomatic relief, Smith et al. [11,20] have reported ample evidence for statistically significant disease-modifying effects of intra-articular HA injections in both animal models and human OA. Mensitieri et al. [11,21], and then Altman et al. [22], have reported 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. [11,23] 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. [11,17] published in 2011, subintimal fibrosis and hypervascularity of the synovium was reduced after intraarticular HA injection in both canine and ovine OA models [11,24,25]. Clinical relevance of such observations is underscored by reports of human OA in which HA has been found to reconstitute the superficial cartilage layer [11,13], reduce synovial inflammation and edema [11,26], reduce the number and aggregation of lining synoviocytes [11,27], as well as reduce the progression of joint space narrowing in patients with high joint space width upon entry into the study [28]. Although the cellular mechanisms of the 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 [11,17] in the knee joint.

Polynucleotides are polymeric molecules which are able to bind a large amount of water and re-organize their structure by orienting and coordinating water molecules to form a 3-D gel. These polymeric molecules, when infiltrated intra-articularly, can deeply moisturize articular surfaces. They undergo enzymatic cleavage and progressively release both water molecules and smaller-sized oligonucleotides into the articular cavity 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 (7,11,29-35) 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, purines, and pyrimidine

bases that cells can use to promote their metabolism.

Figeruosa et al.[35] evaluated the effect of 2 different protocols of intra-articular high molecular weight hyaluronic acid (HHA, hylan G-F20) to articular cartilage regeneration in acute full-thickness chondral defects[35]. Full-thickness chondral defects of 3x6mm were performed into the lateral femoral condyles of New Zealand rabbits, treated with a single or three doses of HA. The animals were sacrificed at 12 weeks and the regenerated tissue was evaluated by direct observation and histology with the ICRS scale. Macroscopically, in both groups treated with HHA, the defects were filled with irregular tissue with areas similar to hyaline cartilage, as well as depressed areas with exposed subchondral bone that were observed in others. Histological analysis showed in both groups treated with HA a hyaline-like cartilage compared to control group. However, the score of the International Cartilage Repair Society (ICRS) scale did not show differences between the groups treated with HHA. Their conclusions were that the use of single dose or 3 doses of HA in acute chondral lesions has a limited and similar benefit in articular cartilage regeneration[35].

In histopathological animal models, a cartilage structure protection effect was demonstrated by HHA[36]. Shen and Gatti [36] confirmed the positive results reported from controlled trials, and suggest that the double HA of low and high ranges of MW may provide patients with a more physiologically dynamic viscosupplementation and hence a more responsive synovial rheology that controls pain and improves joint function in knee osteoarthritis.

In 2014, Carneiro et al. [37] assessed the regeneration of osteochondral defects in the joint cartilage of the knee induced by autologous platelet-rich plasma (PRP). Osteochondral defects were produced in the trochlear groove of both knees of ten sheep. Defects of the right knees were filled with autologous PRP and the left knees were left unfilled. Macroscopic and microscopic evaluation was carried out 12 weeks later [37]. The results were evaluated by comparing the total score of both macroscopic and microscopic evaluations of the right and left knees through the Wilcoxon paired test. Macroscopic appearance was not uniform among animals, nor was it different between the right and left knees ($p=0.3125$). None of the cases showed that the regenerated tissue was equal to the normal surrounding cartilage [37]. At histological examination, apparently normal cartilage was not detected in any knee, but a poorly differentiated cartilage was present in 7 right knees, compared to 3 left knees [37]. Fibrocartilaginous tissue was present in most of the remaining knees, with a significant difference in the overall score between right and left knees ($p=0.0313$) [37]. The PRP used in this study has reparative properties of the joint cartilage of sheep knees, mostly by stimulating the formation of fibrocartilaginous tissue[37]. The authors concluded that PRP has sheep knee articular cartilage repair properties, particularly as it stimulates the formation of fibrocartilaginous tissue and may play a role of stimulating the repair of osteochondral defects of the human knee. The advantage of PRP is that it is an autologous product whose preparation is a simple procedure [37].

In April 2014, Gobbi et al [38] published a prospective and randomized work where they described the outcome of intra-articular PRP knee injections in patients with early stages of OA, and to determine whether cyclical dosing would affect the end result. 93 patients (119 knees) were followed up for a minimum of 2 years [38]. Fifty knees were randomly selected prior to the first injection to receive a second cycle at the completion of 1 year. A cycle consisted of three injections, each given at a monthly interval [38]. The outcome was assessed using the Knee Injury and Osteoarthritis Outcome Score (KOOS), Visual Analogue Scale (VAS), and the Tegner and Marx scoring systems, recorded prior to the first injection and then at 12, 18 and 24 months[38]. There was a significant improvement in all scores over time compared to the pre-treatment value ($p < 0.001$). At 12 months, both groups showed similar and significant improvements [38]. At 18 months, except for KOOS (Symptoms) and Tegner score, all other parameters showed a significant difference between the two groups in favor of the patients who had received the second cycle ($p < 0.001$)[42]. At 2 years, the scores declined in both groups but remained above the pre-treatment value. There was no significant difference between the groups despite the patients treated with two cycles showing higher mean values for all the scores [38]. Intra-articular PRP injections into the knee for symptomatic early stages of OA are a valid treatment option [38]. There is a significant reduction in pain and improvement in function after 12 months, which can be further improved at 18 months by annual repetition of the treatment [38]. Although the beneficial effects were ill sustained at 2 years, the results are encouraging when compared to the pre-treatment function [38]. This work is valued with level of evidence: II[38].

In 2012, Van der Goes et al. [39] described 14 patients with persistent knee arthritis despite at least two previous injections in an outpatient setting. The patients received an intra-articular injection with glucocorticoids, followed by 3 days of admission with bed rest [39]. Clinical efficacy was assessed at 6 and 12 weeks [39]. ST biopsies were performed 2 weeks before and 12 weeks after the injection. The presence of different cell types (T cells, macrophages, fibroblast-like synoviocytes) and numbers of glucocorticoid, androgen, and estrogen α and β

receptor positive cells were evaluated by histochemistry. Patients showed, despite previous failures, good clinical response to glucocorticoid injection. There was significant improvement in erythrocyte sedimentation rate, visual analogue scale (VAS) for pain, and joint disability score [39]. The number of steroid hormone receptor positive cells decreased markedly ($p < 0.05$ for all four receptors)[39]. The decrease in estrogen receptor α positive cells correlated significantly with the improvement in VAS for pain and joint disability score [39]. The number of glucocorticoid, androgen and estrogen α and β receptor positive cells before injection did not predict the effect of treatment. Intra-articular glucocorticoid injections followed by bed rest for persistent arthritis are clinically effective and significantly decrease the number of steroid hormone receptor positive cells in ST [39].

In September 2012, Braun et al. [40] described the effect of local anesthetic and corticosteroid combinations on chondrocyte viability. Local anesthetic and corticosteroid combination injections are often used in clinical practice. However, research investigating the chondrotoxic properties of these combinations is minimal [40]. The goal of this study was to evaluate the effect of single injection doses of 1% lidocaine or 0.25% bupivacaine in combination with single injection doses of dexamethasone sodium phosphate (Decadron), methylprednisolone acetate (Depo-Medrol), betamethasone sodium phosphate and betamethasone acetate (Celestone Soluspan), or triamcinolone acetonide (Kenalog) on human chondrocyte viability [40]. All treatment conditions were delivered to human chondrocytes in vitro for each medication's respective average duration of action using a bioreactor containing a continuous infusion pump constructed to mimic joint fluid metabolism. A two-color fluorescence assay was used to evaluate cell viability [40]. A mixed-effects regression model was used to evaluate the mean differences in cell viability between treatment groups [40]. At 14 days, a single injection dose of 1% lidocaine or 0.25% bupivacaine in combination with betamethasone sodium phosphate and betamethasone acetate solution illustrated significant chondrotoxicity when compared with the local anesthetics alone ($P < 0.01$). Methylprednisolone acetate and Triamcinolone acetonide both showed significant evidence of chondrotoxicity ($P = 0.013$; $P = 0.016$, respectively) when used in combination with 1% lidocaine compared with lidocaine alone, but showed no significant chondrotoxicity in combination with 0.25% bupivacaine (P 's = n.s.). Clinicians should use caution when injecting 1% lidocaine or 0.25% bupivacaine in conjunction with betamethasone sodium phosphate and betamethasone acetate solution due to its pronounced chondrotoxic effect in this study. 1% lidocaine used in combination with methylprednisolone acetate or triamcinolone acetonide also led to significant chondrotoxicity[40].

In 2004, Pyne et al.[41] compared the effectiveness of triamcinolone hexacetonide and methylprednisolone acetate (MPA), given via the intra-articular route at equipotent dosage to patients with symptomatic knee OA with effusion, in a double-blind randomized comparative trial [41]. Consecutive hospital-referred patients who fulfilled the American College of Rheumatology criteria for knee OA (clinical and radiographic) were randomly allocated to receive either triamcinolone hexacetonide 20 mg (1 ml) or MPA 40 mg (1 ml). All patients had synovial fluid aspirated from their knee joint at the time of injection [41]. Assessments were made at 0, 3 and 8 weeks by a second operator, thus blinding both patient and assessor [41]. Outcomes measured at each visit were knee pain in the previous 48 h (expressed on a 100 mm visual analog scale; VAS), stair climb time (SCT), and Lequesne index score (LEQ). Changes in VAS, SCT and LEQ were compared between the groups using a Student's paired t test. Fifty-seven patients were studied (44 female, 13 male) with a mean age of 62.5 years. Both steroids gave significant pain relief (VAS) at week 3 ($p < 0.01$) but only MPA showed an effect on VAS and LEQ scores at week 8 compared to baseline ($p < 0.05$). Triamcinolone hexacetonide was more effective than MPA at pain reduction at week 3 ($p < 0.01$); this difference was lost at week 8 ($p = 0.17$)[41]. There was no significant difference between the two drugs in functional endpoints (SCT, LEQ) at either 3 or 8 weeks. Both triamcinolone hexacetonide and MPA offer at least temporary symptomatic benefit in knee OA[41]. Triamcinolone hexacetonide is more effective than MPA at week 3, but its effect is lost by week 8. MPA still has an effect at week 8[41].

From the first visit and injection at the clinic, our attitude was cautious towards the use of viscosupplementation. Injection therapy was correlated with adequate treatment of Etoricoxib [11,42] and monitoring the physiotherapeutic treatment[11,43,44], which was modified according to the needs and demands of the patient. We did a single patient preparation using a variety of commercially available anti-inflammatory and chondroprotective [drugs] to be taken daily for three months before the start of treatment with PRP injections. Overall efficacy of Low molecular Weight Hyaluronic Acid, Polynucleotid, High Molecular Weight Hyaluronic Acid, and Platelet-Rich Plasma, both in terms of pain reduction and KOOS results, was comparable until to the sixth month. In KOOS results, we can see there was a statistically significant difference ($p < 0.05$) with triamcinolone hexacetonide. The population we studied, although made up of patients mostly around 80 years old, has a population of active people 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, while 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), group B consumed an average of 8.7 tablets per month including Etoricoxib (ranging from 7-18), group C consumed an average of 9.4 tablets per month including Etoricoxib (ranging from 5-16) group D consumed an average of 14.3 tablets per month including Etoricoxib (ranging from 9-21) group E consumed an average of 15.7 tablets per month including Etoricoxib (ranging from 11-23) (**Table 4**). 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 [11,43,44]. 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 management and care of the aging of the knee is complex. Nowadays, modern pharmacology allows us to manage osteoarthritis of the knee until the second grade and to delay the implantation of a knee arthroprosthesis. Unfortunately, the results of cartilage regeneration or physiological microenvironment of the knee had been assessed only in experimental animal models up until now [45]. Unfortunately, when arthritis is not treatable with common viscosupplementation, we have to resort to corticosteroid treatment for palliative purposes, and convince patients that the resolution of biomechanics and pain is in an arthroplasty of the knee [45]. Our study shows that for selected patients, various types of viscosupplementation can result in a big gain in pain, function, and a delay of surgery [45].

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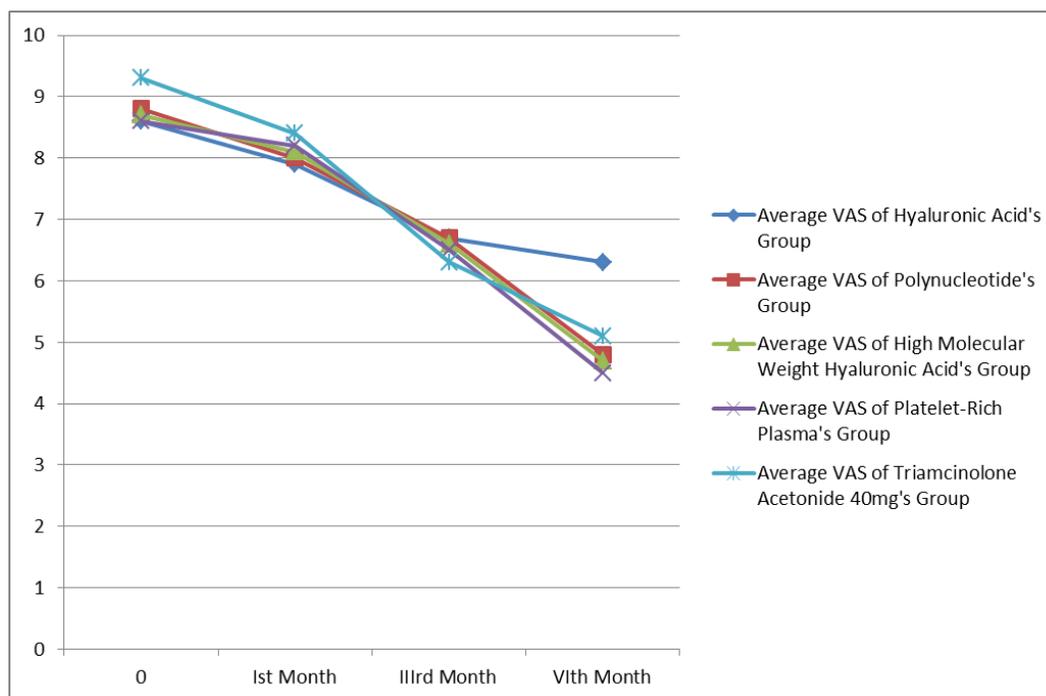
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TABLES:

Tab. 1: Description of the study's population.

<u>Description of Population</u>	<i>Low molecular Weight Hyaluronic Acid</i>	<i>Polynucleotide</i>	<i>High Molecular Weight Hyaluronic Acid</i>	<i>Platelet-Rich Plasma</i>	<i>Triamcinolone hexacetonide 40mg</i>
Number of patients	30	30	36	31	50
Number of Males/Females	15/15	15/15	13/23	16/15	28/22
Average age of patients	70.4	70.6	71.3	72.5	77.6
Age range of patients	55-75	55-78	52-82	50-80	60-85
Class of Gonathrosis	II	II	II	II	III
Average height (cm) of patients	163.4	166.2	165.3	168.2	161.4
Height (cm) range of patients	147-189	148-187	150-188	152-192	143-178
Average weight (Kg) of patients	72.6	74.2	72.3	71.5	77.3
Weight (Kg) range of patients	45-86	48-96	45-96	43-99	42-102
Average BMI of patients	24.6	25.7	25.9	26.3	26.8
BMI range of patients	21.2-27.3	22.4-29.2	21.7-29.5	20.3-28.9	22.3-29.7
Antinflammatory used	etoricoxib	etoricoxib	etoricoxib	etoricoxib	etoricoxib
Kinesis Therapy	all	all	all	all	all

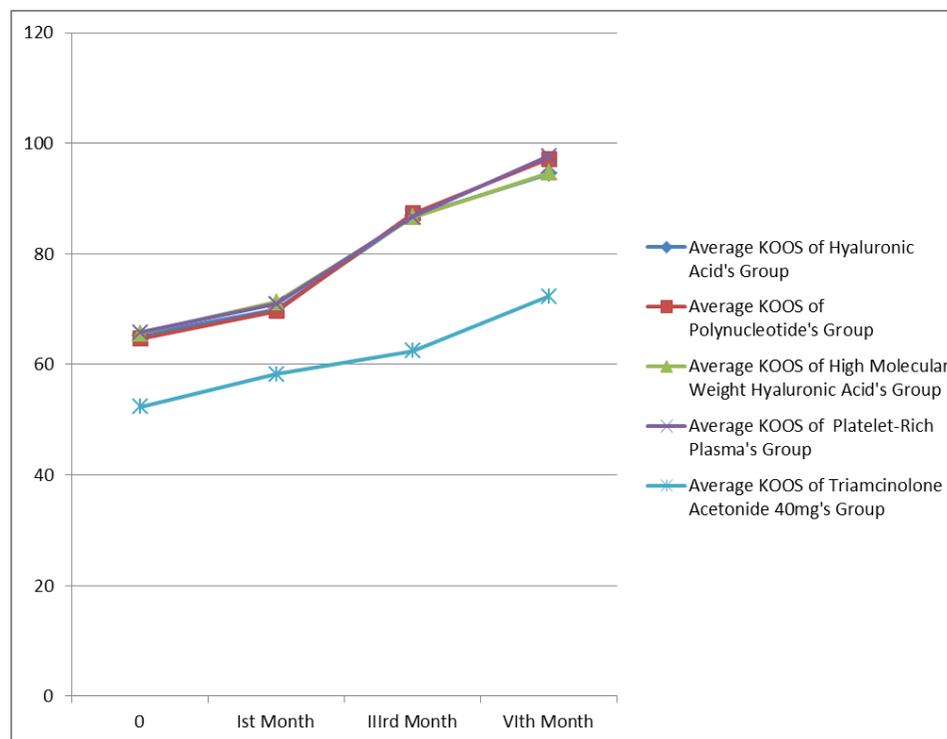
Time of injection	Average VAS of Hyaluronic Acid's Group	Average VAS of Polynucleotide's Group	Average VAS of High Molecular Weight Hyaluronic Acid's Group	Average VAS of Platelet-Rich Plasma's Group	Average VAS of Triamcinolone Acetonide 40mg's Group
0	8.6	8.8	8.7	8.6	9.3
Ist Month	7.9	8	8.1	8.2	8.4
IIIrd Month	6.7	6.7	6.6	6.5	6.3
VIth Month	6.3	4.8	4.7	4.5	5.1



Tab. 2: The difference of VAS in the Five Groups at the six month follow-up. At the sixth month follow-up, VAS it's similar for 4 Groups(Polynucleotide High Molecular Weight Hyaluronic Acid Platelet-Rich Plasma Triamcinolone Acetonide 40mg).

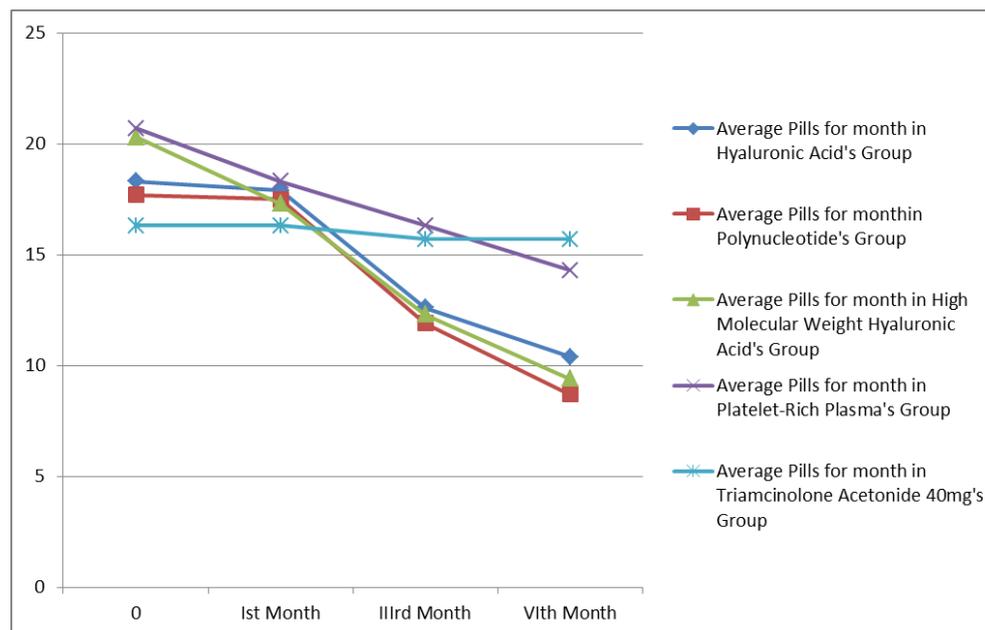
Instead The group of low molecular weight Hyaluronic Acid had a worse outcome in VAS. After the sixth month, Group A VAS was 6.3, Group B 4.8, Group C with 4.7, Group D 4.5 with and Group E with 5.1 this time there was a statistically significant difference ($p < 0.05$) for Group B, Group C, Group D and Group E

Time from start of Kinesis Therapy	Average KOOS of Hyaluronic Acid's Group	Average KOOS of Polynucleotide's Group	Average KOOS of High Molecular Weight Hyaluronic Acid's Group	Average KOOS of Platelet-Rich Plasma's Group	Average KOOS of Triamcinolone Acetonide 40mg's Group
0	65.3	64.7	65.6	65.8	52.3
Ist Month	70	69.6	71.3	70.9	58.2
IIIrd Month	86.8	87.3	86.6	86.7	62.4
VIth Month	94.5	97.2	94.7	97.7	72.3



Tab. 3: The difference of KOOS in Five Groups at the six month follow-up. The group of Triamcinolone hexacetonide had a worse outcome in KOOS. Since first month, there was a statistically significant difference ($p < 0.05$) for Group A, Group B, Group C and Group D in KOOS valuation.

Time from start of Use of Etoricoxib	Average Pills for month in Hyaluronic Acid's Group	Average Pills for month in Polynucleotide's Group	Average Pills for month in High Molecular Weight Hyaluronic Acid's Group	Average Pills for month in Platelet-Rich Plasma's Group	Average Pills for month in Triamcinolone Acetonide 40mg's
0	18.3	17.7	20.3	20.7	16.3
Ist Month	17.9	17.5	17.3	18.3	16.3
IIIrd Month	12.6	11.9	12.3	16.3	15.7
VIth Month	10.4	8.7	9.4	14.3	15.7



Tab. 4: The use of etoricoxib pills during the six months treatment 5 group. The group that took on average more etoricoxib was that of Triamcinolone hexacetonide 40mg.