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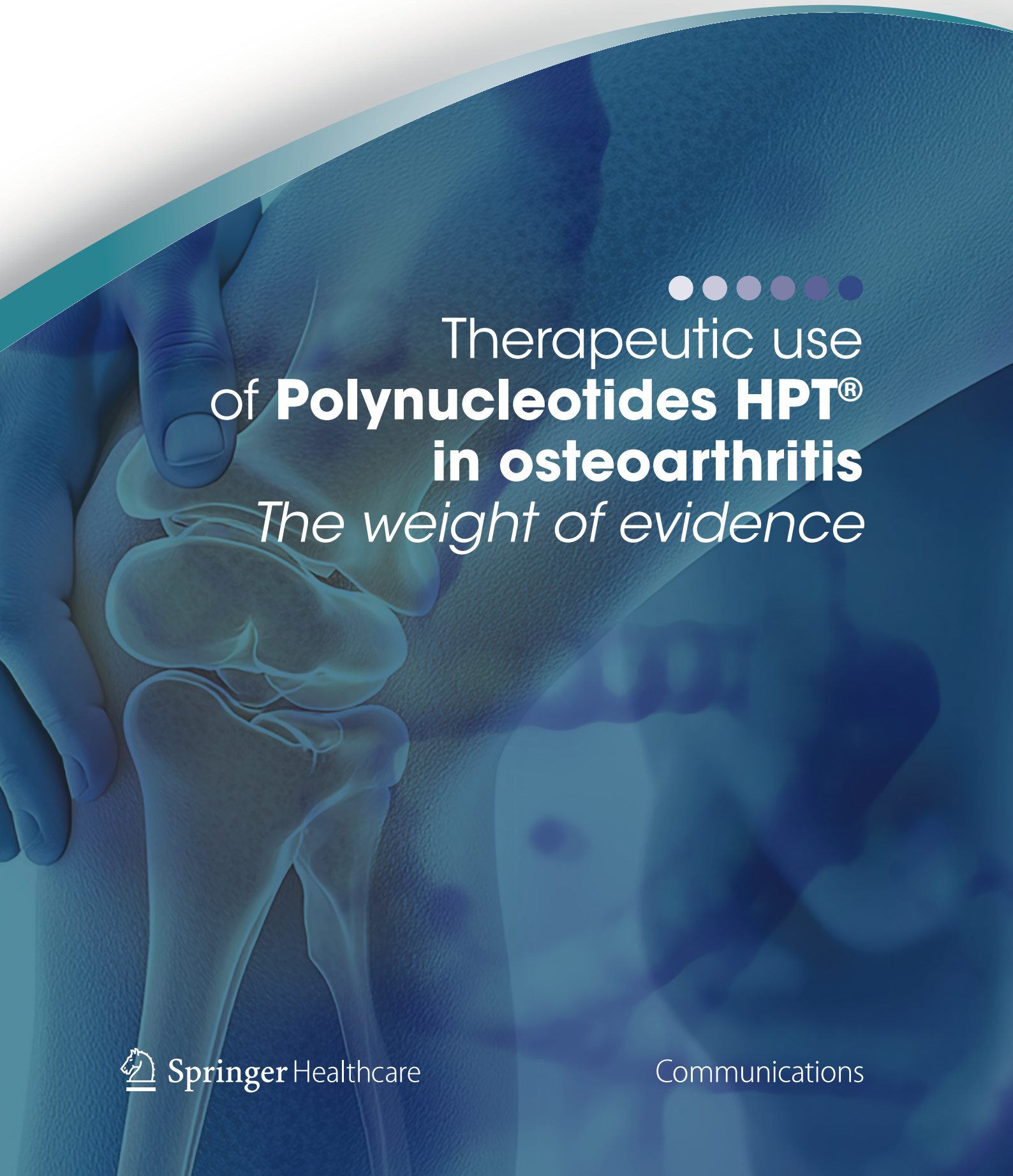

Therapeutic use of **Polynucleotides HPT®** **in osteoarthritis**

The weight of evidence

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Therapeutic use of Polynucleotides HPT® in osteoarthritis

The weight of evidence

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Introduction

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Osteoarthritis (OA) represents a significant and growing public health challenge, affecting millions of individuals worldwide. OA is characterised by the degeneration of joint cartilage and underlying bone, leading to pain, stiffness, and reduced mobility[1]. The World Health Organization estimates that OA affects approximately 10% of men and 18% of women aged over 60, and this prevalence is expected to rise due to ageing populations and increasing obesity rates[2].

Traditional treatment modalities in OA include pharmacological interventions such as non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids, as well as physical therapy and lifestyle modifications. However, these approaches often provide only temporary relief and may be associated with adverse effects, particularly in the long term[1]. Intra-articular injections have emerged as a promising alternative, particularly with the advent of innovative therapies like polynucleotide injections. Polynucleotides are a mixture of natural DNA-derived macromolecules of different length obtained from trout sperm using an original purification technology developed by Mastelli S.r.l., a company boasting more than 70 years of experience and know-how in this field. In the therapeutic area of orthopaedics, Mastelli S.r.l. offers two injectable products: Condrotide® (20 mg/mL of Polynucleotides HPT®) and Condrotide® HA (10 mg/mL of Polynucleotides HPT® and 10 mg/mL hyaluronic acid).

The rationale for using Polynucleotides HPT® lies in their ability to delay degenerative processes within the joint environment and support cellular functions essential for tissue healing[3]. In fact, Polynucleotides HPT® have attracted attention for their potential to help enhancing joint function and alleviate pain in patients with OA. Recent studies demonstrate that their intra-articular injection can significantly reduce pain and improve functional outcomes compared to traditional therapies such as hyaluronic acid injections, both in an animal model of OA[4] and in patients (e.g., refs.[4-9]).

This monograph aims to explore the role of intra-articular Polynucleotides HPT® injections in the management of OA, emphasising their therapeutic efficacy and safety profile. It is crucial to recognise the pressing need for effective interventions to deal with the OA "epidemic" and improve the quality of life of individuals affected by this debilitating condition.

Chapter I – Osteoarthritis: nosological framework and contemporary epidemiology

1.1 Description and classification of osteoarthritis

Osteoarthritis (OA) is a complex chronic disease that affects the entire joint meaning that all structures in the joint, i.e., the cartilage, subchondral bone, ligaments, capsule, synovial membrane and periarticular muscles, are affected by the pathological processes[10].

The diagnosis of OA is made based on symptoms (pain, morning stiffness, functional limitations) and physical signs (crepitus, restricted and painful movement, joint tenderness and bony enlargement)[1]. The Kellgren and Lawrence classification is used for the radiological grading of OA of several joints. This classification is based on a sequence of osteophyte formation, joint space narrowing, and bone sclerosis, and it provides simple and practical scales for each joint. Additional scores are available for further classification of individual radiographic features[11].

The American College of Rheumatology (ACR) classifies OA into two main categories: i) idiopathic OA and ii) secondary OA that occurs due to a known traumatic event or disease. The two categories are further grouped according to anatomical location and whether OA is limited to a particular joint or generalised[12].

OA most commonly affects the hip, knee, and hand joints, but most joints can be involved, with the knee being the most frequent site for OA[13].

1.2 Epidemiology of OA worldwide and in Italy

OA is the most common joint disease affecting an estimated 240 million people worldwide including 10% of men and 18% of women above the age of 60[14]. OA most frequently occurs after the age of 40 and its prevalence increases sharply with age[13].

In 2020, the age-standardised prevalence of OA was more than 5.5% in all world regions, ranging from 5677.4 (5029.8-6318.1) per 100,000 people in southeast Asia to 8632.7 (7852.0-9469.1) per 100,000 people in high-income Asia Pacific. The prevalence of OA was higher in females than in males. The prevalence of total OA and OA at specific sites increases with age. Compared to 2020, by 2050, the number of people with OA is projected to increase by 74.9% (59.4-89.9) for the knee, by 48.6% (35.9-67.1) for the hand, by 78.6% (57.7-105.3) for the hip, and by 95.1% (68.1-135.0) for other types of osteoarthritis[11].

According to the Italian Statistics Institute (ISTAT), almost 40% of Italians suffer from chronic conditions, with arthritis/OA being the second most common chronic disease present in 14.8% of the population[15].

1.2.1 Sport and OA

There is a concern that practising sports may contribute to the development of early OA. Elite athletes engaging in sports involving rapid acceleration and deceleration or those with high joint impact have a higher probability of developing OA. **For example, the incidence of OA in current or former soccer players is 16-80%, i.e., 5 to 12 times higher than in the general population, and OA is diagnosed 4-5 years earlier.** There is a correlation between both sport intensity and duration and the incidence of OA. Moreover, **joint injuries are common amongst athletes (10-35.5 injuries/1000 h of playing soccer) and in 16-46% involve the knee. Joint injury is a major factor in the development of early and disabling OA[16]**.

Following an injury, an early restoration of the appropriate meniscal, ligament and cartilage integrity protects the knee and allows for safe return to training. The risk of developing OA when practising different sports or continuously stopping and restarting sport practice is still unknown, as is the most effective treatment modality. Low-impact sports (walking, swimming and cycling) can have a protective effect[16].

1.3 Economic and social burden of disease

OA is a major source of health-related expenditure[13]. The indirect costs due to work loss and early retirement are also substantial[1]. For example, in the USA in 2016, healthcare expenditures on OA amounted to USD 80 billion, and in Hong Kong in 2003 direct and indirect spending on OA totalled more than HKD 400 million[13].

OA is also a major cause of disability and societal costs[1]. The WHO Global Ageing and Health Report 2015 nominated OA as a leading cause of disability in adults above the age of 60 years[13]. Between 1990 and 2020, the global age-standardised rate of years lived with disability (YLDs) for all sites of OA increased by 9.5% (95% uncertainty intervals 8.6-10.1)[13]. In 2020, OA ranked as the 14th most common cause of age-standardised YLDs across all ages and as the seventh cause of YLDs among people above the age of 70 years. Symptomatic OA may be associated with depression and disturbed sleep, which deepen the disability and the symptoms of OA and negatively impact the patients' quality of life[11].

Chapter II – Polynucleotides High Purification Technology (PN HPT®): an Italian innovation

2.1 Characteristics of Polynucleotides HPT® and mechanism of action

Polynucleotides are DNA-derived macromolecules of varying lengths, naturally sourced from the gonads of freshwater-bred trout, *Oncorhynchus mykiss*, raised for human consumption. These macromolecules are purified through a unique, advanced high-temperature process developed by Mastelli S.r.l. over 70 years ago. This technology ensures the production of an exceptionally pure product, free from allergenic or pharmacologically active protein contaminants. Over the years, Mastelli S.r.l. has accumulated extensive experience and expertise in handling these molecules, solidifying its leadership in this field[8].

Polynucleotide extraction and purification and the manufacturing of medical devices by Mastelli S.r.l. is performed through a specific process, denominated High Purification Technology (HPT®), from fish intended for human consumption. Fish gonads are excised for polynucleotide extraction and the remaining fish enter the food chain. The farming of trout used for polynucleotide extraction takes place in Italy and Europe and rigorously complies with animal welfare recommendations, food hygiene and food safety legal requirements including tests for the presence of heavy metals. **Mastelli S.r.l. fully controls the production chain, from trout breeding to polynucleotide purification and the production of the finished Polynucleotides HPT®-based medical devices.** Once produced, the devices are appropriately packaged, sterilised, quality-assured and stored in controlled warehouses, ready for commercialisation. Polynucleotides HPT® demonstrate strong potential for tissue repair by emulating natural tissue components and replicating natural mechanisms that support physiological healing processes. When applied, Polynucleotides HPT® fill intercellular spaces and act as a supportive extracellular matrix. This matrix not only provides essential hydration for volume maintenance and thus spatial integrity, but it also establishes a scaffold that fosters cell communication. By integrating with the extracellular environment, Polynucleotides HPT® contribute to a stable microenvironment that mimics physiological conditions, which is crucial for the natural tissue regeneration processes.

For osteoarticular health, Polynucleotides HPT® act with a double-edge action for complete joint effectiveness:

1. Initial biomechanical action: Polynucleotides HPT® are polymeric molecules that have the ability to bind large amounts of water and reorganise their structure by orientating and coordinating water molecules to form a three-dimensional hydrogel (**Figure 1**)[8]. This three-dimensional hydrogel deeply hydrates the joint surfaces, improves the rheological properties of the synovial fluid and restores the mechanical dynamics of the joint.

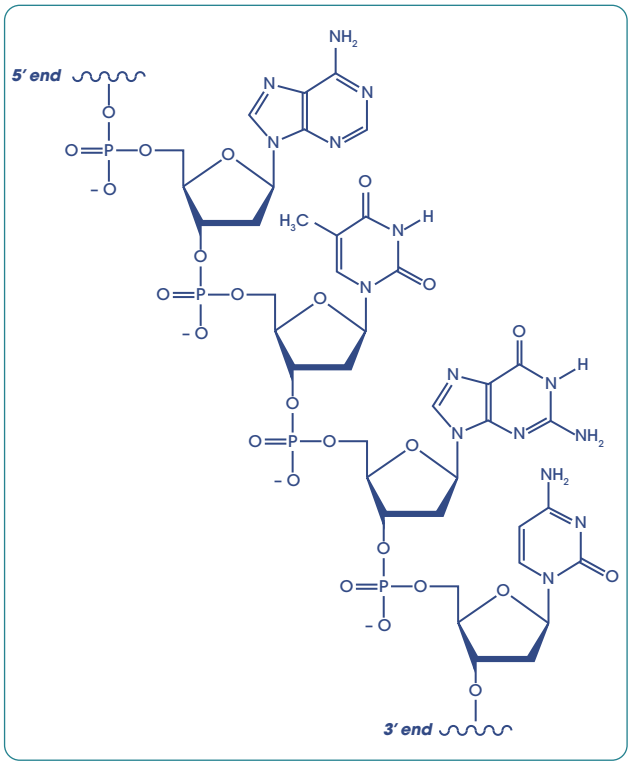


Figure 1. The chemical structure of Polynucleotides HPT®.

2. Recovery of joint physiology: Polynucleotides HPT® hydrogels have been shown to support, by providing a scaffold, the restoration of a physiological microenvironment to promote the development of healthy cartilages[3]. They favour the recovery of chondrocyte vitality with physiological deposition of cartilage matrix.

Polynucleotides HPT® also improve joint function and reduce pain.

2.2 The effect of Polynucleotides HPT® on cartilage: *in vitro* study

Gennero et al. focused on establishing a microenvironment capable of reinducing physiological cell functions in injured cartilage. To do so, different culture media, either promoting (supplemented with Polynucleotides HPT®, hyaluronic acid or specific chondrocyte culture medium) or not promoting (nonspecific culture medium or culture medium without supplements) chondrocyte survival and growth were tested on cartilage biopsies and cartilage-derived cells. Chondrocyte viability, deposition of extracellular matrix components (type II collagen and aggrecan), and explant tissue histology were analysed after 30 days of culture[3].

Cell vitality was physiologically maintained also after 30 days of incubation and was significantly higher in the biopsies cultured in a medium supplemented with 1% Polynucleotides HPT® than in those cultured in a medium supplemented with 1% hyaluronic acid (p<0.001) (Figure 2A). Moreover, the expression of type II collagen and aggrecan was higher on chondrocytes cultured in the medium supplemented with 1% Polynucleotides HPT® than on those cultured in the medium supplemented with 1% hyaluronic acid (Figure 2B, C)[3]. *In vitro* treatment of cartilage explants in the culture medium containing 1% Polynucleotides HPT® showed the presence of all structures of normal hyaline cartilage, whereas explants incubated in the culture medium supplemented with 2% hyaluronic acid appeared to be in a degenerative state[3].

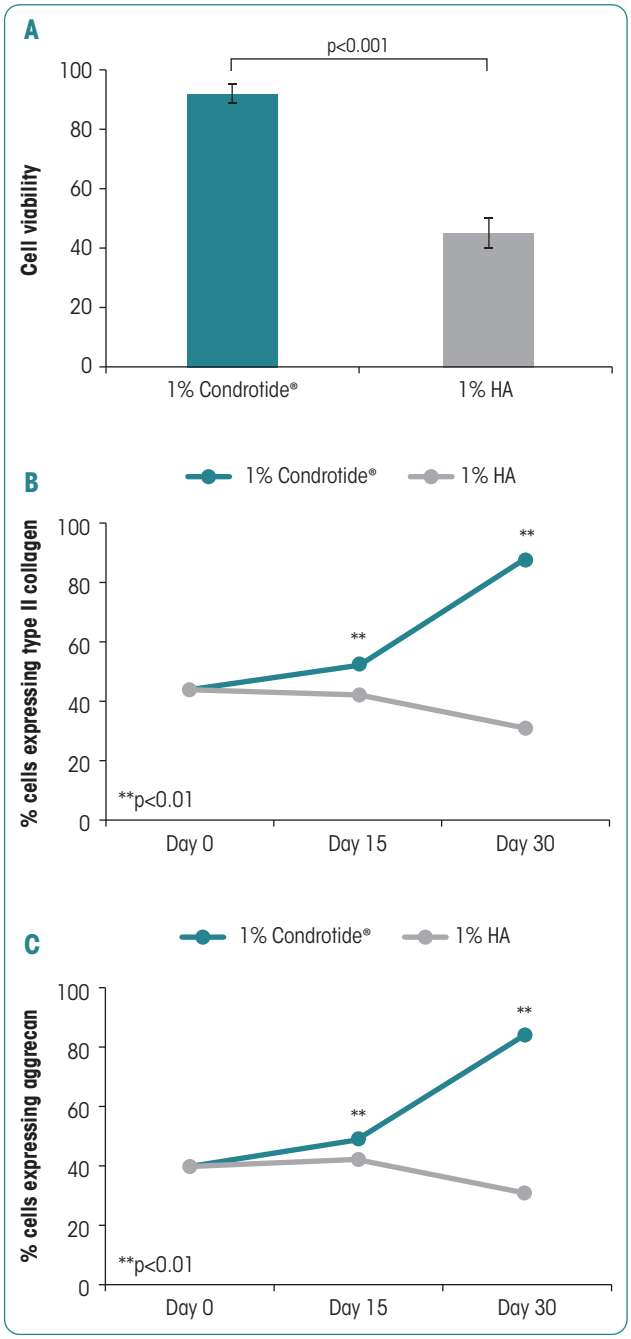


Figure 2. Condrotide® performed better than hyaluronic acid (HA) in supporting chondrocyte viability **(A)** and appropriate deposition of extracellular matrix components (type II collagen and aggrecan) (**B** and **C**, respectively). Graphic elaboration from tables [3].

Chapter III – Clinical benefits of Polynucleotides HPT® in the treatment of osteoarthritis – Evidence-based medicine

3.1 Clinical benefits of the use of Polynucleotides HPT® in the treatment of osteoarthritis (OA) of the knee

3.1.1 Study by Vanelli et al., 2010: the first evidence of the validity of Condrotide® in the treatment of symptomatic OA of the knee from a randomised double-blind clinical trial conducted by the group of Prof. Francesco Benazzo at the University of Pavia.

Reference [8]: Vanelli R, Costa P, Rossi SM, Benazzo F. Efficacy of intra-articular polynucleotides in the treatment of knee osteoarthritis: a randomized, double-blind clinical trial. Knee Surg Sports Traumatol Arthrosc. 2010;18(7):901-7.

Aim of the study

The aim of this study was to assess the efficacy of intra-articular injections of Polynucleotides HPT® (Condrotide®, Mastelli S.r.l., Sanremo, Italy) in the treatment of OA with persistent pain by comparing their effects to standard viscosupplementation with hyaluronic acid.

Study design

Patients: Fifty-nine patients (20 male/39 female, median age 60 and 67 years for the Condrotide® Group and Comparison Group, respectively) with knee OA and persistent pain for at least 2 months.

Interventions: Patients received treatments as detailed in **Figure 3**.

Assessments: The following assessments were made at all study visits (T0-T16):

- VAS score (the higher the score, the worse the pain) for subjective knee pain (global pain, pain at rest, pain on weight bearing, and pain during physical activity)
- Clinical evaluation.

In addition, at baseline (T0) and follow-up visits (T8 and T16), the researchers assessed:

- Knee Injury and Osteoarthritis Outcome Score (KOOS, a questionnaire for the assessment of knee pain, function and QoL on a scale from 0 to 100 points, where higher scores indicate better knee condition) and subscales (Pain, Symptoms, Activity of Daily Living [ADL] Function, Sport/Recreation Function, QoL)
- Non-steroidal anti-inflammatory drugs (NSAIDs) consumption.

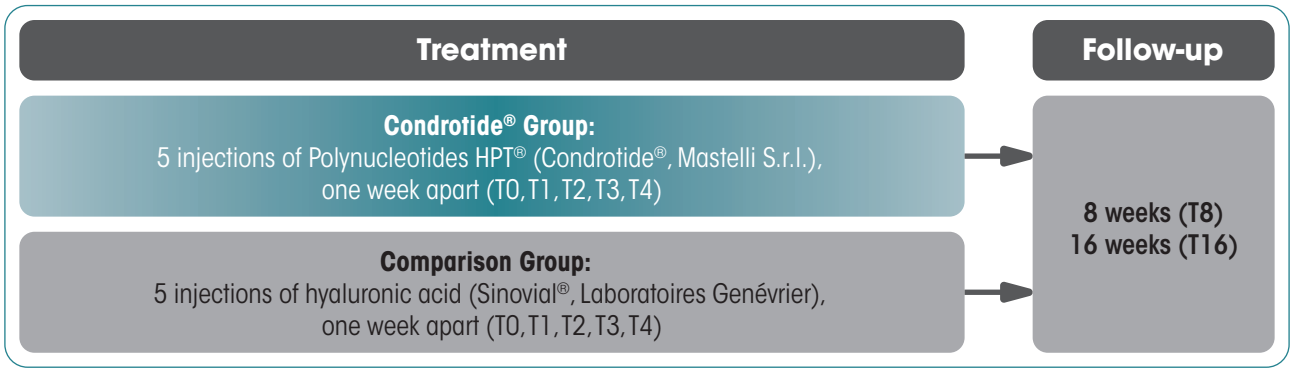


Figure 3. Study design. Graphic elaboration from text [8].

Results

The mean global pain on the VAS decreased for both groups and the changes were statistically significant (**Figure 4A**). The reduction of pain at rest was faster in the Condrotide® Group, whilst the reduction in pain on weight bearing and during physical activity followed a similar trajectory in the two groups. The improvement in KOOS values between baseline and T16 was statistically significant in both groups, although higher in the Condrotide® Group than in the Comparison Group for all subscales (**Figure 4B**); this is particularly evident for the Symptoms and Sport/Recreation subscales. The Sport/Recreation subscale was not subjected to statistical analysis due to the small number of patients doing sports; nevertheless, the data show a trend towards improvement in the Condrotide® Group (from 24.6 ± 20.0 to 38.9 ± 26.7) versus the Comparison Group (from 30.0 ± 12.5 to 33.6 ± 25.6) from baseline to T16. The use of NSAIDs was lower in the Condrotide® Group than in the Comparison Group, especially at T4 and T8 (**Figure 4C**). At the end of the follow-up, one (3.4%) patient in the Condrotide® Group and eight (27%) patients in the Comparison Group continued to take NSAIDs.

Conclusions

This was the first study to evaluate intra-articular injections of Polynucleotides HPT® (Condrotide®, Mastelli S.r.l., Sanremo, Italy) in the treatment of OA of the knee. The results suggest that the use of Polynucleotides HPT® can be a valid therapeutic alternative to hyaluronic acid in the treatment of symptomatic OA. Intra-articular injections of Polynucleotides HPT® substantially reduce OA pain and improve the overall quality of life of patients as shown by the KOOS scores. The authors of this randomised double-blind clinical trial concluded that the product could become a useful addition to the range of treatments available in symptomatic OA.

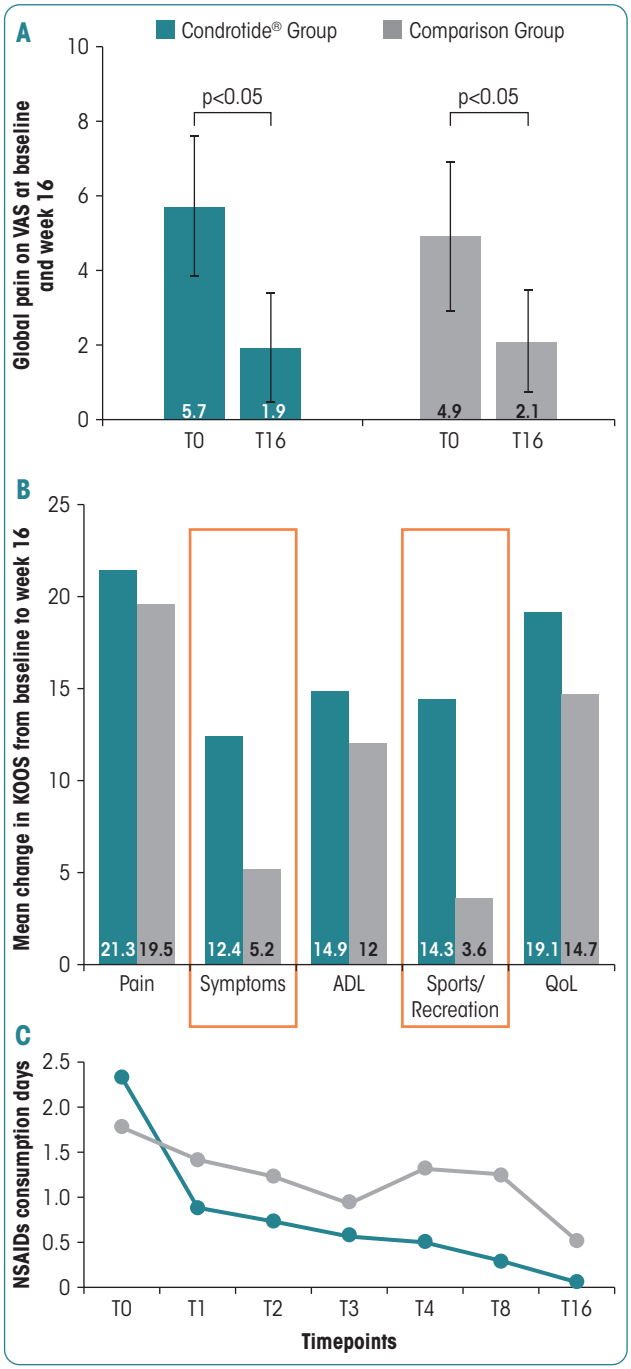


Figure 4. Global pain assessment on VAS **(A)**, mean change in KOOS from baseline to week 16 **(B)** and evolution of NSAIDs consumption (calculated as number of days in the preceeding week in which the patient took NSAIDs) over the duration of follow-up **(C)** in patients in the Condrotide® and Comparison Groups. Orange boxes mark the KOOS subscales in which the improvement in the Condrotide® Group was particularly evident. Graphic elaboration from text and figures [8].

According to the authors of this randomised double-blind trial, Polynucleotides HPT® (Condrotide®) injections could usefully extend the range of treatments available in symptomatic OA.

3.1.2 Study by Giarratana et al., 2014: a randomised double-blind clinical trial led by Prof. Bruno Michele Marelli and Prof. Walter Albisetti confirmed the findings of Vanelli et al. and showed that Polynucleotides HPT® provide faster pain reduction than hyaluronic acid.

Reference [9]: Giarratana LS, Marelli BM, Crapanzano C et al. A randomized double-blind clinical trial on the treatment of knee osteoarthritis: the efficacy of polynucleotides compared to standard hyaluronian viscosupplementation. Knee. 2014;21(3):661-8.

Aim of the study

The aim of this prospective study was to confirm the results of Vanelli et al.[8] by assessing the efficacy of intra-articular injections of Polynucleotides HPT® (Condrotide®, Mastelli S.r.l., Sanremo, Italy) in the treatment of knee OA with persistent pain compared to the effects of standard viscosupplementation with hyaluronic acid.

Study design:

Patients: Seventy-two patients (31 male/41 female, median age 64.9 and 64.1 years for the Condrotide® Group and Comparison Group, respectively) with knee OA and persistent pain for at least 2 months.

Interventions: Patients received treatments as detailed in **Figure 5**.

Assessments: The following assessments were made at different study visits:

- Clinical evaluation at all study visits (T0-T26)
- Knee Injury and Osteoarthritis Outcome Score (KOOS) and subscales on all visits but T1
- VAS score for subjective knee pain (pain at rest, pain during standing, and pain during walking) on all visits
- Non-steroidal anti-inflammatory drugs (NSAIDs) consumption.

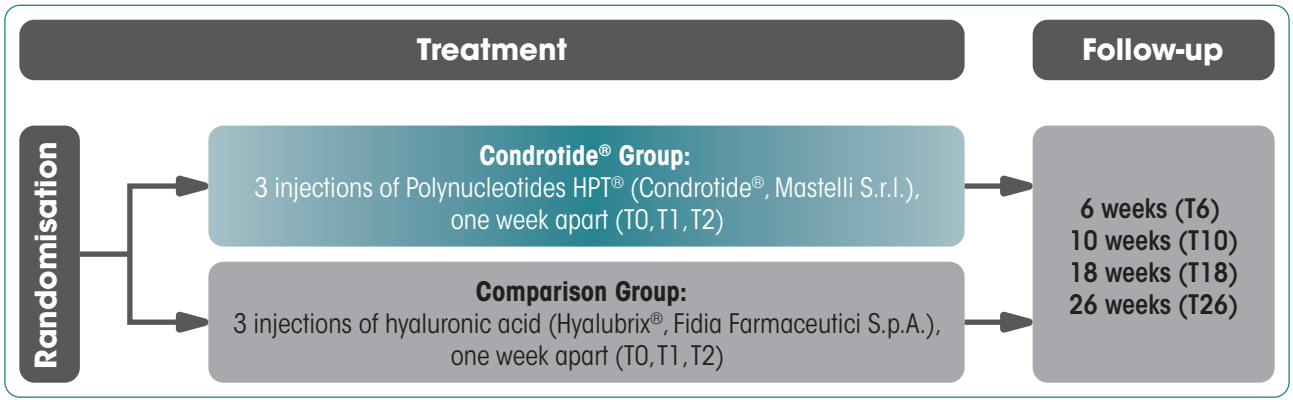


Figure 5. Study design. Graphic elaboration from text [9].

Results

Sixty-eight patients completed the study; two were lost to follow-up and two discontinued due to adverse events unrelated to the study intervention. **Figure 6** shows mean differences from baseline in KOOS subscales, which were considered separately. In the Condrotide® Group, a statistically significant improvement in symptoms occurred at T2 (p=0.003), whereas pain and sport/recreation improved at T6 (p=0.012) since the beginning of the treatment. In the Comparison Group, statistically significant improvements for these three subscales occurred at T18 (p=0.01). Both groups improved in the ADL and QoL subscales at T6. The difference between the two groups was statistically significant at T10 for pain, ADL and sport/recreation in favour of Polynucleotides HPT®.

The VAS score for pain at rest improved at T2 for both groups, whereas pain during standing and during walking improved at

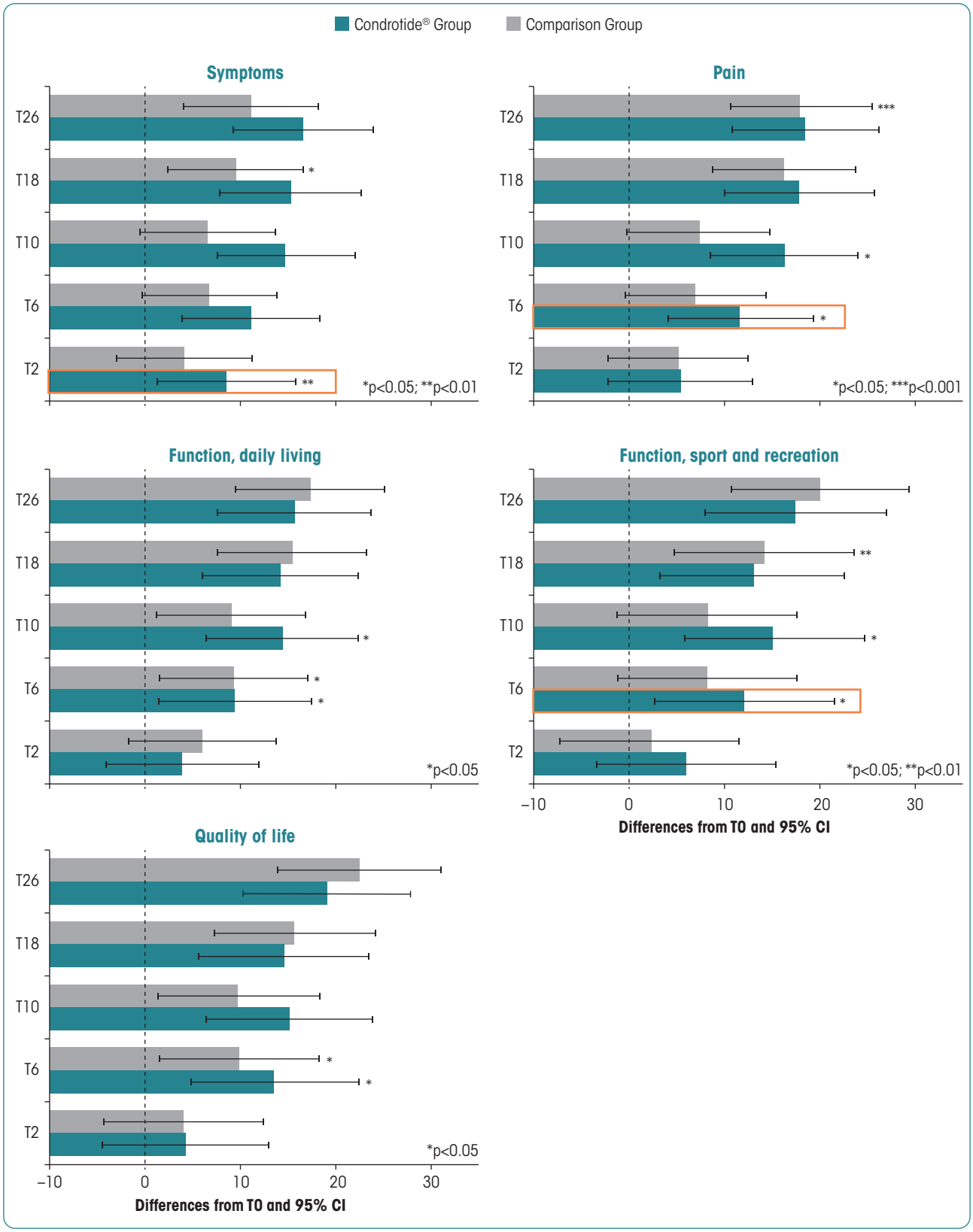


Figure 6. Mean differences from baseline with 95% t-test confidence interval (CI) for all KOOS subscales when considering the Condrotide® and Comparison Group separately. The timepoints at which the differences from baseline became statistically significant are shown (*p<0.05; **p<0.01; ***p<0.001). Orange boxes mark the subscales for which the statistically significant improvement from baseline occurred earlier in the Condrotide® Group than in the Comparison Group. Graphic elaboration from figure [9].

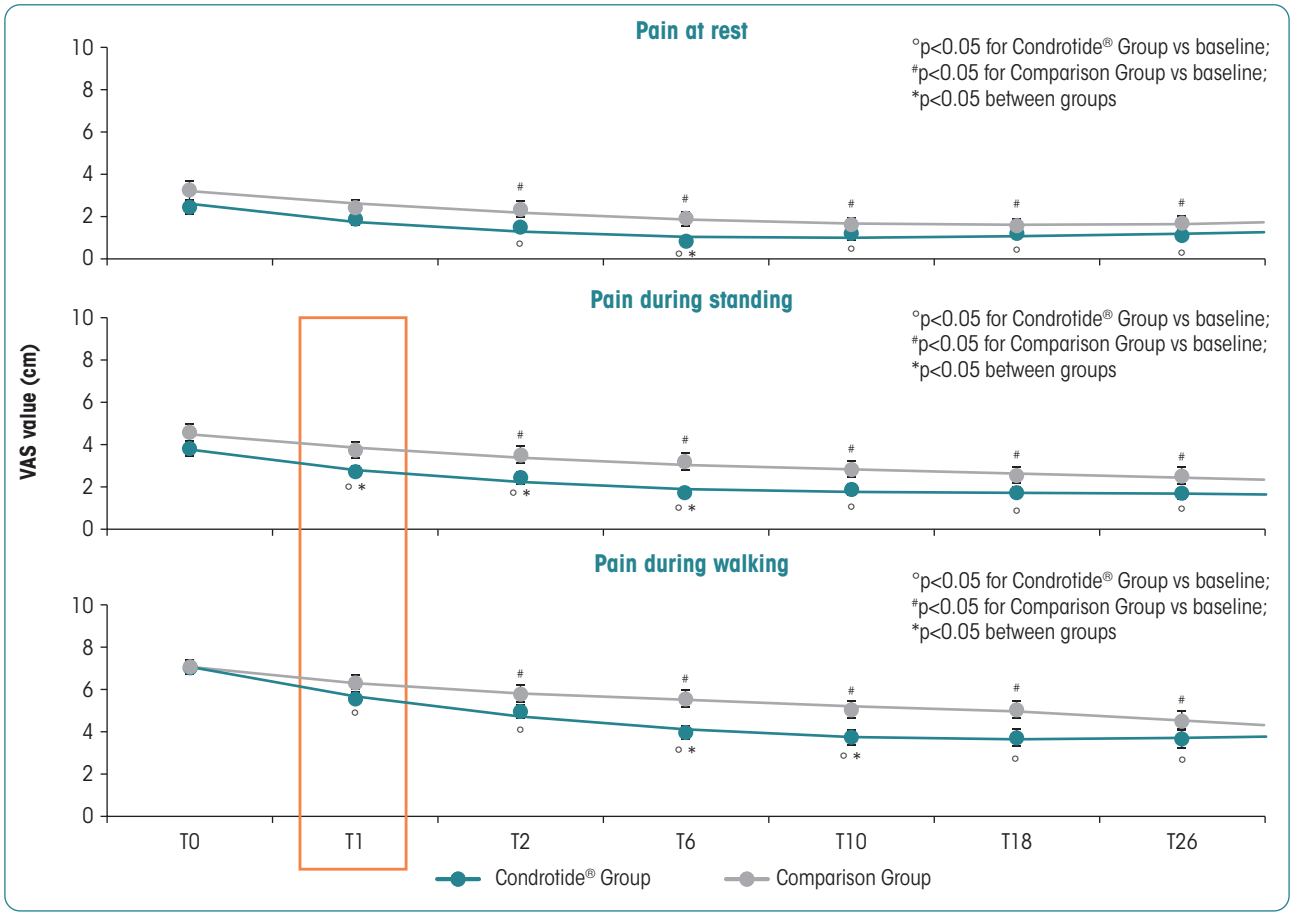


Figure 7. Mean and standard deviation for VAS values for pain at rest, during standing and during walking at all timepoints from baseline to T26 in the Condrotide® and Comparison Group. Statistically significant differences from baseline to a given timepoint within group are shown as ° for the Condrotide® Group and # for the Comparison Group. Statistically significant differences between groups are show as *. All p<0.05. The orange box marks the subscales for which the statistically significant improvement from baseline occurred earlier in the Condrotide® Group than in the Comparison Group. Graphic elaboration from figure [9].

T1 in the Condrotide® Group and T2 in the Comparison Group. **Figure 7** shows the evolution of VAS scores during the study. A clear reduction in NSAIDs use was observed at T10 in the Condrotide® Group and T18 in the Comparison Group. The analysis of crackling, articular mobility limitation and articular oedema showed similar results for both groups.

Conclusions

The study confirmed that intra-articular injections of Polynucleotides HPT® (Condrotide®, Mastelli S.r.l., Sanremo, Italy) are as effective as hyaluronic acid (Hyalubrix®) in reducing symptoms of OA of the knee but with a quicker onset of improvements in pain resulting in a faster improvement in ADL and quality of life.

The authors concluded that the intra-articular use of Condrotide® might represent a valid alternative to the use of hyaluronic acid in the treatment of knee OA with persistent pain. Importantly, it may reduce NSAIDs consumption and intra-articular corticosteroids, and the adverse events associated with these two treatments.

> *The study confirmed that Polynucleotides HPT® (Condrotide®) are as effective as hyaluronic acid (Hyalubrix®) in reducing symptoms of OA of the knee but with a quicker onset of improvements in pain resulting in a faster improvement in the activities of daily living and quality of life.*

3.1.3 Study by Zazgyva et al., 2013: a randomised, double-blind clinical trial to compare the efficacy of Polynucleotides HPT® with that of hyaluronic acid.

Reference [6]: Zazgyva A, Gergely I, Russu OM et al. Polynucleotides versus sodium hyaluronate in the local treatment of knee osteoarthritis. Acta Medica Transilvanica. 2013;2(2):260-3.

Aim of the study

The aim of this prospective study was to evaluate and compare the efficacy of intra-articular injections of hyaluronic acid and Polynucleotides HPT® (Condrotide®, Mastelli S.r.l., Sanremo, Italy) in patients with painful knee OA.

Study design

Patients: Thirty patients aged 18 to 71 who were diagnosed with OA of the knee and reported persistent pain for at least 2 months.

Interventions: Patients received treatments as detailed in **Figure 8**.

Assessments: The following assessments were made:

- VAS score for subjective knee pain
- Knee Injury and Osteoarthritis Outcome Score (KOOS) scale
- Knee Society Score (KSS, that assesses knee pain and functionality on a 0-100 scale with 100 corresponding to optimal knee state)
- Non-steroidal anti-inflammatory drugs (NSAIDs) consumption.

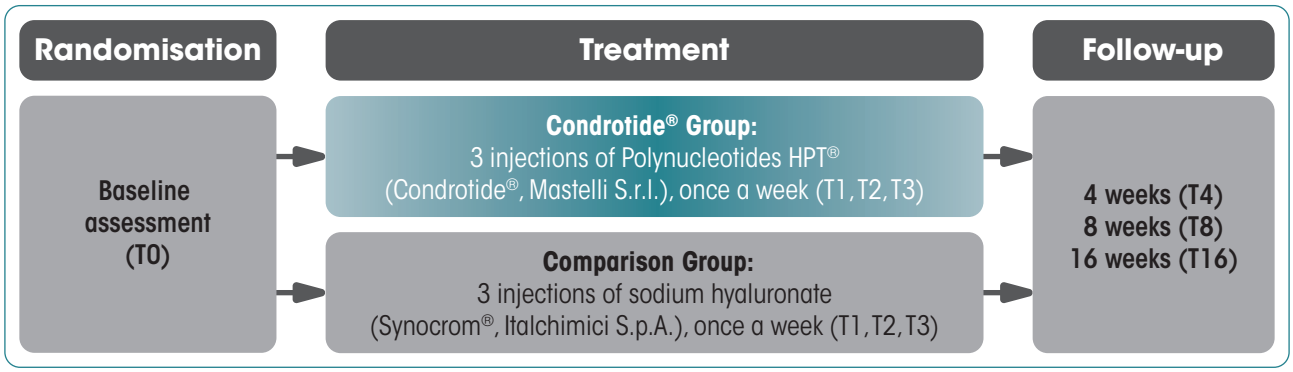


Figure 8. Study design. Graphic elaboration from text [6].

Results

All 30 patients completed the study.

Subjective pain perception on VAS decreased significantly in both groups with a more pronounced improvement in the Condrotide® Group. The evolution of pain at rest is shown in **Figure 9A**. KOOS values improved in both groups from T0 to T16. The increase in KOOS value was greater in the Condrotide® Group (**Figure 9B**). The KSS "knee score" and KSS "functional score" showed a statistical improvement in the Condrotide® Group (**Figure 9C, D**). The reduction in NSAIDs consumption was more pronounced in the Condrotide® Group (**Figure 9E**).

Conclusions

A significant pain reduction was observed in patients with OA treated with intra-articular injections of Polynucleotides HPT® (Condrotide®, Mastelli S.r.l., Sanremo, Italy) and hyaluronic acid. However, the symptomatic and functional improvements were greater in the Condrotide® Group versus the Comparison Group.

Based on the results of this randomised double-blind clinical trial, the authors confirmed that Polynucleotides HPT® injections are a viable alternative in the treatment of early and intermediate stage OA.

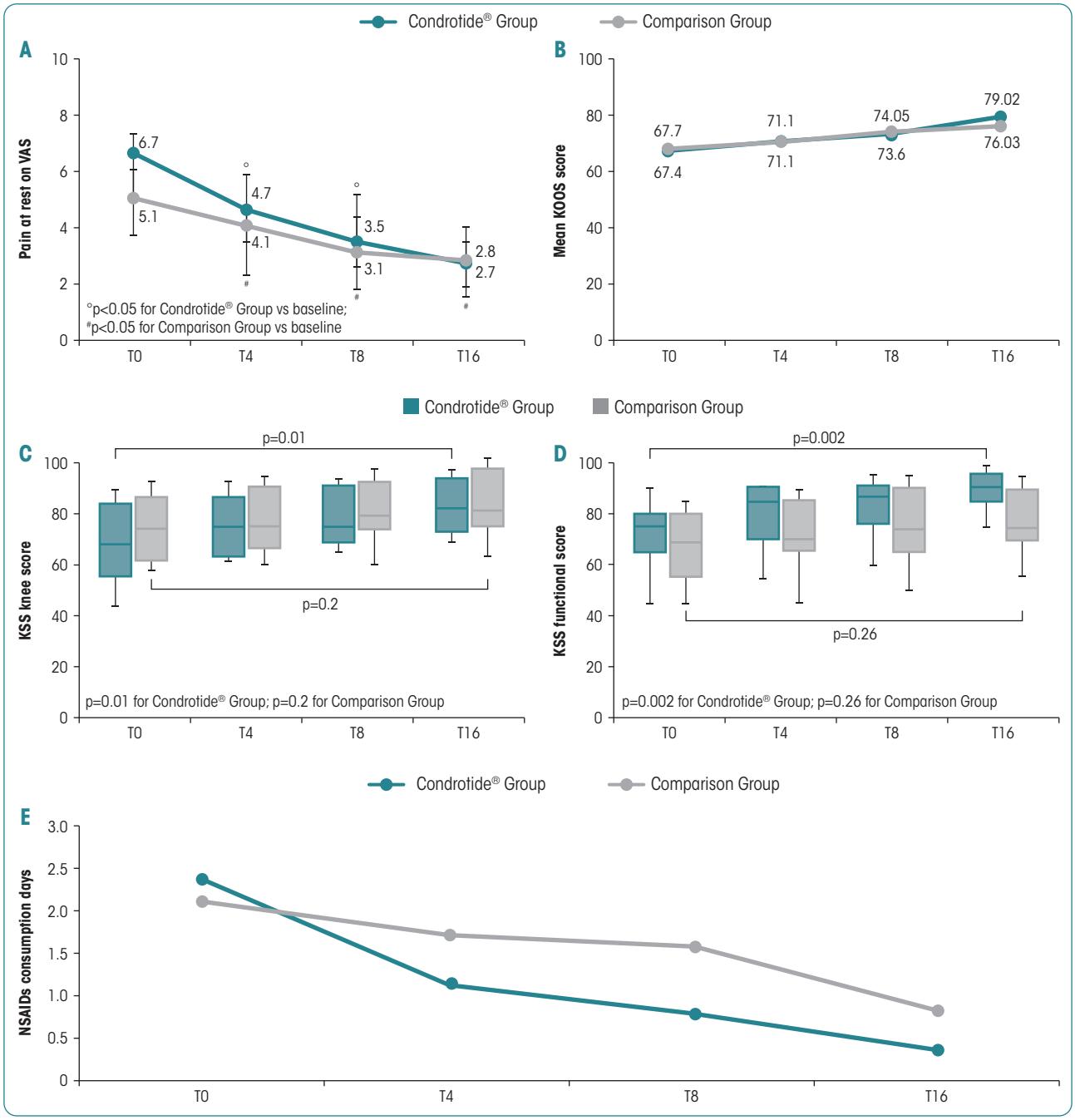


Figure 9. Level of subjective pain at rest on VAS **(A)**, mean KOOS values **(B)**, KSS "knee score" **(C)**, KSS "functional score" **(D)** and NSAIDs consumption **(E)** at all timepoints from baseline to T16. In panel A, statistically significant differences from baseline to a given timepoint within group are shown as ° for the Condrotide® Group and # for the Comparison Group. Graphic elaboration from text, table and figures [6].

Based on the results of this randomised double-blind clinical trial, the authors confirmed that Polynucleotides HPT® (Condrotide®) injections are a viable alternative in the treatment of early and intermediate stage OA.

3.1.4 Study by Meccariello et al., 2015: an international retrospective study that compared the effectiveness of five intra-articular mitigation strategies to treat OA of the knee and showed that, amongst others, Polynucleotides HPT® can delay knee arthroplasty.

Reference [17]: Meccariello L, Fazarano G, Medici A et al. 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 five drugs and review of the literature. Canadian Open Orthopaedics and Traumatology Journal. 2015;2(1):1-13.

Aim of the study

The aim of this retrospective study was to evaluate five intra-articular strategies to treat patients with OA of the knee including intra-articular injections of Polynucleotides HPT® (Condrotide®, Mastelli S.r.l., Sanremo, Italy), low or high molecular weight (MW) hyaluronic acid (HA), platelet-rich plasma (PRP) or triamcinolone hexacetonide (TH).

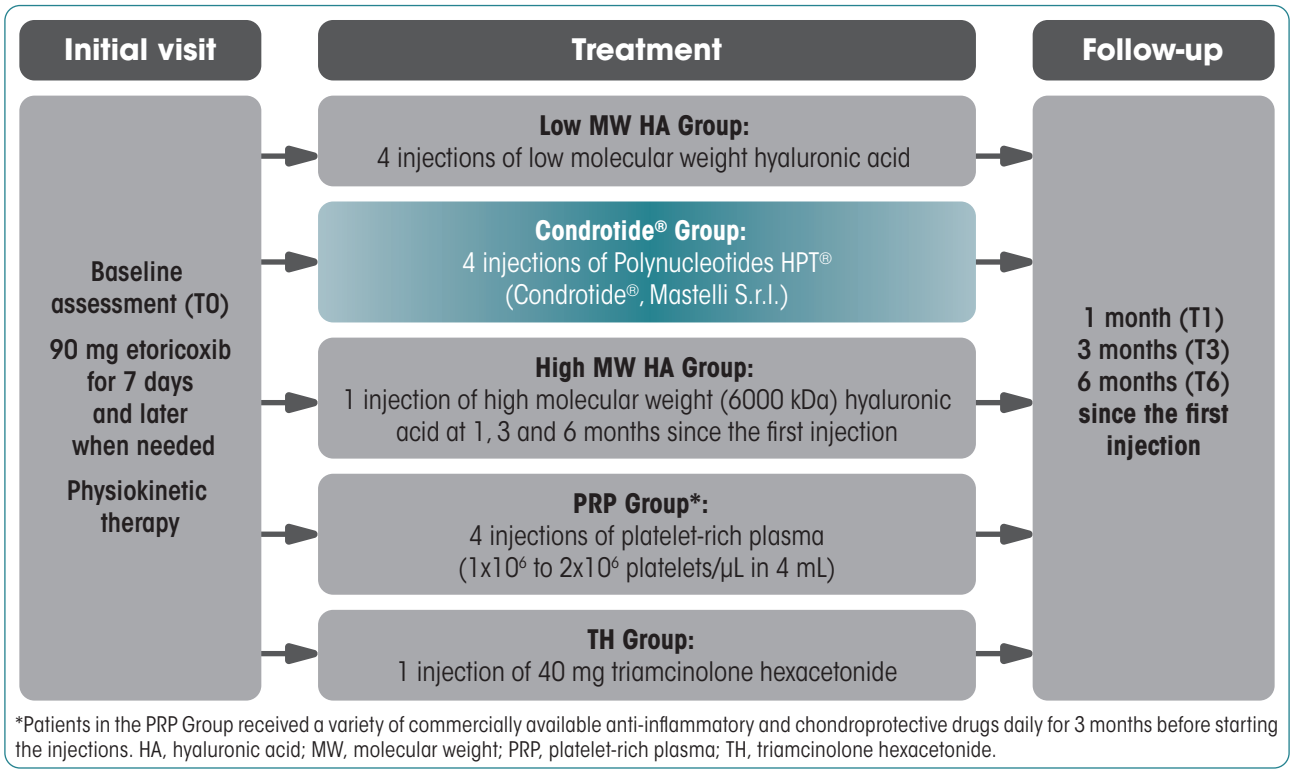
Study design

Patients: A total of 177 patients: 30 each in the Low MW HA Group and Condrotide® Group, 36 in the High MW HA Group, 31 in the PRP Group and 50 in the TH Group (overall 87 males/90 females, age ranging from 50 to 85 years) with class II or III OA of the knee. In the TH Group, the mean age was higher than in the other groups and OA was more advanced (class III versus class II).

Interventions: Patients received treatments as detailed in **Figure 10**. Patients could choose their treatment following an exhaustive explanation provided by their doctors[17,18].

Assessments: The following assessments were made:

- VAS score for subjective knee pain
- Knee Injury and Osteoarthritis Outcome Score (KOOS) scale
- Non-steroidal anti-inflammatory drugs (NSAIDs) consumption (the number of etoricoxib pills used per month).



*Patients in the PRP Group received a variety of commercially available anti-inflammatory and chondroprotective drugs daily for 3 months before starting the injections. HA, hyaluronic acid; MW, molecular weight; PRP, platelet-rich plasma; TH, triamcinolone hexacetonide.

Figure 10. Study design. Graphic elaboration from text [17].

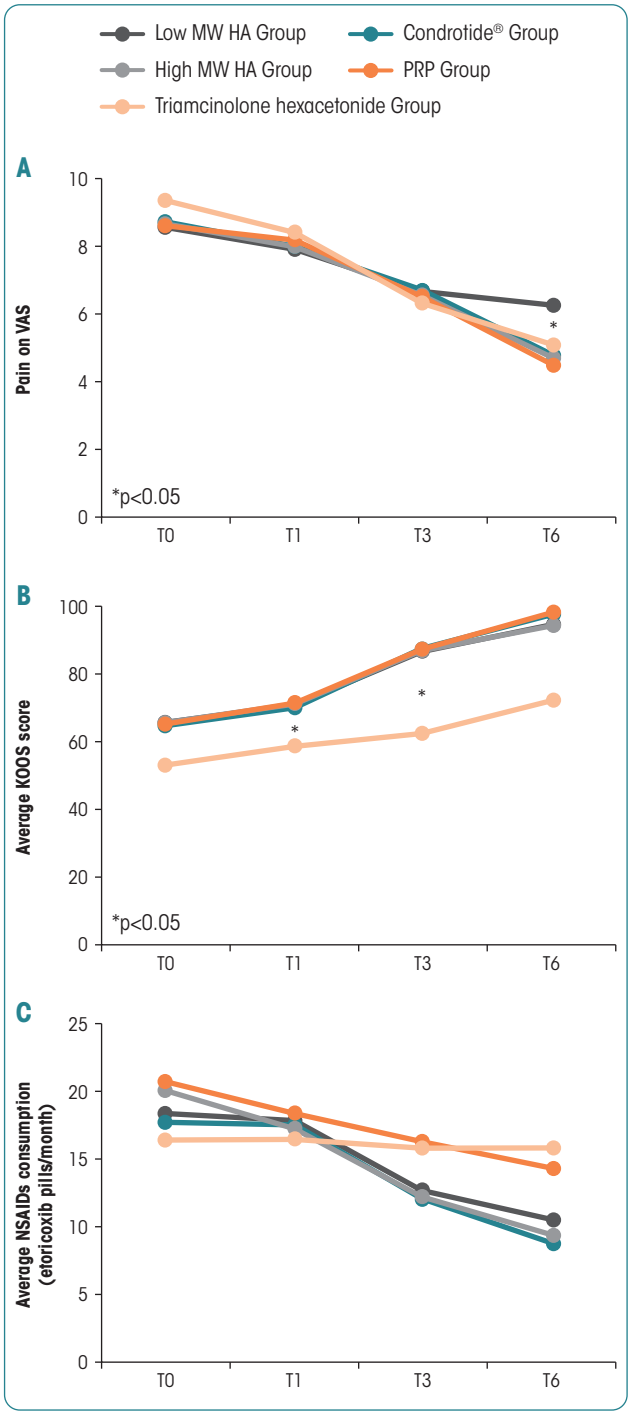


Figure 11. The evolution of subjective pain on VAS **(A)**, KOOS scale **(B)** and NSAIDs consumption **(C)** over the follow-up period in patients in the five treatment groups.
Statistically significant ($p<0.05$) differences between groups are shown as *.
HA, hyaluronic acid; MW, molecular weight; PRP, platelet-rich plasma. Graphic elaboration from text [17].

Results

There was no significant difference in the baseline pain level on VAS at the start of the study. Subjective pain decreased in all groups at all timepoints. At T6, there was a significant difference between the Low MW HA Group, with less improvement, and all other groups (**Figure 11A**).

KOOS values improved in all groups. There was a statistical difference in KOOS values between the TH Group and all other groups at all timepoints including baseline (**Figure 11B**).

At 6 months since the first injection, NSAIDs consumption was lowest in the Condrotide® Group (**Figure 11C**).

Conclusions

The management of OA and care for the ageing knee is complex. In advanced OA nonresponsive to common viscosupplementation, patients are offered knee replacement surgery. For selected patients, the different types of viscosupplementation, including intra-articular injections of Polynucleotides HPT® (Condrotide®, Mastelli S.r.l., Sanremo, Italy) tested in this study can relieve pain, improve function and may delay arthroplasty.

Intra-articular injections of Polynucleotides HPT® (Condrotide®) tested in this study can relieve pain, improve function and may delay arthroplasty in selected patients with advanced OA.

3.1.5 Study by Guelfi et al., 2020: a prospective case cohort versus historical controls to compare the effectiveness of Polynucleotides HPT® versus hyaluronic acid for the treatment of OA of the knee.

Reference [19]: Guelfi M, Fabbrini R, Guelfi MG. Intra-articular treatment of knee and ankle osteoarthritis with polynucleotides: prospective case record cohort vs historical controls. J Biol Regul Homeost Agents. 2020;34(5):1949-53.

Aim of the study

The aim of this study was to present the outcomes of a prospective record study of patients with OA of the knee treated with intra-articular injections of Polynucleotides HPT® (Condrotide®, Mastelli S.r.l., Sanremo, Italy) and to compare the results with historical outcomes obtained in a small subcohort of patients treated with hyaluronic acid.

Study design

Patients: A total of 146 patients (61 male/85 female, mean age 73 years, range: 47-82 years) with OA of the knee; 121 with grade 1-2 and 25 with grade 3-4 OA on the Kellgren-Lawrence scale. Eleven patients from the grade 1-2 subgroup had received injection of hyaluronic acid on average 1 year before receiving Polynucleotides HPT® and acted as a Historical Comparison Group.

Interventions: Patients received treatments as detailed in **Figure 12**.

Assessments: Western Ontario and McMaster Universities (WOMAC) questionnaire (total score ranging between 0 and 96; the higher the score, the worse the knee pain, stiffness and functional limitations) at baseline and follow-up.

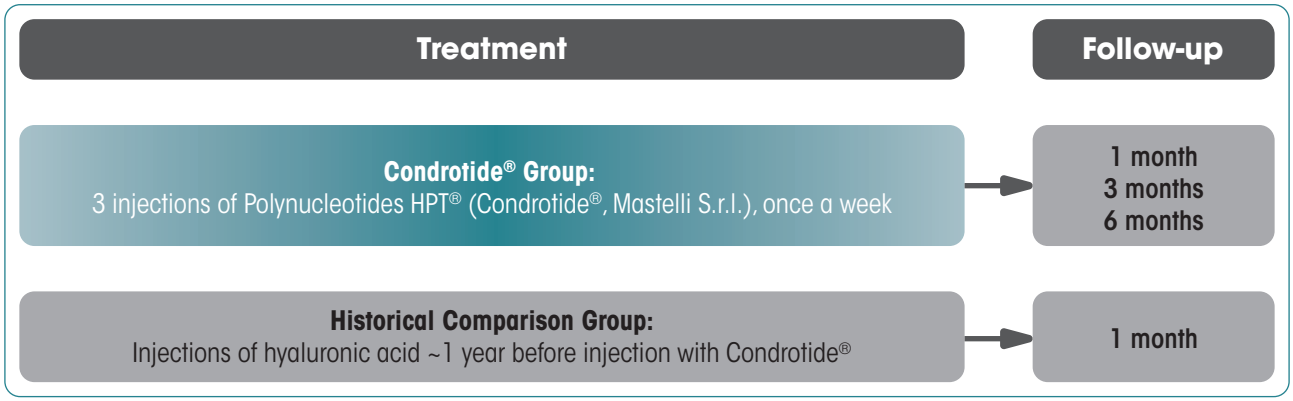


Figure 12. Study design. Graphic elaboration from text [19].

Results

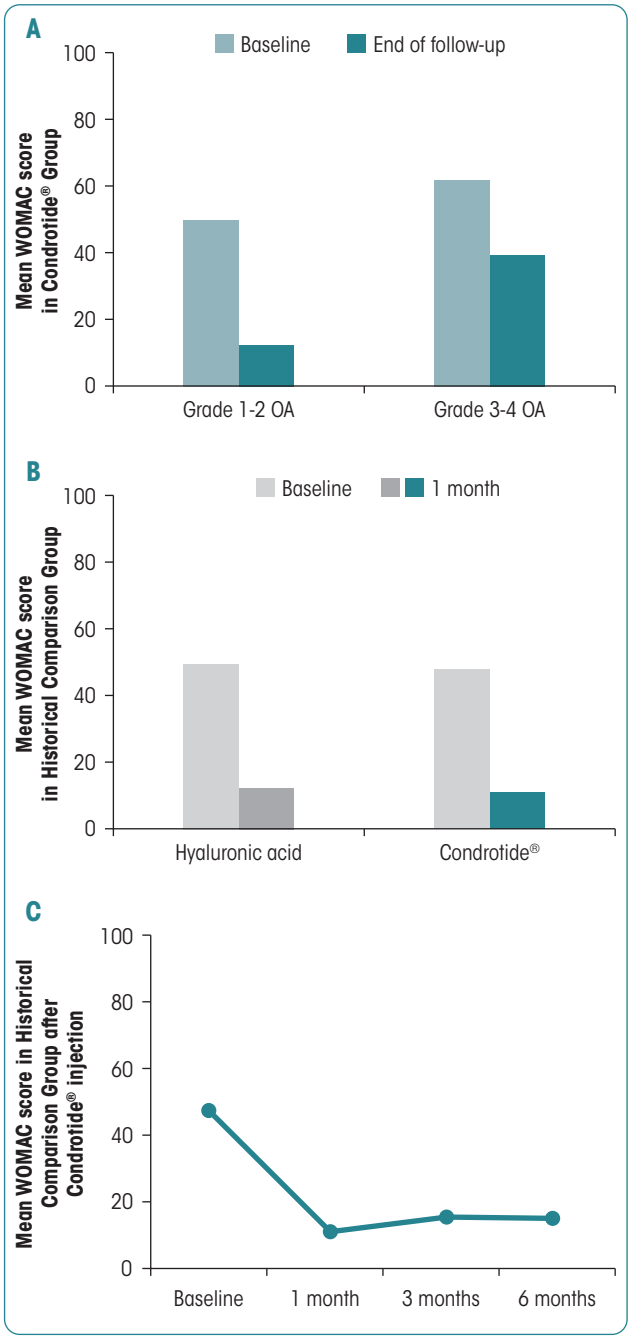
Following the treatment with Polynucleotides HPT®, the WOMAC score decreased from baseline to the end of follow-up by 75.5% for patients with grade 1-2 disease and by 37.7% for those with grade 3-4 OA of the knee (**Figure 13A**). The decrease in the WOMAC scale at month 1 was similar in patients treated with Polynucleotides HPT® (-76.6%) and in the Historical Comparison Group treated with hyaluronic acid (-75.5%) (**Figure 13B**). The WOMAC score decreased after one month and remained stable for the rest of the follow-up period (**Figure 13C**).

All patients reported less pain, a reduction in knee friction noises and an improvement in ROM.

Conclusions

With all the limitations of a retrospective non-controlled design, the study confirmed that intra-articular injections of Polynucleotides HPT® (Condrotide®, Mastelli S.r.l., Sanremo, Italy) can be an alternative, and possibly a complement, to hyaluronic acid in the relief of symptoms and improvement of QoL in patients with OA of the knee. Functional improvement measured by the WOMAC score at 1-month

Figure 13. Changes in WOMAC score: from baseline to month 6 in patients from the Condrotide® Group with grade 1-2 and 3-4 OA **(A)**; from baseline to month 1 in the Historical Comparison Group **(B)**; evolution of WOMAC score after intra-articular injections of Condrotide® over the duration of follow-up in the Historical Comparison Group **(C)**. The Historical Comparison Group is a subcohort of the Condrotide® Group treated with hyaluronic acid up to 1 year before receiving Condrotide®. Graphic elaboration from table [19].



follow-up was more pronounced in patients with grade 1-2 OA (-75.5%). However, a substantial WOMAC score decrease was also seen in patients with grade 3-4 disease, who would normally be candidates for arthroplasty. Based on this study and on published literature, the authors speculated that Polynucleotides HPT® might leverage their demonstrated chondrocyte activation. The chondrocyte activation obtained with Polynucleotides HPT® is stronger than that obtained with hyaluronic acid. Polynucleotides HPT® act as primers of cartilage reactivation, and their preliminary action is later completed by hyaluronic acid.

The study confirmed that Polynucleotides HPT® (Condrotide®) can be an alternative, and possibly a complement, to hyaluronic acid in the relief of symptoms and improvement of QoL in patients with OA of the knee.
Functional improvement measured by the WOMAC score at 1-month follow-up was more pronounced in patients with grade 1-2 OA (-75.5%). However, a substantial WOMAC score decrease was also seen in patients with grade 3-4 disease, who would normally be candidates for arthroplasty.

3.1.6 Study by Conforti, 2020: a retrospective study from a member of the International Association of Laser Therapy on the benefits of Polynucleotides HPT® combined with laser needling in physiatry and sports medicine to treat patients with primary and secondary OA of the knee.

Reference [20]: Conforti M. Laser needling® and natural origin, highly purified polynucleotides (PN-HPT®) in knee osteoarthrosis: benefits in physiatry and sports medicine. Int J Sports Sci Med. 2020;4:030-7.

Aim of the study

The aim of this study was to compare the 3-month efficacy and 6-month persistence of the clinical and functional benefits of the application of low level laser therapy either externally or intra-articulary (Laser Needling® technique), the latter combined with intra-articular injections of Polynucleotides HPT® (Condrotide®, Mastelli S.r.l., Sanremo, Italy) before the laser session, in patients with compromised efficiency of sports activities due to persistent pain and disability despite past treatment.

Study design

Patients: A total of 105 patients (55 male/50 female, mean age 58.4 ± 12.8 years, range: 25-75 years) with degenerative OA of the knee who had tibiofemoral lesions and refused surgery were treated with intra-articular injections of Polynucleotides HPT® followed by intra-articular AG8 laser therapy (Condrotide® Group). A total of 109 patients (54 male/55 female, mean age 47.9 ± 12.4 years) with similar disease severity were treated with a Fiber Power 3 (FP3) external treatment protocol and constituted the Comparison Group.

Interventions: Patients received treatments as detailed in **Figure 14**.

Assessments: The following assessments were made:

- Western Ontario and McMaster Universities (WOMAC) questionnaire at baseline and after a 2-week (T2) and 3-month (T3) follow-up period
- Subjective pain assessment on VAS immediately before and at the end of each treatment session.

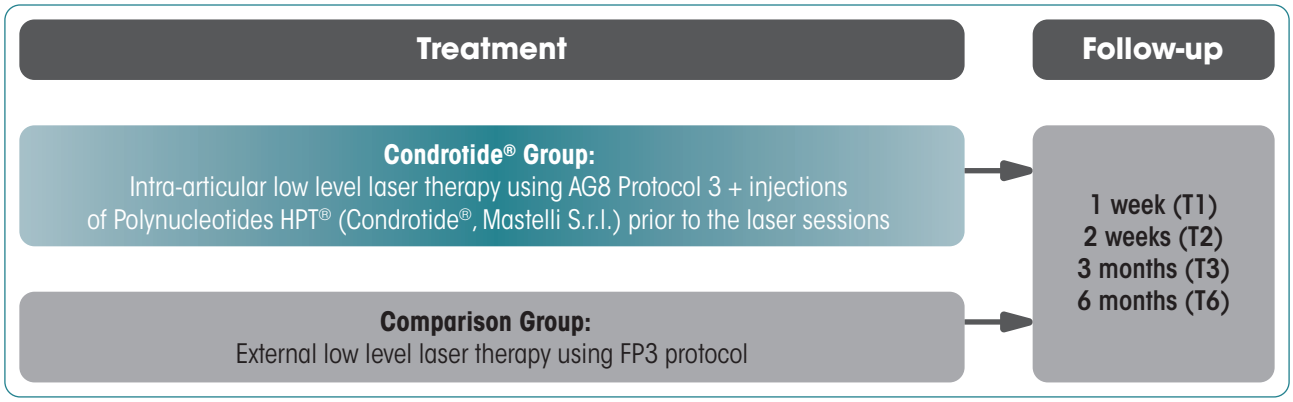


Figure 14. Study design. Graphic elaboration from text [20].

Results

The improvements in total WOMAC and subscores for pain and function at T2 were statistically greater in the Condrotide® Group than in the Comparison Group. The improvement in WOMAC stiffness was borderline not statistically significant (**Figure 15A-D**).

Similarly to the WOMAC Pain subscore, subjective pain on VAS improved to a greater extent in the Condrotide® Group (**Figure 16**). The improvement persisted after T6 (data not shown). Both patients with primary and secondary grade 2 OA benefited from the AG8/Polynucleotides HPT® treatment, especially those with primary grade 2 OA.

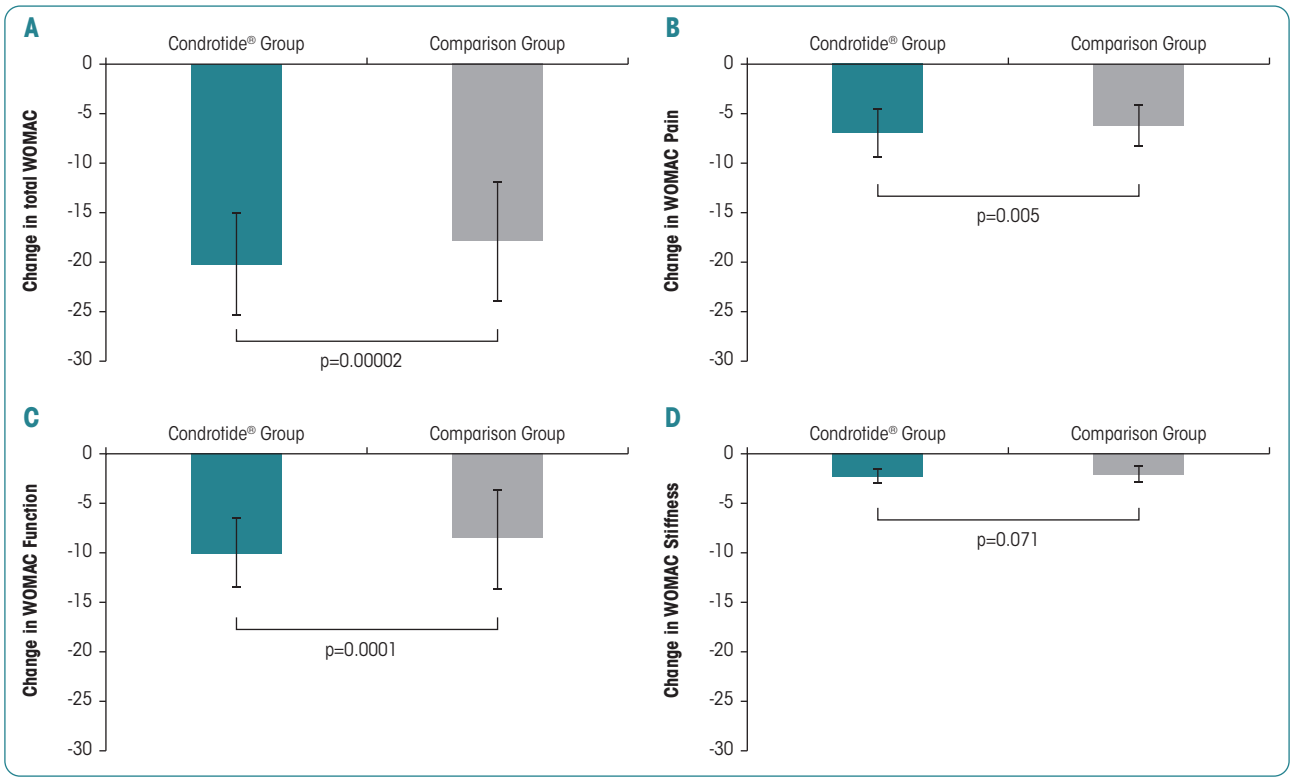
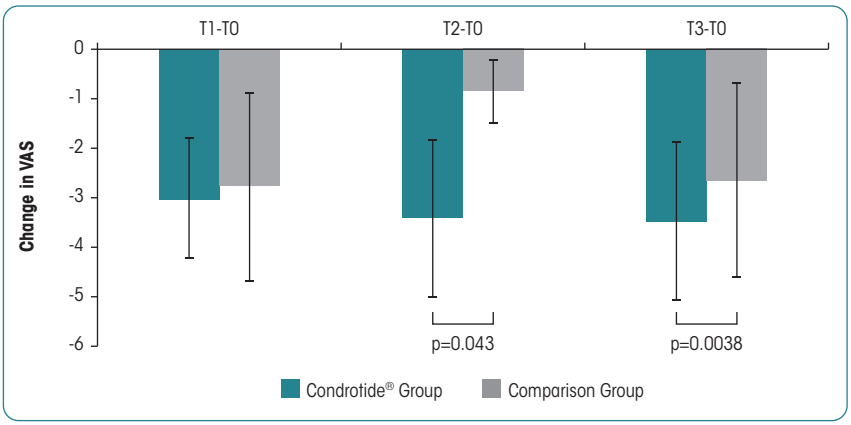


Figure 15. Changes in total WOMAC **(A)** and WOMAC Pain **(B)**, Function **(C)** and Stiffness **(D)** subscores from baseline to week 2 in the Condrotide® and Comparison Groups. Graphic elaboration from table [20].

Figure 16. Changes in subjective pain on VAS from baseline to T1, T2 and T3 in the Condrotide® (AG8+Polynucleotides HPT®) and Comparison (FP3) Groups. Graphic elaboration from table [20].



Conclusions

The intra-articular injections of Polynucleotides HPT® (Condrotide®, Mastelli S.r.l., Sanremo, Italy) followed by the intra-articular Laser Needling® technique using the multi-channel AG8 laser device is a novel procedure to target OA-related pain. This procedure was shown to be more effective than the traditional external FP3 laser technique at reducing pain in OA of the knee and especially the pain associated with primary OA.

The intra-articular injection of Polynucleotides HPT® (Condrotide®) followed by the intra-articular Laser Needling® technique using the multi-channel AG8 laser device is a novel procedure to target OA-related pain. This procedure was more effective than the traditional external FP3 laser at reducing pain in OA, and especially the pain associated with primary OA.

3.2 Clinical benefits of the use of Polynucleotides HPT® in the treatment of OA of the hip joint

3.2.1 Study by Tormenta et al., 2013: important early evidence of the suitability of intra-articular injections of Polynucleotides HPT® to treat patients affected by hip OA.

Reference [21]: Tormenta S, Arduini F, Migliore A, Bizzi E. Report of results in terms of efficacy and safety for the use of Condrotide® in 23 patients suffering for a monolateral hip osteoarthritis undergoing to a cycle of ultrasound-guided intra-articular injections. European Congress of Radiology; 2013; Wien. Poster number C-2250.

Aim of the study

The aim of this study was to assess the efficacy and safety of the ultrasound-guided intra-articular injections of 4 mL of Polynucleotides HPT® (Condrotide®, Mastelli S.r.l., Sanremo, Italy) in patients affected by unilateral OA of the hip.

Study design

Patients: Twenty-three patients with grade 1-3 OA of the hip on the Kellgren-Lawrence scale.

Interventions: Patients received treatments as detailed in **Figure 17**.

Assessments: The following assessments were made:

- VAS for subjective pain
- Lequesne index for hip joint function (11 items resulting in a total score of 24; the lower the score, the better the hip joint status)
- Knee Injury and Osteoarthritis Outcome Score (KOOS) subscales
- Non-steroidal anti-inflammatory drugs (NSAIDs) consumption.

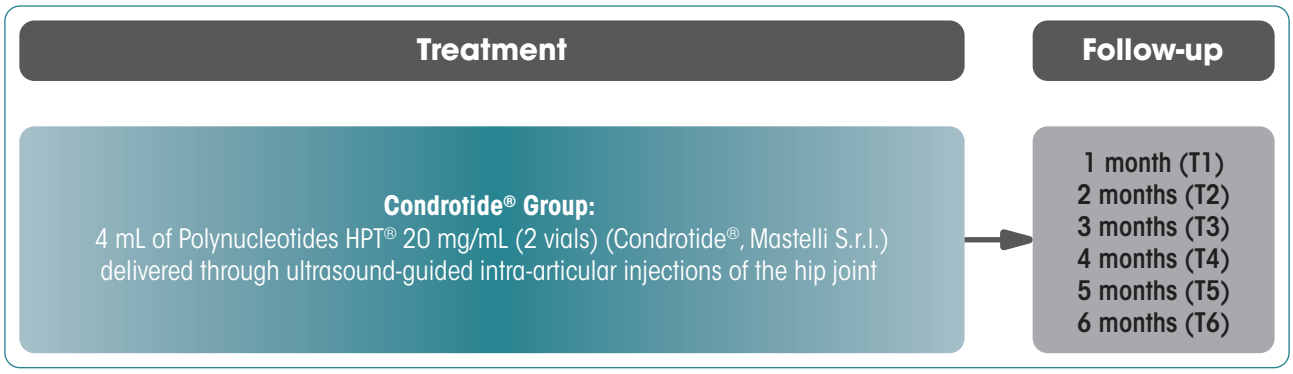


Figure 17. Study design. Graphic elaboration from text [21].

Results

The improvement in pain assessed on VAS occurred early and lasted for the entire duration of the study (**Figure 18A**). There was a reduction in joint function impairment measured by Lequesne index (**Figure 18B**) and KOOS score (**Figure 18C**). There was also a statistically significant reduction of NSAIDs consumption ($p<0.05$).

Conclusions

The use of ultrasound-guided intra-articular injections of Polynucleotides HPT® (Condrotide®, Mastelli S.r.l., Sanremo, Italy) seemed to be effective and safe in patients with OA of the hip. The reduction in pain, the functional improvements and the reduction of NSAIDs consumption ameliorate the quality of life of patients with OA and may result in savings for both patients and healthcare systems. Thus, the intra-articular use of Polynucleotides HPT® represents a suitable option for patients affected by OA of the hip.

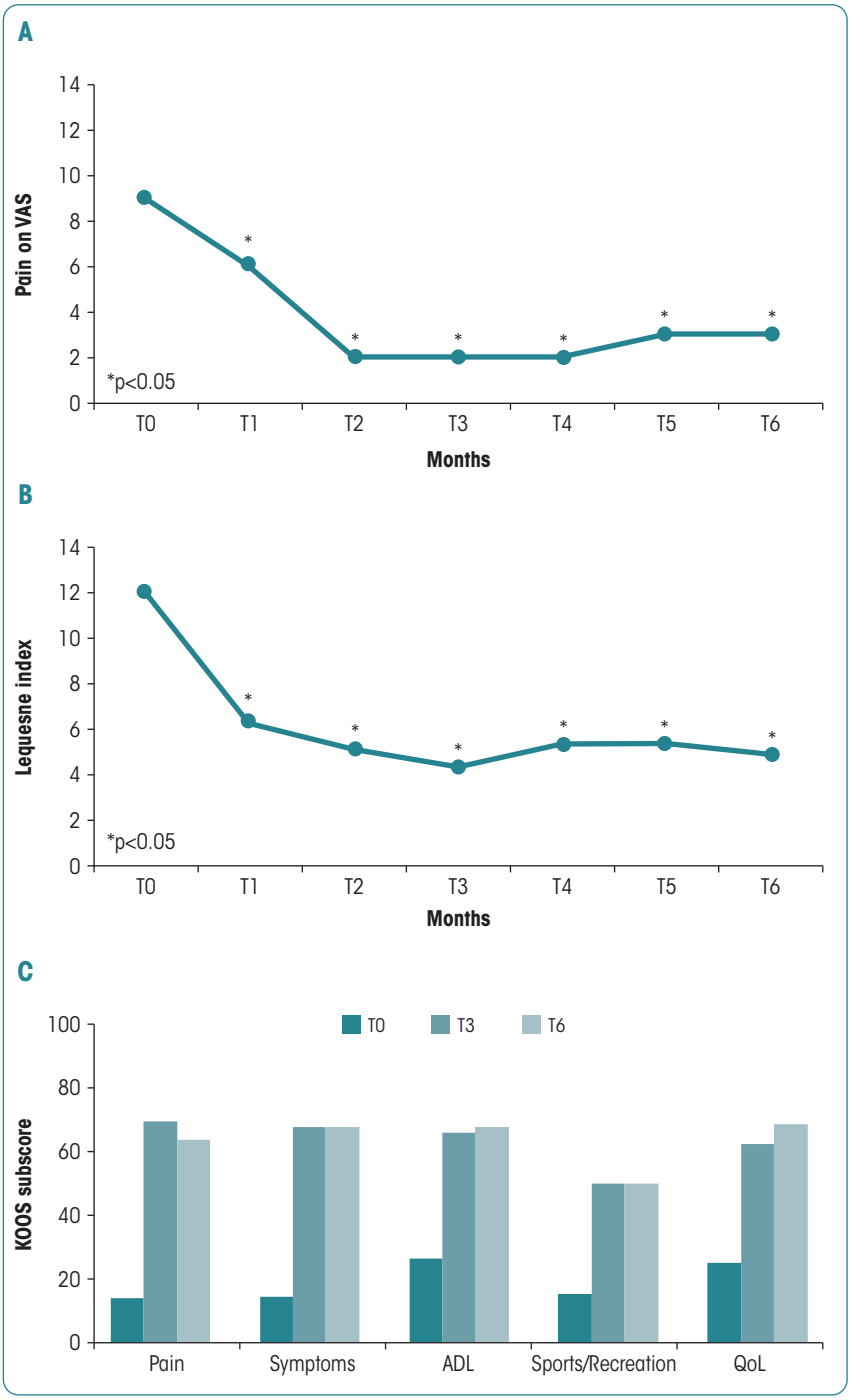


Figure 18. Improvements in subjective pain on VAS **(A)**, in Lequesne index for joint function **(B)** and in KOOS subscores **(C)** in patients treated with Condrotide®. ADL, activities of daily living; QoL, quality of life. Graphic elaboration from table and figure [21].

The use of ultrasound-guided intra-articular injections of Polynucleotides HPT® (Condrotide®), seemed to be effective and safe in patients with OA of the hip. The reduction in pain, the functional improvements and the reduction of NSAIDs consumption ameliorate the quality of life of patients with OA and may result in savings for both patients and healthcare systems.

3.2.2 Study by Migliore et al., 2021: a real-life retrospective cohort study of patients treated with intra-articular Polynucleotides HPT® injections to treat OA of the hip joint with a 3-year follow-up.

Reference [22]: Migliore A, Graziano E, Martin LSM et al. Three-year management of hip osteoarthritis with intra-articular polynucleotides: a real-life cohort retrospective study. J Biol Regul Homeost Agents. 2021;35(3):1189-94.

Aim of the study

The aim of this study was to illustrate the real-life clinical evolution over a 3-year follow-up of patients with OA of the hip joint treated with intra-articular injections of Polynucleotides HPT® (Condrotide®, Mastelli S.r.l., Sanremo, Italy).

Study design

Patients: Forty-three patients (20 male/23 female, mean age 60 ± 18.5 years) with uni- or bilateral OA of the hip of at least 1 year's duration; 47% with grade 2 and 53% with grade 3 OA on the Kellgren-Lawrence scale.

Interventions: Patients received treatments as detailed in **Figure 19**.

Assessments: The following assessments were made:

- Subjective pain on VAS
- Lequesne index
- Non-steroidal anti-inflammatory drugs (NSAIDs) consumption
- Global Medical and Patient Assessments (GMA/GPA).

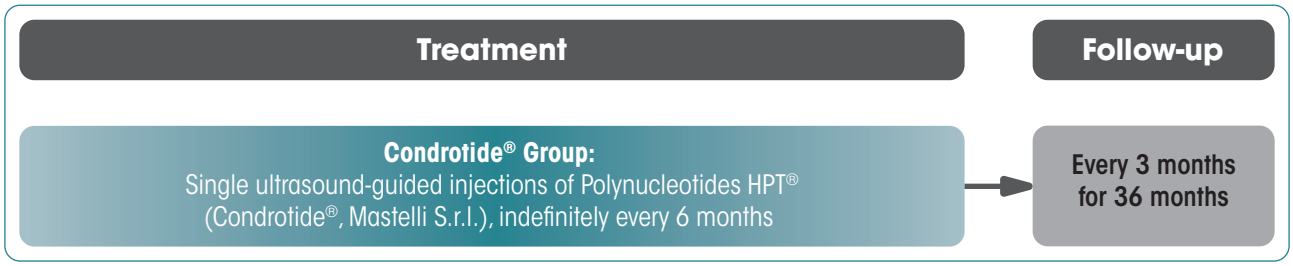


Figure 19. Study design. Graphic elaboration from text [22].

Results

Twenty-one patients completed the study; 11 patients dropped out as they underwent total hip replacement, 9 were lost to follow-up and two died. There was a significant reduction in subjective pain on VAS, in the Lequesne index score and NSAIDs consumption from baseline to month 6 ($p<0.05$). After this initial improvement of all three parameters, subjective pain remained stable over the second year of follow-up and fell again at the end of the 36-month follow-up. NSAIDs consumption was further reduced at month 18 and 36. The Lequesne index continued to improve over the second year of follow-up to the end of follow-up at 36 months (**Figure 20A**). Moreover, the GMA (structured medical assessment) of hip pain and function and GPA (subjective patient assessment) showed a steady improvement over the 36 months of follow-up (**Figure 20B**).

Conclusions

The study confirmed the published effectiveness and safety of intra-articular injections of Polynucleotides HPT® (Condrotide®, Mastelli S.r.l., Sanremo, Italy) and demonstrated that polynucleotides do not lose effectiveness over time and after more than two injection cycles. The authors concluded that the rapid and steady improvement in pain and function, and the reduction in NSAIDs consumption, suggest that viscosupplementation with Polynucleotides HPT® can be helpful in all age groups. The improvements occurred rapidly over the first 6 months and continued throughout the remaining 30 months of follow-up.

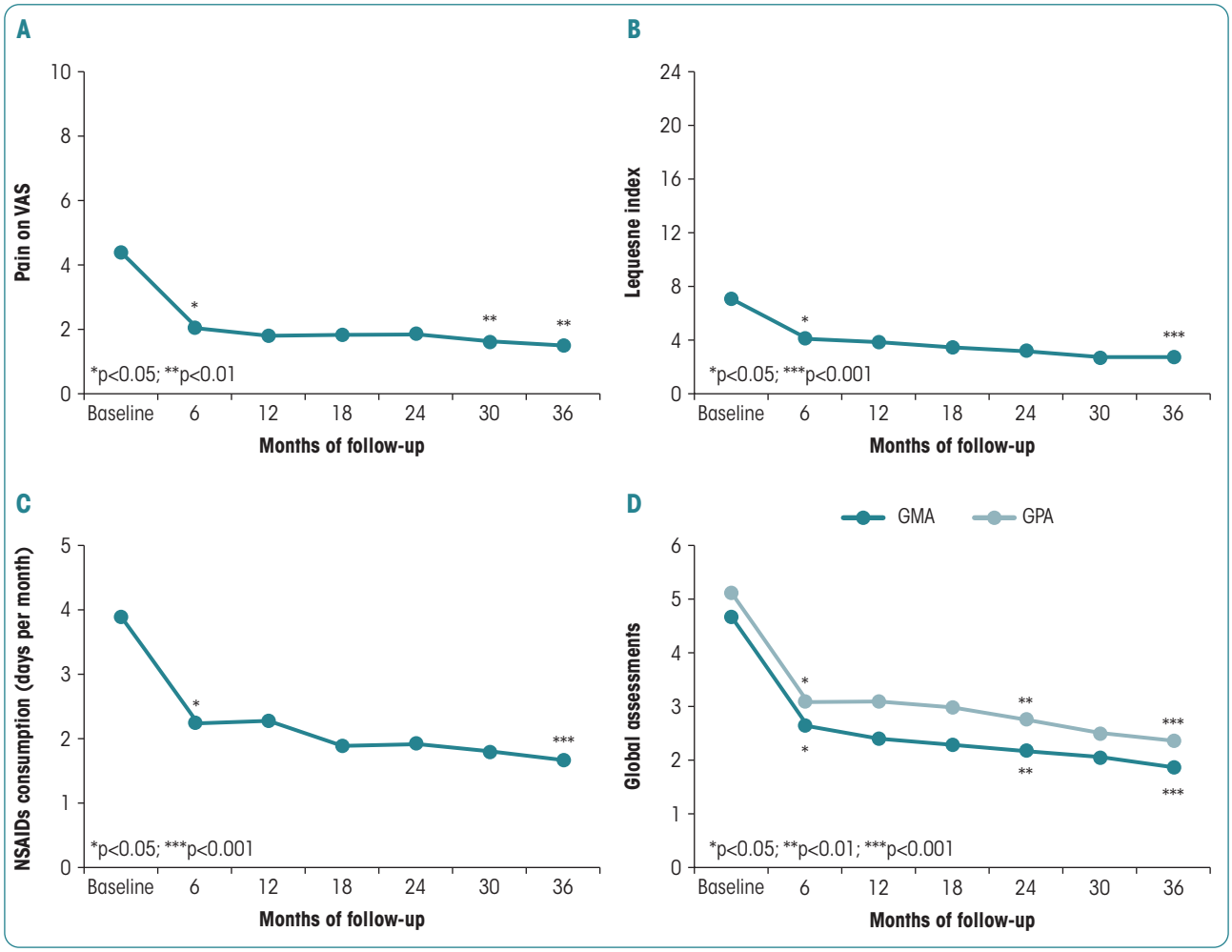


Figure 20. Evolution of subjective pain on VAS **(A)**, Lequesne index **(B)** and NSAIDs consumption **(C)** and of GMA and GPA **(D)** over the follow-up of 36 months in patients treated with Condrotide®. Statistically significant differences from baseline are shown as * p<0.05; ** p<0.01; *** p<0.001. GMA, Global Medical Assessment; GPA, Global Patient Assessment. Graphic elaboration from figures [22].

The rapid and steady improvement in pain and function, and the reduction in NSAIDs consumption, suggest that viscosupplementation with 4 mL of Polynucleotides HPT® (Condrotide®) can be helpful in all age groups. The improvements occurred rapidly over the first 6 months and continued throughout the remaining 30 months of follow-up.

3.3 Clinical benefits of the use of Polynucleotides HPT® in the treatment of OA of the shoulder

3.3.1 Study by Saggini et al., 2014: a good size randomised study of intra-articular injections of Polynucleotides HPT®, hyaluronic acid and lidocaine to treat OA of the shoulder.

Reference [23]: Saggini R, Distefano AG, Capogrosso F et al. Viscosupplementation with hyaluronic acid or polynucleotides: results and hypothesis for condro-synchronization. J Clin Trials. 2014;4:1-4.

Aim of the study

The aim of this study was to compare the efficacy of viscosupplementation with intra-articular injections of hyaluronic acid versus Polynucleotides HPT® (Condrotide®, Mastelli S.r.l., Sanremo, Italy) in the treatment of patients with rotator cuff syndrome with incomplete lesion of the supraspinatus muscle.

Study design

Patients: A total of 165 patients (97 male/68 female, average age 55 years) with shoulder pain due to rotator cuff syndrome with incomplete injury of the supraspinatus tendon confirmed clinically and by ultrasound and magnetic resonance imaging (MRI).

Interventions: Patients received treatments as detailed in **Figure 21**.

All patients were subjected to three weekly 45-minute sessions of upper limb proprioception and joint range of motion (ROM) functional recovery with a Multi Joint System.

Assessments: The following assessments were made at baseline, at the end of the treatment period (30 days) and at 90 and 120 days from baseline:

- VAS score for subjective pain
- Constant-Murley score (a simple standardised method for clinical assessment of shoulder function on a scale from 0 to 100 points; the higher the score, the better the function)
- Measurement of shoulder's ROM for flexion and abduction-adduction
- Davies isokinetic test at an angular velocity of 90°/sec.

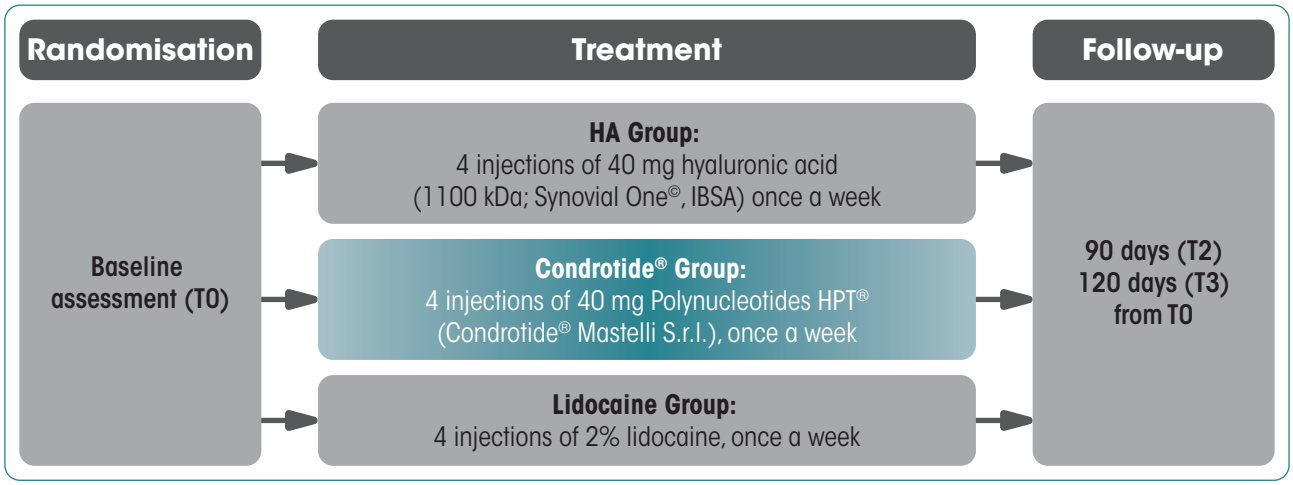


Figure 21. Study design. Graphic elaboration from text [23].

Results

In the Hyaluronic Acid and Condrotide® Groups, a significant reduction of pain on VAS, an increase in Constant-Murley score, joint ROM and in the values of peak moment of maximum force, both for the external and intra-rotators were observed.

Patients in the Lidocaine Group experienced a non-significant reduction of pain only at the end of treatment (T1) (VAS 8.05 at T0 and 5.5 at T1) (**Figure 22**).

Conclusions

The results of viscosupplementation with intra-articular injections of either hyaluronic acid or Polynucleotides HPT® (Condrotide®, Mastelli S.r.l., Sanremo, Italy) provided short and medium-term improvements and were comparable in the two groups. The authors hypothesised that combined viscosupplementation with hyaluronic acid and Polynucleotides HPT® given together or delayed could provide further improvement in the long term or that alternating the two agents would be a better treatment.

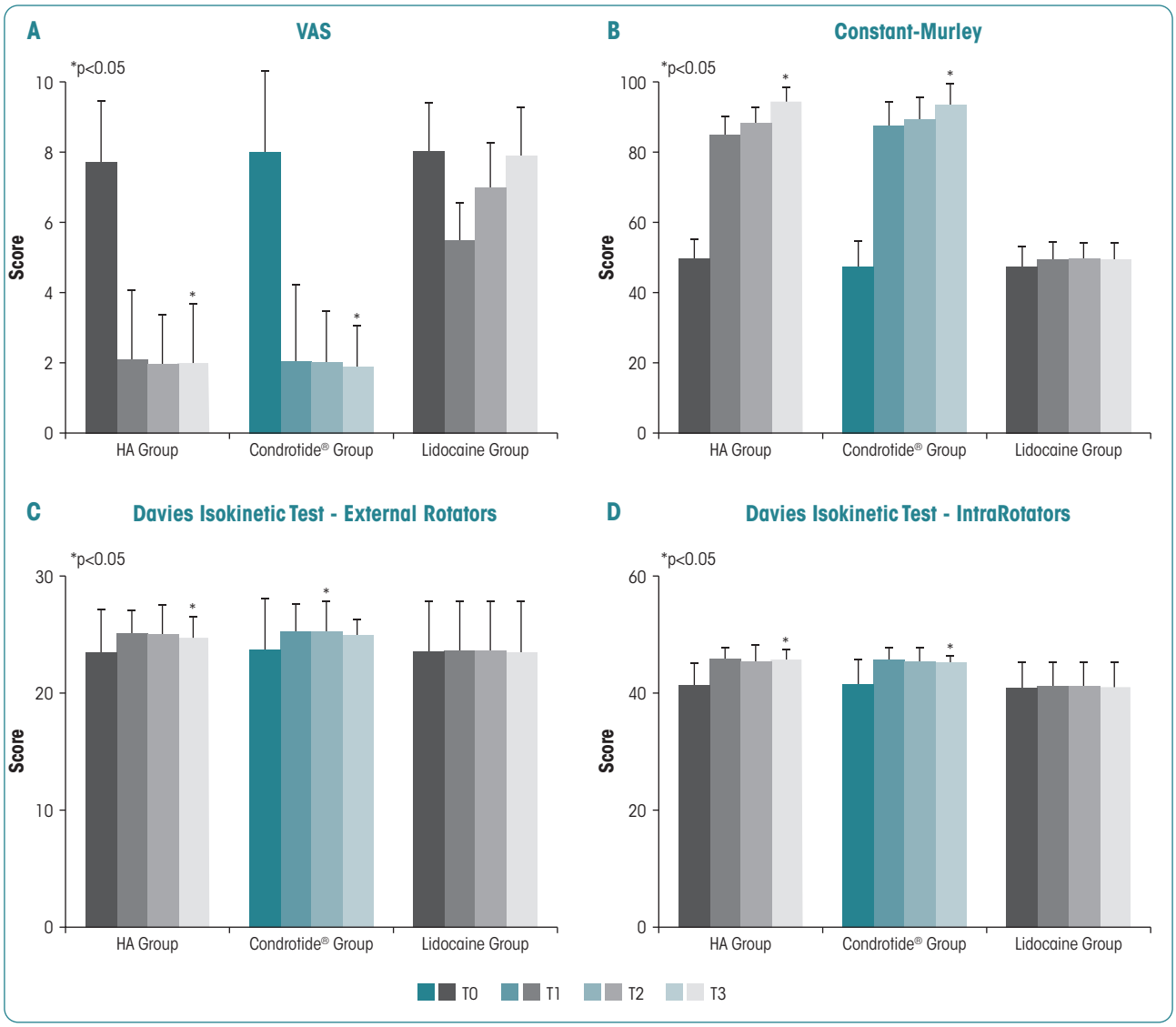


Figure 22. Evolution of pain on VAS **(A)**, Constant-Murley score **(B)** and Davies isokinetic tests **(C, D)** at baseline (T0), end of treatment (T1) and follow-up at 90 (T2) and 120 (T3) days in the Hyaluronic Acid, Condrotide® and Lidocaine Groups. Statistically significant differences from baseline are marked with * (p<0.05). Graphic elaboration from figures [23].

> *The authors hypothesised that combined viscosupplementation with hyaluronic acid and Polynucleotides HPT® (Condrotide®) given together or delayed could provide further improvement in the long term or that alternating the two agents would be a better treatment.*

3.4 Clinical benefits of the use of Polynucleotides HPT® in the treatment of OA of the ankle

3.4.1 Study by Guelfi et al., 2020: a prospective case cohort versus historical controls to compare the effectiveness of Polynucleotides HPT® versus hyaluronic acid for the treatment of OA of the ankle.

Reference [19]: Guelfi M, Fabbrini R, Guelfi MG. Intra-articular treatment of knee and ankle osteoarthritis with polynucleotides: prospective case record cohort vs historical controls. J Biol Regul Homeost Agents. 2020;34(5):1949-53.

Aim of the study

The aim of this study was to present the outcomes of a prospective case record study of patients with OA of the ankle treated with intra-articular injections of Polynucleotides HPT® (Condrotide®, Mastelli S.r.l., Sanremo, Italy) and to compare the results with historical outcomes obtained in a small cohort of patients treated with hyaluronic acid.

Study design

Patients: A total of 56 patients (32 male/24 female, mean age 62 years, range: 40-70 years) with OA of the ankle; 50 with grade 1-2 and six with grade 3-4 OA on the Kellgren-Lawrence scale. Nine patients from the grade 1-2 subgroup had received several intra-articular injections of a medium molecular weight hyaluronic acid (HA) gel on average 1 year before receiving Polynucleotides HPT® and acted as a Historical Comparison Group.

Interventions: Patients received treatments as detailed in **Figure 23**.

Assessments: 42-item Foot and Ankle Outcome Score (FAOS) questionnaire (total score ranging between 0 and 100; the higher the score, the better the foot or ankle status) at baseline and follow-up.

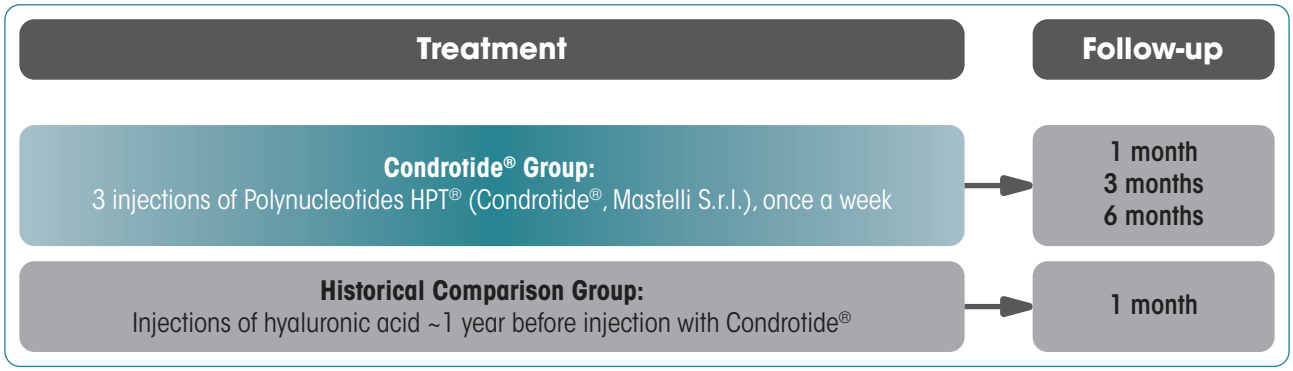


Figure 23. Study design. Graphic elaboration from text [19].

Results

The FAOS score increased from baseline to the end of follow-up by 94.3% for patients with grade 1-2 disease and by 323.1% for those with grade 3-4 OA (**Figure 24A**). The increase in the FAOS score at month 1 was higher in patients treated with Polynucleotides HPT® in the Condrotide® Group (80.7%, $p<0.05$ versus hyaluronic acid) than in the Historical Comparison Group treated with hyaluronic acid (67.8%) (**Figure 24B**). After treatment with Polynucleotides HPT®, the FAOS score increased after one month and remained stable for the rest of the follow-up period (**Figure 24C**).

All patients reported less pain, a reduction in joint friction noises and an improvement in range of motion.

Conclusions

Despite the limitations of a retrospective non-controlled design, the study confirmed that intra-articular injections of Polynucleotides HPT® (Condrotide®, Mastelli S.r.l., Sanremo, Italy) can be an alternative, and possibly a complement, to hyaluronic acid in the relief of symptoms and improvement of QoL in patients with OA of the ankle. Functional improvement measured by the FAOS score at 1-month follow-up was more

pronounced in patients with mild and moderate OA, i.e., grade 1-2. However, a substantial FAOS score improvement was also seen in patients with grade 3-4 disease, who would normally be candidates for joint replacement surgery.

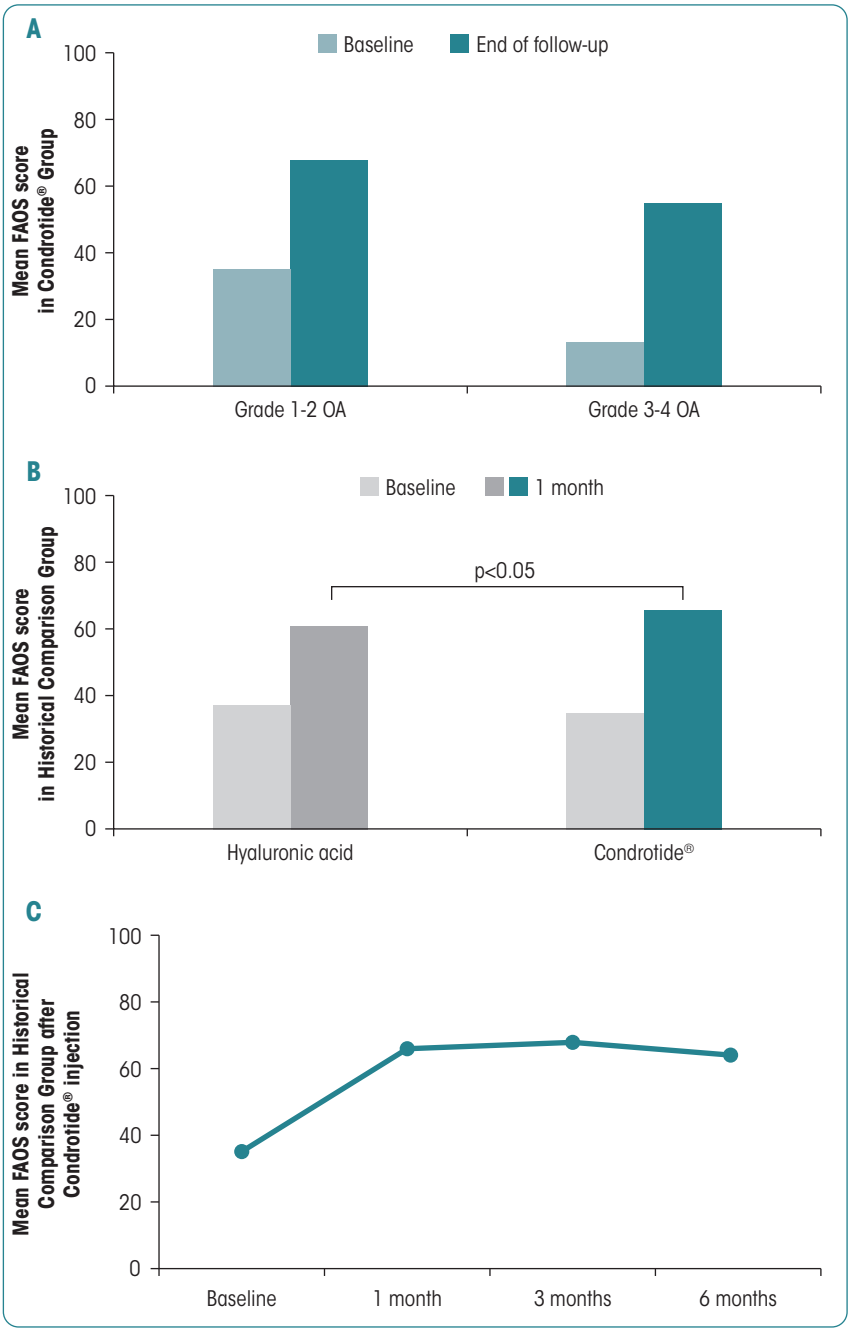


Figure 24. Changes in FAOS score: from baseline to month 6 in patients with grade 1-2 and 3-4 OA in the Condrotide® Group **(A)**; from baseline to month 1 in patients in the Historical Comparison Group **(B)**; evolution of FAOS score over the duration of the follow-up in the Historical Comparison Group **(C)**. The Historical Comparison Group is a subcohort of the Condrotide® Group treated with hyaluronic acid up to 1 year before receiving Condrotide®. Graphic elaboration from table [19].

The study confirmed that Polynucleotides HPT® (Condrotide®) intra-articular injections can be an alternative, and possibly a complement, to hyaluronic acid use in the relief of symptoms and improvement of QoL in patients with OA of the ankle.

3.5 Combined treatment with Polynucleotides HPT® and hyaluronic acid in the treatment of OA

3.5.1 Study by Dallari et al., 2020: a randomised double-blind controlled clinical trial of intra-articular injections of combined Polynucleotides HPT®/hyaluronic acid versus hyaluronic acid alone in the treatment of OA of the knee from the Rizzoli Orthopaedic Institute in Bologna.

Reference [24]: Dallari D, Sabbioni G, Del Piccolo N et al. Efficacy of intra-articular polynucleotides associated with hyaluronic acid versus hyaluronic acid alone in the treatment of knee osteoarthritis: a randomized, double-blind, controlled clinical trial. Clin J Sport Med. 2020;30(1):1-7.

Aim of the study

The aim of this study was to compare the outcomes of intra-articular injections of the combination of Polynucleotides HPT®/hyaluronic acid (Condrotide® HA, Mastelli S.r.l., Sanremo, Italy) versus hyaluronic acid alone in patients affected by OA of the knee.

Study design

Patients: A total of 98 out of 100 screened patients were enrolled (46 male/54 female, mean age 63.8 years, range: 50-75 years) with OA of the knee; 49 patients were randomly assigned to the Condrotide® HA Group (Polynucleotides HPT®/hyaluronic acid) and 49 to the Comparison Group (hylauronic acid). There were no differences between the groups regarding baseline demographic and disease characteristics.

Interventions: Patients received treatments as detailed in **Figure 25**.

Assessments: Knee Society Score (KSS) at all timepoints, Western Ontario and McMaster Universities (WOMAC) questionnaire at all timepoints.

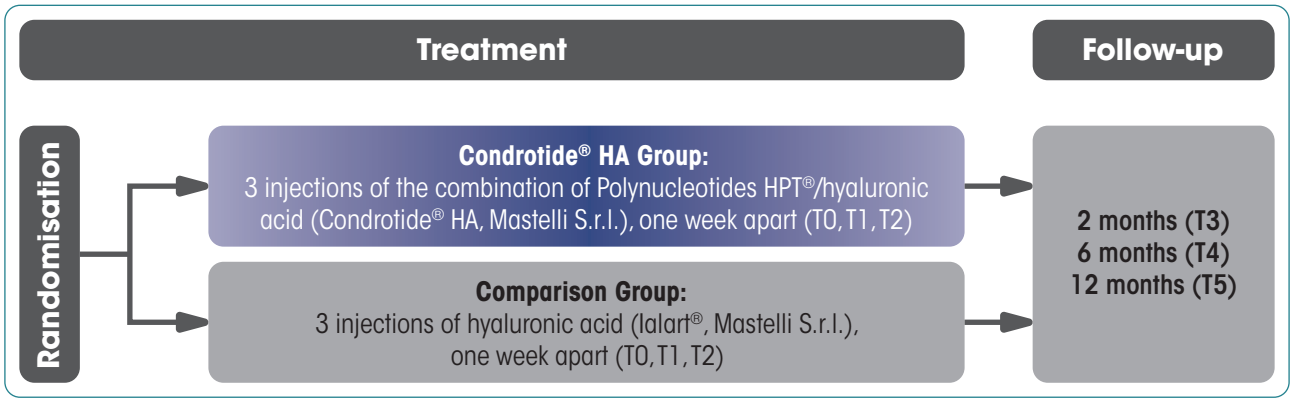


Figure 25. Study design. Graphic elaboration from text [24].

Results

The total KSS score showed significantly better results in the Condrotide® HA than in the Comparison Group ($p<0.05$ at T3, T4, and $p=0.009$ at T5) (**Figure 26A**). The results were also significantly better in the Condrotide® HA Group than in the Comparison Group for the KSS Pain subscore at T3 and at T5 ($p<0.05$) (**Figure 26B**).

A significant decrease was observed for the WOMAC Pain subscore between T0-T3, T0-T4 ($p<0.0005$), and T0-T5 ($p<0.005$) in the Condrotide® HA Group. In the Comparison Group, a significant reduction of pain was observed between T0-T3 and T0-T4 ($p<0.05$) but to a lesser extent than in the Condrotide® HA Group (**Figure 26C**).

Conclusions

This was the first clinical study conducted as a randomised double-blind controlled clinical trial that used intra-articular injections of a combination of Polynucleotides HPT® and hyaluronic acid in a single formulation (Condrotide® HA, Mastelli S.r.l., Sanremo, Italy) for the treatment of OA of

the knee and compared it to hyaluronic acid alone (Ialart®). After 1 year of follow-up, the study showed the superiority of the combined Polynucleotides HPT®/hyaluronic acid treatment over hyaluronic acid alone in reducing pain and improving overall knee function measured by the KSS score.

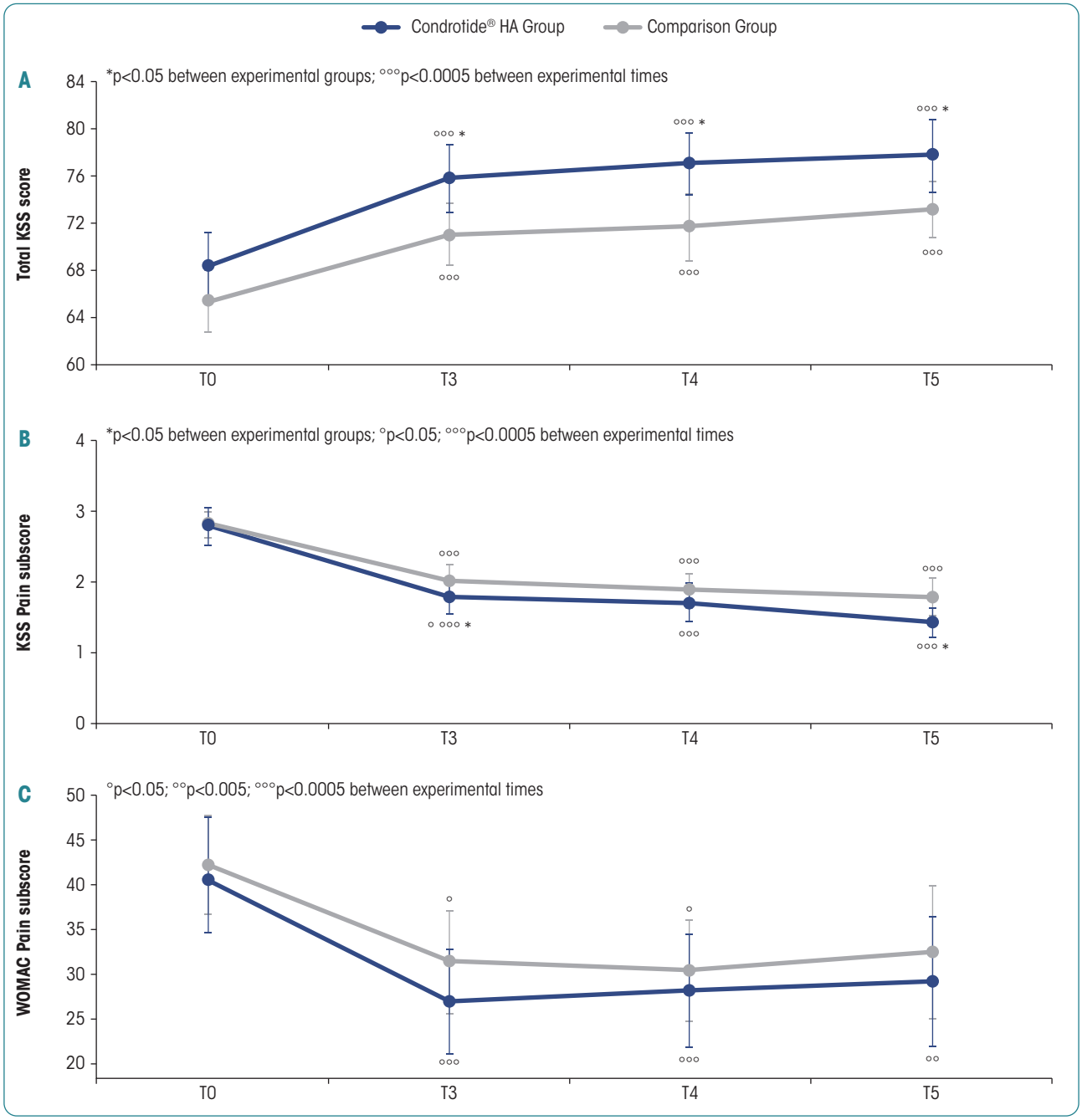


Figure 26. Mean and 95% CI of the improvements in the total KSS score **(A)**, KSS Pain subscore **(B)** and WOMAC Pain subscore **(C)** from baseline to the indicated timepoints. * p<0.05 between experimental groups; ° p<0.05, °° p<0.005, °°° p<0.0005 between experimental times. Graphic elaboration from figures [24].

This was the first clinical study conducted as a randomised double-blind controlled clinical trial that used a combination of Polynucleotides HPT® and hyaluronic acid in a single formulation (Condrotide® HA) for the treatment of OA of the knee and compared it to hyaluronic acid alone.

3.5.2 Study by Stagni et al., 2021: 2-year follow-up of the randomised double-blind controlled clinical trial of intra-articular injections of combined Polynucleotides HPT®/hyaluronic acid versus hyaluronic acid alone in the treatment of OA of the knee from the Rizzoli Orthopaedic Institute in Bologna originally published by Dallari et al. in 2020.

Reference [25]: Stagni C, Rocchi M, Mazzotta A et al. Randomised, double-blind comparison of a fixed co-formulation of intra-articular polynucleotides and hyaluronic acid versus hyaluronic acid alone in the treatment of knee osteoarthritis: two-year follow-up. BMC Musculoskelet Disord. 2021;22(1):773.

Aim of the study

The aim of this study was to verify whether intra-articular injections of the combination of Polynucleotides HPT®/hyaluronic acid (Condrotide® HA, Mastelli S.r.l., Sanremo, Italy) would reduce pain and restore function more than hyaluronic acid (Ialart®) alone in patients affected by OA of the knee and to assess whether such synergy persisted over a follow-up of 2 years. This study follows on from the study by Dallari et al.[23].

Study design

Patients: A total of 98 out of 100 screened patients were enrolled (46 male/54 female, mean age 63.8 years, range: 50-75 years) with OA of the knee; 49 patients were randomly assigned to the Condrotide® HA Group (Polynucleotides HPT®/hyaluronic acid) and 49 to the Comparison Group (hyaluronic acid). There were no differences between the groups regarding baseline demographic and disease characteristics.

Interventions: Patients received treatments as detailed in **Figure 27**.

Assessments: Western Ontario and McMaster Universities (WOMAC) questionnaire at all timepoints (WOMAC Pain – the primary endpoint), Knee Society Score (KSS) at all timepoints.

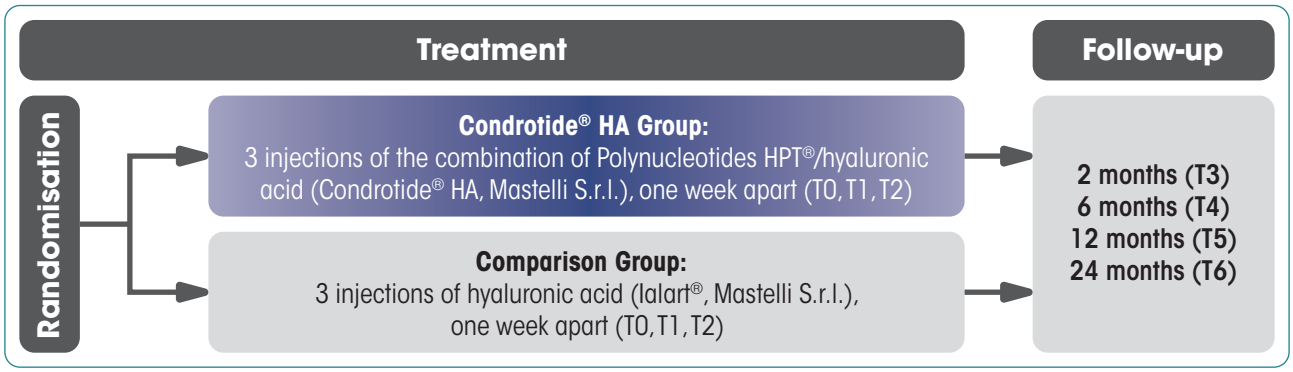


Figure 27. Study design. Graphic elaboration from text [25].

Results

Seventy-nine patients completed the 2-year study.

The reduction in WOMAC Pain score over time in the Condrotide® HA Group was greater than in the Comparison Group and the two curves were statistically different (one-way ANOVA, p=0.029). The separation of the two curves occurred early and persisted over time (**Figure 28A**). The other WOMAC subscores did not show differences between the two groups. The item "Walking on a flat surface" and the total WOMAC score tended to show more improvement in the Condrotide® HA Group than in the Comparison Group.

The KSS total scores over the first year were always significantly higher in the Condrotide® HA Group compared to the Comparison Group at all follow-up assessments (p=0.02 at T3 and p=0.001 at both T4 and T5) (**Figure 28B**). Eighty-seven % of patients in the Condrotide® HA Group and 66% of patients in the Comparison Group reported improvement of joint pain over the follow-up period (**Figure 28C**). Mean KSS

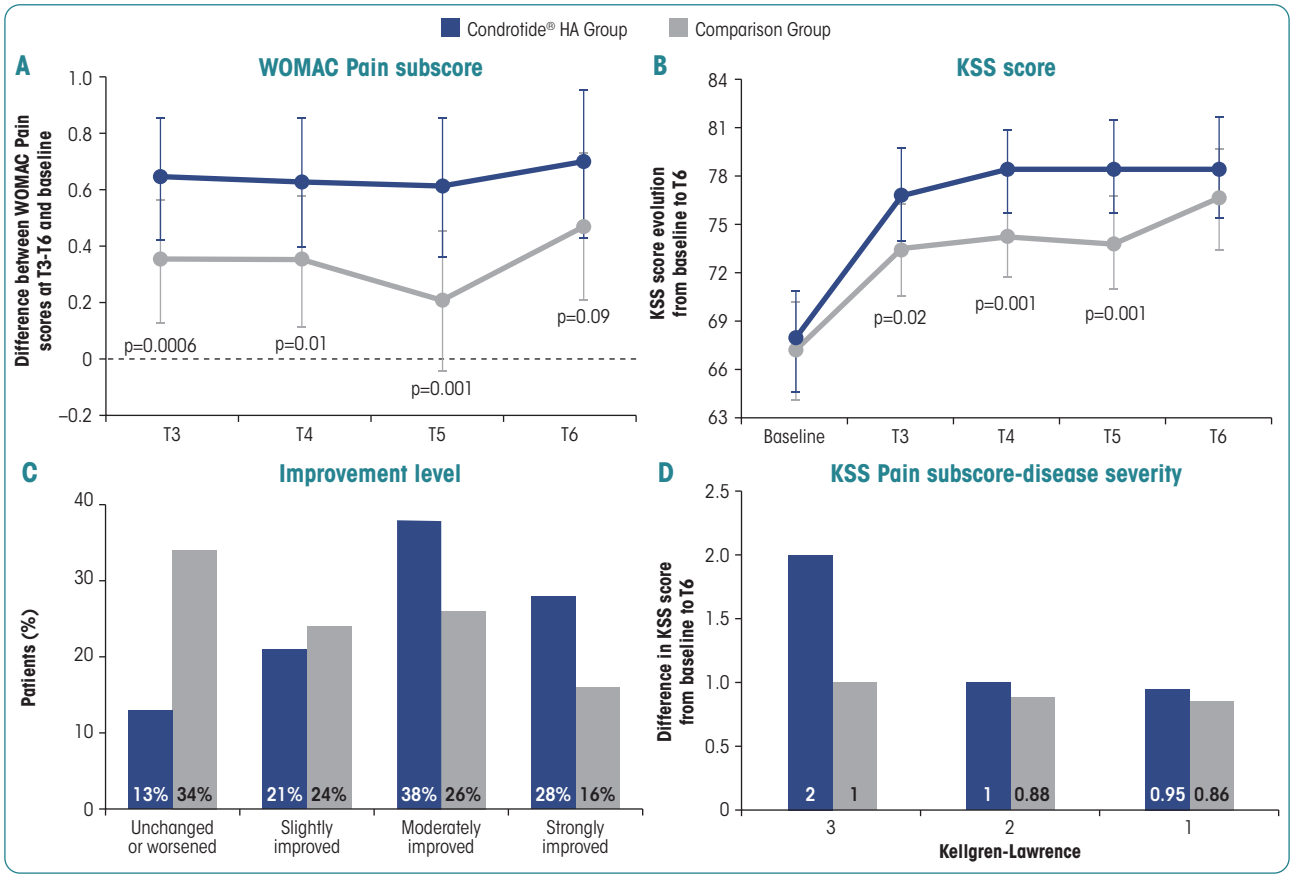


Figure 28. Study outcomes: difference between WOMAC pain score at any given point and baseline **(A)**; evolution of the KSS score over the follow-up of 2 years **(B)**; percentages of patients in the two groups reporting improvement at the end of the 2-year follow-up **(C)**; change in KSS Pain subscore according to disease severity on the Kellgren-Lawrence scale **(D)**. Graphic elaboration from figures [25].

pain scores improved by 2 points and by 1 point in the Condrotide® HA Group and the Comparison Group, respectively, in patients with grade 3 disease. The improvements were similar in patients with grade 1 and 2 disease (**Figure 28D**).

Conclusions

The 2-year evolution of the WOMAC Pain subscale, the primary endpoint of this study, demonstrated a steady, long-term improvement of knee pain related to OA in patients treated with intra-articular injections of the combination of Polynucleotides HPT® and hyaluronic acid (Condrotide® HA, Mastelli S.r.l., Sanremo, Italy). The benefit on pain reduction of injection of the Polynucleotides HPT®/hyaluronic acid combination versus hyaluronic acid alone was significant at all timepoints and greater in patients with a higher baseline severity of OA on the Kellgren-Lawrence scale. The study outcomes confirmed the original finding by Dallari et al. that Polynucleotides HPT® are a valuable complement to hyaluronic acid in the relief of pain and functional symptoms in patients with OA of the knee.

> *The benefit on pain reduction of injection of the Polynucleotides HPT®/hyaluronic acid combination (Condrotide® HA) versus hyaluronic acid alone was significant at all timepoints and greater in patients with a higher baseline severity of OA on the Kellgren-Lawrence scale. The study outcomes confirmed the original finding by Dallari et al. that Polynucleotides HPT® are a valuable complement to hyaluronic acid in the relief of pain and functional symptoms in patients with OA of the knee.*

Chapter IV – The use of Polynucleotides HPT® in special clinical contexts

4.1 Clinical benefits of the use of Polynucleotides HPT® in osteoarthritis (OA) of the temporomandibular joint

4.1.1 Study by Cenzato et al., 2024: a randomised single-blind 3-month study to compare the injections of the combined formulation of Polynucleotides HPT®/hyaluronic acid with self-delivered physiotherapy from the Department of Biomedical, Surgical and Dental Sciences of the University of Milan.

Reference [26]: Cenzato N, Crispino R, Russillo A, Tartaglia GM. Clinical effectiveness of polynucleotides TMJ injections compared to physiotherapy. A 3 months randomized clinical trial. Br J Oral Maxillofac Surg. 2024;62:807-12.

Aim of the study

The aim of this study was to assess the clinical effectiveness of peri-capsular injection of Polynucleotides HPT® in combination with hyaluronic acid (Condrotide® HA, Mastelli S.r.l., Sanremo, Italy) in the improvement of signs and symptoms of OA of the temporomandibular joint compared to clinical management with physiotherapy.

Study design

Patients: A total of 60 patients (25 male/35 female; mean age 53 ± 13 years, range 22-65 years in the study group, and 58 ± 15 years, range 30-63 years in the control group) with OA of the temporomandibular joint; 30 patients were randomly assigned to the Condrotide® HA Group (Polynucleotides HPT®/hyaluronic acid) and 30 to the Comparison Group (physiotherapy).

Interventions: Patients received treatments as detailed in **Figure 29**.

Assessments: Changes in unassisted mouth opening, overbite, lateral movements of the mandible, subjective pain on VAS.

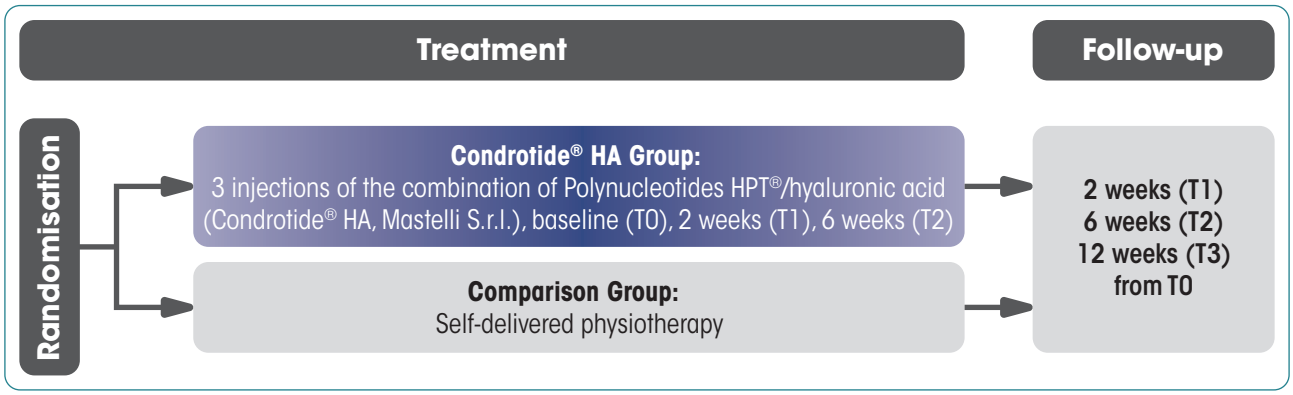


Figure 29. Study design. Graphic elaboration from text [26].

Results

Twenty-six patients in the Condrotide® HA Group and 25 in the Comparison Group completed the 2-year study.

In the Condrotide® HA Group, maximum mouth opening (the primary endpoint) showed a continuous increase from baseline to T3, but the increase with respect to T0 was not statistically significant (p=0.09 at T3). Maximum mouth opening in the Comparison Group increased by 2.8% at

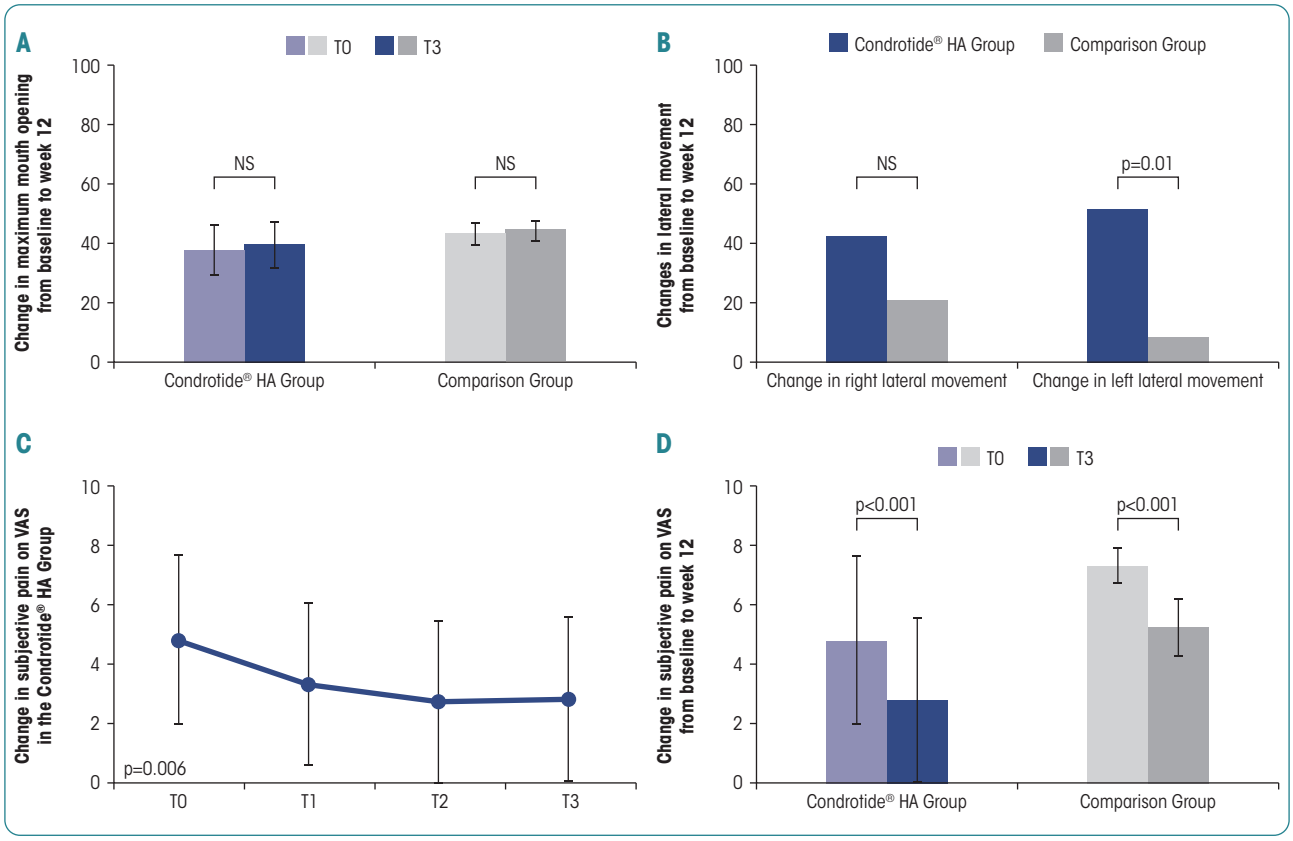


Figure 30. Study outcomes: changes in maximum mouth opening **(A)** and lateral movements **(B)** from baseline to T3 in both groups; evolution of subjective pain on VAS in the Condrotide® HA Group (p=0.006) **(C)**; changes in subjective pain on VAS from baseline to T3 in both groups **(D)**. Graphic elaboration from text, table and figure [26].

T3 and this change was not significant compared to baseline (within-group comparison). The difference between groups at T3 was also not statistically significant (p=0.42) (**Figure 30A**).

Lateral movements to the right and left increased by 42.5% and 51.8%, respectively, in the Condrotide® HA Group and by 30.4% and 8.3% in the Comparison Group. This increase was significant on both sides in the Condrotide® HA Group. The difference between groups was statistically significant for the left side only (p=0.01) (**Figure 30B**).

Subjective pain on VAS decreased significantly from baseline to T1 and continued to decrease at T2 and T3 in the Condrotide® HA Group (p=0.006 at all timepoints) (**Figure 30C**).

The decrease observed at T3 for the Comparison Group was statistically significant (p<0.001), and it was significantly less than the Condrotide® HA Group (p<0.0001) (**Figure 30D**).

Conclusions

Articular peri-capsular injections of the Polynucleotides HPT®/hyaluronic acid combination (Condrotide® HA, Mastelli S.r.l., Sanremo, Italy) represent a minimally invasive procedure that effectively manages OA of the mandibular condyle. Peri-capsular injections are easy to perform. Following treatment with the Polynucleotides HPT®/hyaluronic acid combination, both pain relief and an improvement of all mandibular excursive movements were observed.

Following treatment with the Polynucleotides HPT®/hyaluronic acid combination (Condrotide® HA), both pain relief and an improvement of all mandibular excursive movements were observed.

Chapter V – Guidelines for the treatment of osteoarthritis

5.1 Overview of the principal guidelines

Based on the available evidence, the American College of Rheumatology (ACR) made either strong or conditional recommendations for or against the approaches evaluated. Strong recommendations included exercise, weight loss in overweight or obese patients with osteoarthritis (OA) of knee and/or hip, self-efficacy and self-management programs, tai chi, use of a cane, hand orthoses for OA of the first carpometacarpal joint, tibiofemoral bracing for tibiofemoral knee OA, topical NSAIDs for knee OA, oral NSAIDs, and intra-articular glucocorticoid injections for knee OA. ACR recommends against a number of physical (e.g., transcutaneous nerve stimulation), psychosocial, and mind-body approaches[27].

The European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO) promotes a basic principle and core set that states that pharmacological and non-pharmacological therapies should be combined. Similarly to ACR, ESCEO recommends weight loss if overweight and an exercise programme. In symptomatic patients, symptomatic slow-acting drugs in OA (glucosamine and chondroitin sulphate) plus topical NSAIDs, if still symptomatic, plus a referral to a physical therapist to control malalignment. In severely symptomatic patients, oral NSAIDs and intra-articular hyaluronic acid or corticosteroids are recommended[28].

The Osteoarthritis Research Society International (OARSI) developed a patient-centred treatment algorithm that incorporates cycles of assessment and treatment and considers comorbidity profiles. Initially, the structure of the treatment pathway is decided based of joint localisation (item 1) and comorbidities (item 2). Clinical, emotional and environmental factors constitute items 3 and 4. Primary options promoted by OARSI are based on the strongest level of evidence[29].

5.2 Italian Sports Medicine Federation 2020 guidelines: intra-articular treatment in athletes

Intra-articular therapy is common in athletes. **The Italian Sports Medicine Federation (FSMI)** issued a consensus statement on the indications and procedures of intra-articular therapy in elite athletes. Polynucleotides HPT® are discussed as one of the newer options for intra-articular treatment[30]. **In particular, the consensus documents suggest faster recovery of joint function when patients are treated with Polynucleotides HPT® compared with hyaluronic acid. Also, Polynucleotides HPT® could be an option in patients who have failed to respond to hyaluronic acid[30].**

Chapter VI – Safety and tolerability of Polynucleotides HPT®

Evidence on safety and tolerability of Polynucleotides HPT® from clinical studies

The available studies, including biocompatibility studies performed on the active ingredient, consistently confirm the high safety and tolerability of Polynucleotides HPT®. Since its market introduction in 2008, more than 1,500,000 syringes have been sold across various countries, with only one serious adverse event (not directly related to the product) and five non serious adverse events reported in pharmacovigilance reports (Periodic Safety Update Reports, Mastelli internal documents). Six of the 14 studies described in Chapter III reported no adverse events[5,9,17,24-26].

Guelfi et al. described joint tenderness and effusion in a small percentage of patients that resolved in 5 days with rest and ice packs[19]. Five studies reported no serious or systemic adverse events, but mild local pain or burning sensation at the site of the injection that disappeared spontaneously after a few (1-12) hours[6,8,20-22]. In addition, Conforti et al. reported laser-induced hyperthermia in some of their patients, and Kim et al. listed three serious adverse events unrelated to the study interventions[20,31]. One study did not publish their safety analysis[23].

Chapter VII – Products based on Polynucleotides HPT® for intra-articular use

7.1 Condrotide® – product characteristics and indications for use

Condrotide®, gel for intra-articular infiltrations with Polynucleotides HPT®.

Characteristics: Condrotide® is a viscoelastic, transparent, colourless solution with Polynucleotides HPT®; it presents in the form of a glass, pre-filled, sterile, non-pyrogenic, single-use syringe containing 2 mL of solution. The Polynucleotides HPT® are highly purified, fish-derived and have a concentration of 20 mg/mL. Condrotide® is characterised by viscoelasticity and by a pronounced potential to bind several molecules of water; it therefore makes it possible to lubricate and promote the normalisation of the synovial fluid's viscosity[32].

Indications: Painful conditions that affect the joints and that can be attributed to degenerative, post-injury ailments or to alterations of the joints[32].

Dosage: As a guideline, unless decided otherwise by the physician, infiltrate 2 mL of product (40 mg of Polynucleotides HPT®) intra-articularly once a week for 3 to 6 weeks.

7.2 Condrotide® HA – product characteristics and indications for use

Condrotide® HA, gel for intra-articular infiltrations with Polynucleotides HPT® and hyaluronic acid.

Characteristics: Condrotide® HA is a medical device with Polynucleotides HPT® at a concentration of 10 mg/mL and sodium hyaluronate at the concentration of 10 mg/mL. It presents as a sterile, non-pyrogenic, viscoelastic solution packaged in a single-use syringe containing 2.5 mL of solution. Polynucleotides are highly purified and resorbable substances of natural origin and have viscoelastic abilities. Hyaluronic acid is one of the main components of the synovial fluid to which it confers viscosity and elasticity. By improving the characteristics of the synovial fluid, Condrotide® HA protects the joints, promoting both the improvement of joint functionality and the reduction of pain[33].

Indications: Painful conditions that affect the joints and that can be attributed to degenerative, post-injury ailments or to alterations of the joints[33].

Dosage: The recommended treatment regimen involves 3 infiltrations in the joint to be treated, 1 to 3 weeks apart.

7.3 Corroborating evidence from Prof. Marelli

Prof. Marelli at the Istituto Ortopedico Gaetano Pini in Milan began to use Condrotide® in 2009 and has treated a total of 100 patients with knee osteoarthritis with pain lasting at least 2 months. Initially, the injections were performed at weekly intervals (as indicated in the product insert). The dosing was later modified to intervals of 2 or 3 weeks. Prof. Marelli observed that the injections performed at an interval of 3 weeks produced better long-term results than the outcomes obtained with once-weekly injections. Moreover, the results showed superiority of Polynucleotides HPT® over hyaluronic acid. The results lasted up to 1 year after treatment delivery[34].

Chapter VIII – Conclusions on the use of Polynucleotides HPT® in orthopaedics

- Polynucleotides HPT® are a mixture of natural DNA-derived macromolecules of different length obtained from trout sperm using an original purification technology developed by Mastelli S.r.l. and denominated High Purification Technology (HPT®).
- The available evidence supports the safety and tolerability of the intra-articular injections of Polynucleotides HPT® (Condrotide®, Mastelli S.r.l., Sanremo, Italy) and Polynucleotides HPT® in combination with hyaluronic acid (Condrotide® HA, Mastelli S.r.l., Sanremo, Italy) in patients with osteoarthritis (OA).
- The use of medical devices containing Polynucleotides HPT® has been shown to favour the improvement of pain and function of several joints including the knee, ankle, hip, shoulder and the temporomandibular joint in patients with OA.
- Some studies confirmed the superiority of the injections of Polynucleotides HPT® over injections of hyaluronic acid, especially as regards the parameters 'pain', 'symptoms' and 'function in sport and recreation activities'.
- The injections of Polynucleotides HPT® can be a useful alternative to the injections of linear high molecular weight hyaluronic acid in the treatment of knee OA.
- The injections of Polynucleotides HPT® significantly relieve pain more and relieve pain faster in patients with knee OA than classic and cross-linked hyaluronic acid, with improved health-related quality of life.
- The use of medical devices containing Polynucleotides HPT® may delay the need for joint replacement surgery.
- The use of medical devices containing Polynucleotides HPT® results in a more rapid onset of action than injections of hyaluronic acid.
- The injections of Polynucleotides HPT® have been shown to reduce NSAIDs consumption compared to the injections of hyaluronic acid.
- The injections of the combination of Polynucleotides HPT® and hyaluronic acid were superior to hyaluronic acid alone in favouring pain and function improvement in patients with OA.
- Treatment with Polynucleotides HPT® in athletes can result in a faster recovery than treatment with hyaluronic acid or be used in patients resistant to hyaluronic acid.

Chapter IX – Clinical cases

Here we present a selection of clinical cases that benefited from the treatment with Condrotide® or Condrotide® HA in the real-world setting.

9.1 Case 1 - Treatment of bilateral temporomandibular joint osteoarthrosis with peri-capsular injections of Polynucleotides HPT® and hyaluronic acid (Condrotide® HA)

Niccolò Cenzato, Roberta Crispino, Antonio Russillo, Massimo Del Fabbro, Gianluca Martino Tartaglia

University of Milan, Department of Biomedical, Surgical and Dental Sciences and Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Maxillo-Facial Surgery and Dental Unit, Milan, Italy

Case presentation

A patient suffering from temporomandibular joint (TMJ) osteoarthrosis, referred to the Orthodontics and Gnathology Department of Ospedale Maggiore Policlinico (Milan, Italy), presented to our clinic. A thorough medical history, including personal and family history, was acquired together with relevant data such as age, height, weight, and lifestyle habits. No significant findings were noted from a systemic perspective. However, the patient reported two past episodes of TMJ locking, both of which resolved spontaneously.

A gnathological examination was performed according to protocol no. 173901, approved by the Ethics Committee of Fondazione IRCCS Ca' Granda (Ospedale Maggiore Policlinico, Milan, Italy). Measurements of maximum mouth opening and lateral movements were taken, and the patient was asked to provide a VAS pain score. A magnetic resonance imaging (MRI) scan of the TMJ and a surface electromyography test were requested for further assessment.

The patient was clearly and thoroughly informed about the study methods and implications before enrolment, and written informed consent was obtained. The diagnosis was made of bilateral TMJ osteoarthrosis with a limited mouth opening of 30 mm and restricted lateral movement of 4 mm on both sides. The reported pain level on the VAS score was 6/10.

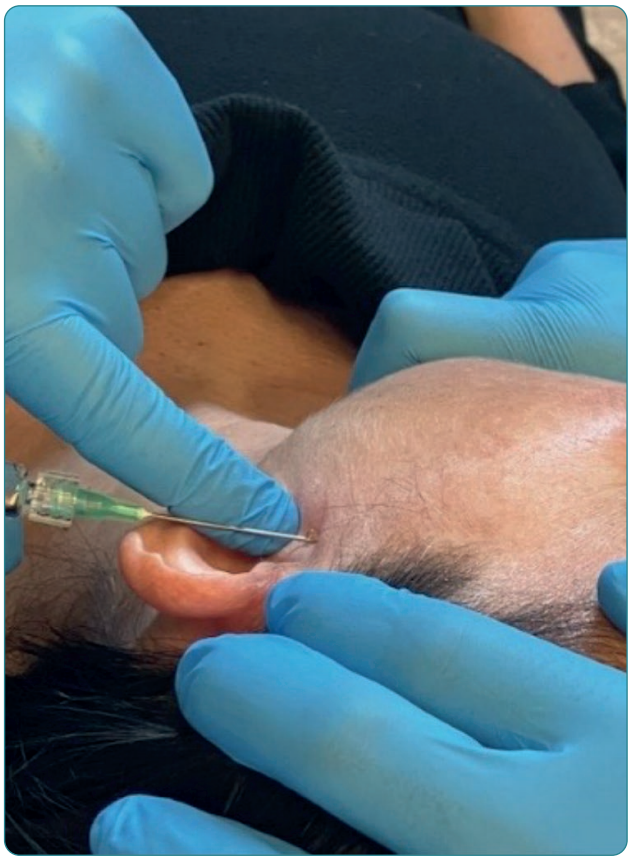


Figure 31. Cenzato-Russillo Injection Technique. While the mandible is in an open and protruded position, palpation of the preauricular area is performed to locate the lateral pole of the condyle, and the first injection is administered posteriorly to the condyle at an acute angle (45°). Then, while the mandible is in a closed position, the TMJ is located through palpation and the second injection is administered anteriorly to the TMJ at an acute angle (45°).

Treatment and clinical course

Peri-capsular injection of 1 mL of Polynucleotides HPT® and

hyaluronic acid solution (Condrotide® HA, Mastelli S.r.l., Sanremo, Italy) was administered at the cutaneous tragal point between the condyle and glenoid fossa. This was a peri-capsular injection with dual access, without perforation of the capsule and without anaesthetic, using a standardised technique (**Figure 31**). The patient received three injections (T0, T1 and T2) in accordance with the Condrotide® HA leaflet, as advised in the 'dosage' section.

After each of the three injections, the parameters were remeasured. An increase in maximum mouth opening was already observed after the second dose: 37 mm after the second and 38 mm after the third. The patient's reported pain also improved, decreasing from 6/10 to 3/10 after the third injection. At the 6-month follow-up, the values remained stable.

Discussion and conclusions

These observations suggest that peri-capsular Condrotide® HA injection may effectively control and alleviate the symptoms of osteoarthrosis and osteoarthritis without the need for invasive procedures or discomfort for the patient. TMJ osteoarthritis is a complex disease in which degenerative changes in the cartilage and bone develop through intricate mechanisms[35-37]. It is noteworthy that this treatment also shows promise in improving the mobility of compromised joints[26]. A longer follow-up would be valuable to assess the long-term effects and to better understand the mechanism of action of this substance.

9.2 Case 2 - Conservative management of degenerative medial meniscus lesion in a professional dancer with intra- and peri-meniscal Polynucleotides HPT® (Condrotide®) injections: a case report

Giuseppe Anzillotti, Pietro Conte, Elizaveta Kon

IRCCS Humanitas Research Hospital, Rozzano, Milan, Italy and Department of Biomedical Sciences, Humanitas University, Milan, Italy

Case presentation

A 47-year-old male professional dancer, 75 kg, 180 cm, with a silent past medical history, presented with progressively worsening right medial knee pain for two months, rated at 4/10 on the VAS and unresponsive to non-steroidal anti-inflammatory drugs. The Knee Injury and Osteoarthritis Outcome Score (KOOS), International Knee Documentation Committee (IKDC) score and Tegner activity score were 45, 40 and 3, respectively. No catching or locking-like symptoms were reported. The patient had no history of recent trauma and was willing to pursue his career in dancing. Physical examination revealed pain during palpation of the posterior medial joint line, no joint effusion, antero-posterior stability and a range of motion (ROM) from 0° to 130° with pain in full flexion. The patient demonstrated a positive McMurray's and Apley's test. Magnetic resonance imaging (MRI) was performed and demonstrated a degenerative lesion in the posterior root of the medial meniscus and a modest effusion; other structures exhibited no signs of abnormality (**Figure 32**).

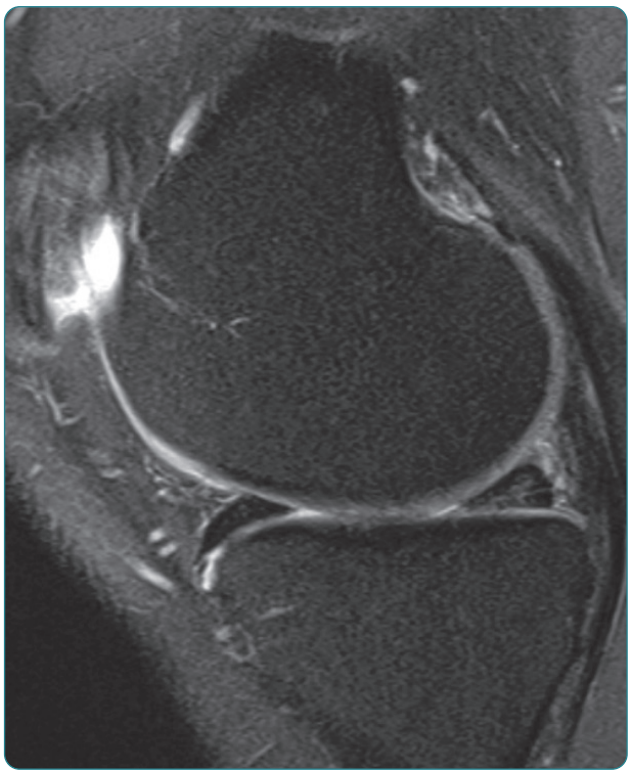


Figure 32. The right knee MRI shows degenerative changes in the posterior root of the medial meniscus (sagittal view).

Treatment and clinical course

After discussion of the possible treatment options, the patient underwent conservative treatment involving a combination of physical therapy and three peri-meniscal Polynucleotides HPT® (Condrotide®, Mastelli S.r.l., Sanremo, Italy) injections, administered at 2-week intervals. Following the third injection, pain reduced significantly to sporadic, mild discomfort (VAS 2/10). Within a month after the last injection, the patient resumed dancing, progressing to full practice without pain, and after one year he reported stable pain reduction and full ROM. At 4-year follow-up evaluation the patient reported no pain and no discomfort in the right knee, and the KOOS, IKDC and Tegner activity scores recorded the highest values of the scales.

Discussion and conclusions

This case supports the utility of Polynucleotides HPT® injections in managing degenerative meniscal lesions in professional athletes in the absence of mechanical symptoms, allowing for pain reduction and functional recovery without surgical intervention. Polynucleotides HPT® injections, as reported in recent studies, offer an effective alternative for pain management in degenerative meniscal pathology, promoting improved biomechanics and tissue healing through their viscoelastic and biochemical properties[8,9,24,38,39]. This case highlights the effectiveness of modern conservative treatments in achieving lasting functional benefits for patients affected by degenerative meniscal lesions.

9.3 Case 3 - Efficacy of intra-articular Polynucleotides HPT® (Condrotide®) injections in the treatment of knee osteoarthritis in an elderly patient with obesity and comorbidities: a case report

Francesco Fiacchi, Giulia Lodi

Orthopaedics and Trauma Division, Suzzara Hospital, Mantova, Italy

A 68-year-old woman presented with persistent bilateral knee pain lasting more than six months. She reported significant discomfort over the anterior and lateral aspects of both knees, which intensified with standing or squatting. The patient had no history of trauma and had a BMI of 37. Her comorbidities included insulin-treated diabetes, venous insufficiency in the right leg, and obesity (**Figure 33**).

Radiography revealed grade 3 knee valgus osteoarthritis. Upon physical examination, there were no signs of swelling, warmth, or redness in the knees. Crepitus was noted during flexion and extension, and the patient exhibited bilateral valgus deformity and quadriceps wasting, though her gait was normal.

The Lequesne index score was 13/24, reflecting nocturnal pain without movement, 15 minutes of morning stiffness, pain when standing, walking, or rising from a chair, a maximum walking distance of 1 km without assistance, and moderate difficulties while walking and significant difficulty when going down stairs. The Numeric Pain Rating Scale (NPRS) score was 7/10.

The patient had no relief from non-steroidal anti-inflammatory drugs (NSAIDs) and, due to decompensated diabetes, corticosteroid injections were avoided. Given her acute venous insufficiency, no surgical intervention was considered. The

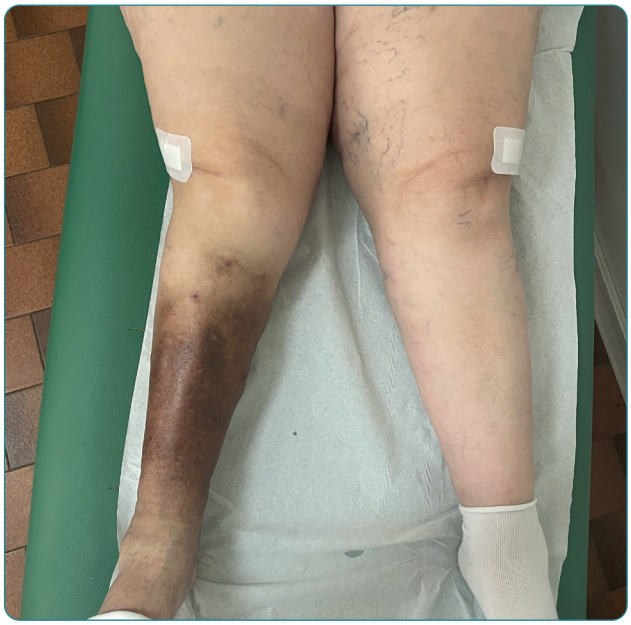


Figure 33. Obese patient with bilateral valgus knee and vascular insufficiency in the right leg.

treatment plan consisted of three intra-articular injections of Polynucleotides HPT® (Condrotide®, Mastelli S.r.l., Sanremo, Italy) administered every two weeks. The follow-up period was set for one month after the final injection.

Results

Two weeks after the first injection the patient reported that the knee pain had improved by about 50%, and that the improvement lasted for almost a week. Then the pain reappeared while walking, but no pain appeared at night.

Two weeks after the second injection she reported that the knee pain had improved almost completely for almost two weeks. The pain reappeared slightly while walking.

One month after the third injection she reported that the knee pain had improved almost completely. The pain did not reappear while walking, rising from a chair, or at night. She mentioned a temporary discomfort during squatting for a few seconds.

During treatment she did not take any other medication such as pain killers or NSAIDs.

No adverse reactions occurred.

Discussion and conclusions

Knee pain associated with osteoarthritis is a common and debilitating condition that significantly affects patients' quality of life, with a notable impact on daily functioning. The management of this condition requires effective, safe, and well-tolerated therapeutic approaches capable of providing long-lasting relief and improving joint functionality. Intra-articular Polynucleotides HPT® injections have proved to be an interesting therapeutic modality for knee osteoarthritis[8,9], as confirmed by the results of the presented clinical case.

The data collected suggest that Polynucleotides HPT® can promote a significant improvement not only in joint pain but also in functional abilities, with the effect lasting beyond the immediate post-treatment period. Specifically, the treatment led to a substantial reduction in pain and an improvement in daily activities, such as walking and rising from a chair, without the need for analgesics or NSAIDs, and without any report of significant side effects.

9.4 Case 4 - Conservative management of bilateral patellofemoral dysplasia in a young track and field athlete using intra-articular Polynucleotides HPT® (Condrotide®) injections: a case report

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Case presentation

A 16-year-old male professional track and field athlete, 65 kg, 178 cm, with a silent past medical history, presented with progressively worsening bilateral patellofemoral dysplasia with pain for 6 months, rated at 6 on the Visual Analogue Scale (VAS) and unresponsive to non-steroidal anti-inflammatory drugs (NSAIDs) (ibuprofen for 3-4 months, pain relief only at rest). The patient had no history of recent trauma and his symptoms were probably related to overuse due to sport activity.

Physical examination revealed a slight patellar misalignment, pain on palpation, no joint effusion, no sign of inflammation or swelling, antero-posterior stability and complete range of motion (ROM) from 0° to 110° with pain in full flexion. Magnetic resonance imaging (MRI) was performed and demonstrated bilateral patellofemoral dysplasia with no laxity or patellofemoral luxation.

Treatment and clinical course

After discussion of the possible treatment options available, the patient underwent conservative treatment involving a combination of physical therapy and three intra-articular Polynucleotides HPT® (Condrotide®, Mastelli S.r.l., Sanremo, Italy) injections, administered at two-week intervals. Following the third injection, pain reduced significantly VAS 0. Within a month after the last injection, the patient resumed

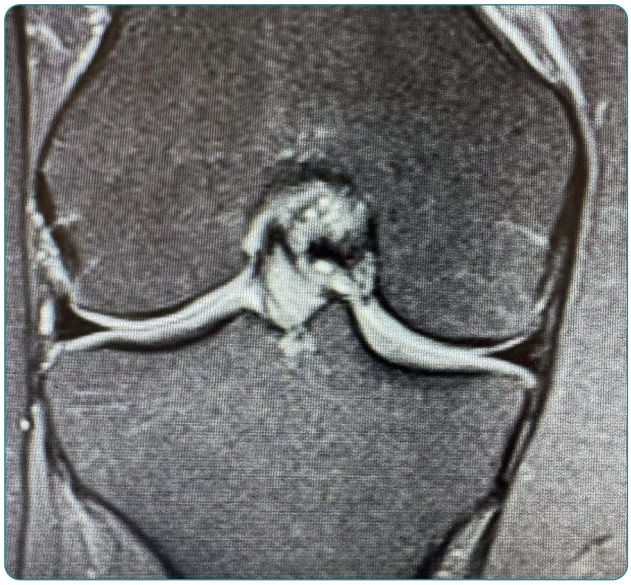

Figure 34. The MRI shows an improvement in cartilage trophism with increased thickness, greater signal homogeneity, and reduced surface irregularities, suggesting a regenerative effect in a young athlete.

sport activities, progressing to full practice without pain and without use of NSAIDs. **Figure 34** shows MRI scan after treatment.

Discussion and conclusions

This case underscores the efficacy of Polynucleotides HPT® injections in managing pain and facilitating functional recovery in professional athletes, particularly when mechanical symptoms are absent. Recent studies have demonstrated that Polynucleotides HPT® injections provide an effective alternative for treating chondropathies by enhancing biomechanics and supporting tissue healing through their viscoelastic and biochemical properties[8,9]. **This example highlights the potential of modern conservative treatments to deliver sustained functional improvements in young athletes with bilateral patellofemoral dysplasia.**

9.5 Case 5 - Effectiveness of intra-articular Polynucleotides HPT® (Condrotide®) injections in managing shoulder osteoarthritis with chronic rotator cuff tears

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Case presentation

Shoulder osteoarthritis, often complicated by chronic rotator cuff tears, is a debilitating condition that results in severe pain, reduced range of motion, and diminished quality of life. This case series evaluates the combined effect of Polynucleotides HPT® (Condrotide®, Mastelli S.r.l., Sanremo, Italy) injections and physiotherapy in a cohort of 12 patients.

Twelve patients (7 male and 5 female) aged 55 to 75 years (mean age 65) with chronic shoulder pain and reduced function due to osteoarthritis and chronic rotator cuff tears were retrospectively analysed. All patients had experienced persistent pain and limited shoulder function for over six months. **Figures 35** and **36** show X-ray images of a patient with shoulder osteoarthritis.

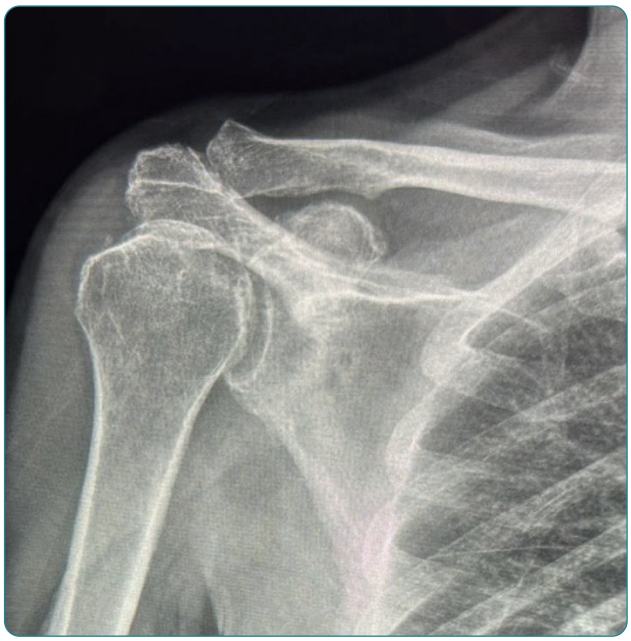

Figure 35. Patient with shoulder osteoarthritis. X-ray in antero-posterior projection.

Treatment and clinical course

The therapeutic protocol included:

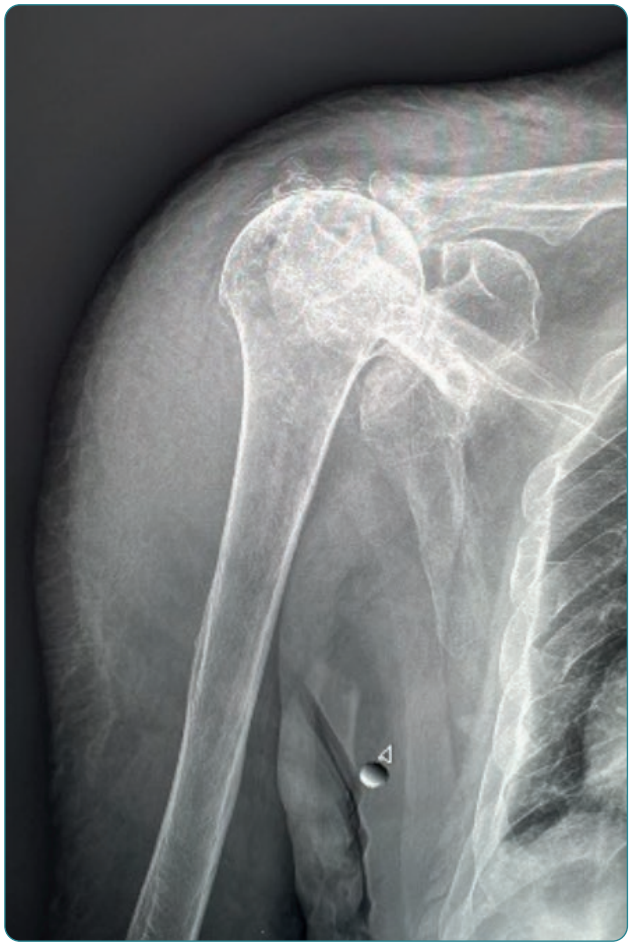

Figure 36. Patient with shoulder osteoarthritis. X-ray in lateral projection.

- **Intra-articular injections**: one injection of Polynucleotides HPT® every three weeks.
- **Physiotherapy**: a structured six-week program starting the day after the first injection, focused on postural exercises and joint mobility recovery.

Outcomes were measured using the following:

- **Pain assessment**: VAS (0-10).
- **Shoulder function**: Constant-Murley Score (CMS).
- **Patient satisfaction**: Qualitative survey at the end of treatment.

A historical control group treated solely with physiotherapy was used for comparison.

At the six-week follow-up, patients who received Polynucleotides HPT® injections combined with physiotherapy demonstrated significant improvements compared to baseline:

- **Pain reduction**: VAS scores decreased from an average of 7.5 ± 1.2 to 2.3 ± 1.0 ($p<0.01$).
- **Functional improvement**: CMS increased from 35 ± 5 to 70 ± 8 ($p<0.01$).
- **High satisfaction rates**: 92% of patients reported being very satisfied with their treatment.

Compared to the control group (which received only physiotherapy), patients in the Polynucleotides HPT® group showed faster pain reduction (within two weeks) and greater improvements in CMS at six weeks (+15 points on average).

Discussion and conclusions

The combination of intra-articular Polynucleotides HPT® injections and physiotherapy has proved effective in alleviating pain and improving shoulder function in patients with chronic rotator cuff tears and osteoarthritis[23,40-42]. The effects of Polynucleotides HPT®, combined with the biomechanical benefits of physiotherapy, likely contributed to these positive outcomes.

This case series supports a multimodal approach to managing shoulder osteoarthritis, particularly in complex cases involving chronic rotator cuff tears. The findings highlight the potential of Polynucleotides HPT® injections as an adjunct to standard physiotherapy, facilitating a faster and more comprehensive recovery.

Intra-articular Polynucleotides HPT® injections combined with physiotherapy offer a safe and effective strategy for managing shoulder osteoarthritis with chronic rotator cuff tears. This approach not only accelerates recovery but also improves overall patient outcomes compared to physiotherapy alone, providing a valuable option for enhancing the quality of life in affected individuals.

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Appendix – Outcome measures used by the cited studies

Constant-Murley Scale is a simple standardised method for clinical assessment of shoulder function on a scale from 0 to 100 points; the higher the score, the better the function. The scale assesses four aspects related to shoulder pathology, two of which subjective (pain and activities of daily living [ADL]) and two objective (range of motion [ROM] and strength). The subjective components can receive up to 35 points and the objective ones 65, resulting in a possible maximum total score of 100 points. Pain and ADL are answered by the patient; ROM and strength require a physical evaluation and are answered by the orthopaedic surgeon or the physiotherapist[1].

Davies isokinetic testing uses a variety of protocols ranging from power to endurance tests in an athlete with shoulder injury. Isokinetics means that exercise is performed at a fixed velocity with an accommodating resistance. Isokinetic exercise with an accommodating resistance is the only way to dynamically load a muscle to its maximum capacity at every point throughout the range of motion[2].

EQ-D5 (EuroQoL Group-5 level) tool is a concise, generic measure of self-reported health which is accompanied by weights reflecting the relative importance to people of different types of health problems. It is made up of two parts: a descriptive part one and a visual analogue scale part two to assess the respondent's overall health on a scale from 0 (worst imaginable health) to 100 (best possible health)[3].

FAOS (Foot and Ankle Outcome Score) is a 42-item questionnaire assessing patient-relevant outcomes in five separate subscales (Pain, Other Symptoms, Activities of Daily Living, Sport and Recreation Function, Foot- and Ankle-Related Quality of Life). Each subscale's score is derived by adding up all of the subscale's individual scores and dividing the result by the subscale's maximum score. The normalized score is converted to a scale of 0 to 100, with 100 denoting no problems and 0 denoting severe problems[4].

KOOS (Knee Injury and Osteoarthritis Outcome Score) is an extension of the WOMAC. The KOOS's five patient-relevant dimensions are scored separately: Pain (9 items); Symptoms (7 items); Activity of Daily Living (ADL) Function (17 items); Sport and Recreation Function (5 items); Quality of Life (4 items). A Likert scale is used, and all items have five possible answer options scored from 0 (no problems) to 4 (extreme problems). Each of the five scores is calculated as the sum of the items included. Scores are then transformed to a 0-100 scale, with zero representing extreme problems and 100 representing no problems with the knee[5].

KSS (Knee Society Score) is made up of two components: State of the Knee (7 items) and Functionality (3 items). The first one evaluates pain, range of motion and stability; the second analyses gait for 100 m, going up and down stairs and the use of walking aids. Components have a maximum score of 100 (optimum state of the patient)[6].

Lequesne index of severity for osteoarthritis of the hip is an 11-item questionnaire designed to obtain information of a subjective nature, from patients, about their diseased hip. The index score ranges from 1 to 24 points based on summed responses to 11 items. The higher the score the worse the condition of the hip joint (e.g., >14 extremely severe)[7].

VAS (Visual Analog Scale) is most commonly a straight 100-mm line, without demarcation, that has the words "no pain" at the left-most end and "worst pain imaginable" (or something similar) at the right-most end. Patients are instructed to place a mark on the line indicating the amount of pain that they feel at the time of the evaluation. The distance of this mark from the left end is then measured, and this number is used as a numeric representation of the severity of the patient's pain, often converted to a 1-10 scale[8].

WOMAC (Western Ontario and McMaster Universities) is a 24-item, condition-specific questionnaire to be used for hip and knee osteoarthritis first published in 1982. The WOMAC consists of three subscales: Pain (5 questions), Stiffness (2 questions), and Physical Function (17 questions). The subscale scores can vary, with Pain ranging from 0 to 20 points; Stiffness, 0 to 8 points; and Physical Function, 0 to 68 points. Higher scores represent worse pain, stiffness, and functional limitations[9].

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