RESEARCH PROTOCOL

Study title: Safety and effectiveness of hyaluronic acid and sorbitol with overuse knee pain in sportsmen

Protocol Reference ethics commitee number: CEI/0504/PI./2022

ClinicalTrials.gov: NCT05450458

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Abstract:

Introduction: The presence of overuse syndrome has been found with increasing frequency in patients who perform impact sports activities. Repetitive micro-trauma as a result of intense sport will cause the onset of joint degeneration that will generate pain, functional disability and in some cases limitation to continue carrying out sports activities.

Aims: the aims of this prospective and longitudinal intervention cohort study is to evaluate the safety and efficacy of hyaluronic acid plus sorbitol through clinical and functional analysis of sports patients undergoing overuse knee syndrome.

Patients and Methods:

According to the inclusion criteria, the participants who agree to part of the study will be enrolled, two dose of hyaluronic acid plus sorbitol will be applied in each knee, then strategies techniques for continue with sports activities. The KOOS and IKDC scores will be evaluated at 15 days 3 and 6 months. Once we obtain all data results a statistical analysis will be made.

Introduction:

It is increasingly common to find patients who refer knee pain after any kind of sports, overuse syndrome of the knee has been the most common cause. This entity can be conditioned by repetition microtrauma which are in direct relation with the repenting rise of the intensity, duration and volume in sports activity, and also we could find incorrect training techniques or also do not count with appropriate equipment during training.

Knee Overuse Syndrome

Musculoskeletal conditions are common during competitive practices and correspond to 80% of sports injuries. Of these, joint pathologies, especially of the knee, have increased significantly due to the large number of people who practice activities, both professionally and recreationally. Athletes who push their physical capacity to the limit, will present a type of joint injury that has been classified as excessive use of a joint, representing up to 42% of all sport-related musculoskeletal conditions. An overuse injury could be defined as one of gradual origin, caused by repetitive micro-traumas without an identifiable injury mechanism that triggered it. Therefore, the overuse syndrome is related to chronic repetitive injuries caused by sports activities, where one of its characteristics is that they occur when there is not enough time for small injuries to heal properly, these being the result of microtraumas associated with physical activity and exercise that exceed the tissue tolerance of the affected structure. There are distinct types of overuse injuries, which depend on the affected anatomical area: tendinitis, bursitis, stress fractures, osteoarthritis among others. The presence of these micro-traumas related to the increased intensity and frequency in the use of a joint Will eventually cause inflammation and wear of the cartilage,

resulting in an overuse injury. The lower extremity is most affected, due to the overload imposed in sports involving running and jumping, in which the force of the knees can reach up to 10 times body weight.

Etiology

It has been observed that between 35 and 45% of all injuries related to sports activity are due to people with overuse syndrome and that approximately one third of these are related to the knee joint. The overall prevalence of knee overuse injuries varies between sports activities: For example, patellofemoral pain syndrome constitutes 25% of knee injuries in runners, patellar tendinopathy has a prevalence of 40 % to 50% in elite volleyball players and 2.8 to 4.8 in runners. It is common for patients with a history of knee overuse and who practice professional sports to develop degenerative cartilage injuries, causing knee osteoarthritis. It has been observed that knee osteoarthritis affects more frequently patients who practice sports activities on a regular basis. Despite the great benefits obtained from sports practice, an increase in pain and joint damage caused during training has been observed. This Will later lead to functional limitation, conditioning a decrease in physical performance or even premature withdrawal from the sport.

Diagnosis

The diagnosis of overuse injuries and early osteoarthritis in sports patients is carried out through physical examination, obtaining information related to the type of sport, weekly practice time and time spent practicing it, this can offer us a clear idea of what whether it is an injury caused by micro-traumas, in addition, to the fact that there is already an evidence limitation to complete the sports activity or even withdraw from it, can confirm the diagnosis. Adequate inspection for the identification of biomechanical factors that predispose to specific conditions are femoral anteversion, valgus or varus of the knee, patellar malposition, excessive lateral insertion of the patellar tendon, foot pronation, decreased muscle mass vastus medialis and abnormal trajectory of the patella. This i show the clinical recurrence of pain, discomfort, intermittent periods of inflammation or edema followed by long periods with minimal symptoms and anterior knee pain caused during the squat, Will lead us to the clinical diagnosis of overuse. As for radiographic studies, by ultrasound, magnetic resonance, or arthroscopy, these will allow us to stage the degrees of joint injury.

Radiologic diagnosis:

- Simple X rays help to detect causes of knee pain, such as bipartite patella, osteoarthritis, loose bodies, occult fractures, and tumors. Several risk factors have

even been identified, such as patella alta or lateralization of the patella in the femoral Groove. A radiographic study is required that allows us to identify specific injuries where degrees of joint injury in the knee can be stratified. Therefore, the diagnosis could be confirmed, by visualizing osteophytes, joint space narrowing, subcondral sclerosis, bone cysts, and grading these changes according to the Kellgren and Lawrence II to IV scale.

- MRI can provide information on degenerative changes, such as fissures or thinning of cartilage, subchondral bone marrow edema and cysts.
- Musculoskeletal ultrasound can be a useful tool to identify focal changes in tendon and subtle changes in vascularity (by mean of color / Doppler), one of its benefits, although it's low cost, Will be the absence of radiation and patient comfort, compared with another image modalities.

CLASSIFICACION

Overuse injuries of the knee in adults include patello femoral Paint syndrome, quadriceps-patellar tendinopathy, and iliotibial band syndrome. As an addition to the classification criterion described for osteoarthritis, a classification has been proposed to identify the subpopulation of patients in the early stage who have a high risk of presenting Frank osteoarthritis of the knee. This type of classification for early osteoarthritis, a classification has been proposed to identify the subpopulation of patients in the early stage who have an elevated risk of presenting Frank osteoarthritis of the knee. This type of classification for early osteoarthritis is focused not as an individual diagnostic method but allows comparison of groups or subgroups of populations with similar characteristics, allowing standardization in clinical studies. Classifying osteoarthritis in initial stages is complex since conventional imaging criterion as well as signs and symptoms appear more sporadically, manifesting when there is heavy physical activity or repetitive sports. Therefore, a patient can be classified as having early osteoarthritis based on clinical and radiographic findings that must be integrated into the following 3 criteria:

1.- Knee pain (at least 2 episodes in les tan 10 days)

2.- Simple X-rays with Kellgren-Lawernce grade 0 or I or II osteoarthritis (osteophytes only)

3.- At least one for the following criterion:

- Arthroscopic findings of condral injury

- Findings of joint or meniscal degeneration by magnetic resonance imaging

The U-s National Athletic Injury Reporting System (NAIRS) divides overuse injuries into the following categories:

a) Undetectable – where the athlete does not stop their athletic activities,
b) Minor leaving1-7 days of sports activity
c) Moderate: from 8 to 21 days of abandonment of activities and
d) Major: more than 21 days of loss of activities and serious injuries, resulting in permanent disability.

TREATMENT OF KNEE OVERUSE SYNDROME:

There is no specific treatment guideline for most conditions caused by knee overuse. It is essential to have an adequate diagnosis of osteoarthritis at an early stage to incorporate the most appropriate treatment. The most recommended treatment for early osteoarthritis, includes weight loss, physical therapy, non-steroidal anti-inflammatory drugs, nutraceutical supplements, topical treatments, and steroid injections. In knee overuse syndrome, starting with a decrease in overload, correcting gait abnormalities, improving training techniques, adding strengthening and stretching exercises, as well as adapting the use of footwear and adding physical therapies with ice, have resulted effective methods as first line treatment.

NON-SURGICAL

The first line of treatment in early osteoarthritis of the knee caused by overuse in sports should be given conservatively and without surgery. The main objective of this treatment is to delay arthroplasty through a protocol that includes non-steroidal anti-inflammatory drugs, joint injections, as well as general measures of weight loss following a series of low-impact exercises. Physical therapy has an important role in the treatment of early osteoarthritis in athletes, stretching the extensor and abductor muscles of the knee can reduce pain and improve function. Cold therapy can also decrease the level of prostaglandins in synovial tissue resulting in decreased inflammation, reducing atherogenic muscle inhibition and facilitating vastus medialis motor neuron activity. Cryotherapy may allow more effective strengthening of the quadriceps in patients with knee joint abnormality; therefore, despite the current lack of clear research evidence, cryotherapy is recommended as a mainstay of conservative treatment in physiotherapy.

NON-STEROID ANTI-INFLAMMATORY AGENTS

Drug treatments commonly include the use of pain relievers such as aspirin or acetaminophen, and nonsteroidal anti-inflammatory drugs (NSAIDs); The use of NSAIDs is controversial due to the absence of histological inflammatory response in knee overuse syndrome. There is also concern that NSAIDs may interfere with the normal healing response of muscles and tendons.

INFILTRATIONS

- Platelet Rich Plasma (PRP) injections have been studied for the treatment of tendinopathy and osteoarthritis, obtaining Good medium-term results in the treatment of recalcitrant patellar tendinopathy by applying multiple injections. The use of PRP has been qualified by the Clinical Practice Guidelines of the American Academy of Orthopedic Surgeons (AAOS) for the treatment of knee osteoarthritis, however their decision was that it's use cannot be recommended for or against treatment of knee osteoarthritis.

  INFILTRATION WITH HIALURONIC ACID

  Visco-supplementation with hyaluronic acid is one of the most recommended treatments for the non-surgical management of osteoarthritis, it can be recommended as first-line therapy, or when corticosteroids and non-steroidal anti-inflammatory drugs are inefficient, contraindicated or poorly tolerated; viscosupplementation is a safe procedure, without any systemic or local side effects, excluding possible injection pain and a feeling of heaviness for a few hours or days after treatment. Hyaluronic acid is one of the most used methods to preserve the cartilage and intra-articular structures of the knee. It protects the chondrocytes and lubricates the joint to stabilize the cartilage and the synovial membrane, benefits have also been described in its analgesic and intra-articular structures of the knee. It protects the chondrocytes and lubricates the joint to stabilize the cartilage and the synovial membrane, benefits have also been described in its analgesic and anti-inflammatory effects. Viscosupplementation significantly reduces knee pain during the first months, after which the effect is maintained for another 12 to 18 months. During this time joint function can improve and therefore patients can quickly return to sports activities.

  Physiotherapy

  A fundamental part of the overuse syndrome treatment is to know that mistakes in techniques of training could be avoided by guidelines of different type of exercises. Physical therapy should focus on stretching inflexible muscles and tendons (for

example: iliotibial band and hip external rotators in ITBS, hamstrings in patellar tendinopathy) and strengthening weak / core muscles (quadriceps and hip external rotators in PFPS/patella tendinopathy), in addition to the eccentric muscles. Specific training should be instituted for some conditions, such as quadriceps and patella tendinopathies. It has been found that physical therapy as a treatment for osteoarthritis in early stages has symptomatic benefits, and in sports patients it Will allow them to adapt a specific toning program that limits joint impact.

TYPES OF HYALURONIC ACID

Native HA. Has a molecular weight of 4-10 million Daltons and is present in joint fluids at a concentration of approximately 0.35 g/100 ml; Hyaluronic Acid is a glycosaminoglycan, linear polysaccharide, composed of repeating units (D-glucuronic acid and N-acetyl-glucosamine), is one of the main components of the extracellular matrix. It is part of the connective, epithelial and neuronal tissues. Infiltrations with hyaluronic acid are a viable option for athletes diagnosed with early osteoarthritis by reducing the absorption of loads in the knee, improving lubrication as well as having a certain degree of chondroprotection. Its principal biological effects are the regulation of anti-inflammatory mechanisms with antioxidants, reduction in the induction of cytokines, anabolic effect on cartilage and blockade of joint nociceptors that reduce pain.

Hyaluronic Acid with Sorbitol
Trade Name: Synolis VA
Approved chemical or generic name: hyaluronic acid (NaHa), sorbitol (C3H8O3), sodium chloride (NaCl), phosphate salts (Na2HPO4 + NaH2PO4) and sterile water for injection (SWFI).

Synolis VA is a viscoelastic, sterile, non-pyrogenic, isotonic, buffered solution of 2% hyaluronic acid. The hyaluronic acid used in synolis VA is obtained from bacterial fermentation and has a high molecular weight of 2 Mdaltons, it has a neutral pH of 6.8 - 7.4 like synovial fluid. High concentration and high molecular weight of hyaluronic acid combined with sorbitol limits its degradation and confers the capacity of viscoelastic solution to restore joint lubrication and shock absorption properties. Synolis VA work by restoring physiological and viscoelastic properties of synovial fluid that have been progressively lost during the development of osteoarthritis. Synolis VA therefore reduces pain and discomfort caused by symptomatic OA and improves joint mobility.

Composition: Each 1 ml contains: hyaluronic acid 20 mg, Sorbitol 40 mg, phosphate buffered solution 1ml. Synolis VA contains a 2 ml siringe of viscoelastic solution.

Contraindications.

Synolis VA should not be used in:

- Patients known to be hypersensitive to hyaluronic acid or sorbitol.
- Pregnant lactating patients
- Minors
- Skin disease or infection at the level of the application site.

CLINICAL EVALUATION

The knee injury and Osteoarthritis Outcome Score (KOOS) is a new, well-designed, and simple self-administered instrument developed to assess short, and long-term symptoms and function in patients with knee injuries and osteoarthritis. It has good evidence of reliability, validity, and responsiveness in different populations with different pathologies, injury duration, ages, and activity levels. The KOOS scale has been shown to be very effective in Young and active patients; it is intended to be used in short and long-time intervals; to assess week-to-week changes induced by treatment (medication, surgery, physical therapy). All items were scored from 0 to 4, and each of the five scores was calculated as the sum of the included items; scores are then converted to a scale of 0-100, where zero represented extreme knee problems and 100 represented no knee injury, this can be represented as a percentage.

The INTERNATIONAL KNEE DOCUMENTATION COMMITTEE IKDC, is a patient. oriented score to qualify symptoms and functions related to the activity of daily living; evaluates knee injuries and categorizes them into subjective variables, symptoms, ranges of motion and ligamentous exploration, which is subcategorized into normal, almost normal, abnormal and severely abnormal, the objective of this scale is to provide the physician with information on patient satisfaction and their knee. Point son the *Subjective Knee Assessment Form* are calculated by adding the points for the individual items, and then transforming the points on a scale from 0 to 100. The transformed points are interpreted as a measure of the ability to function, with higher points representing higher levels of functioning and lower levels of symptoms. One hundred points are interpreted to mean that there is no limitation in activities of daily living or sports activities, and the absence of symptoms.

Justification and Statement of the Problem

Currently there is a major influence to promote sport in the population, however, despite its great benefits, the development of early osteoarthritis secondary to micro-trauma due to overuse must be taken into consideration. In fact, the presence of early osteoarthritis following a prolonged or intense period of physical activity, or in those who practice impact sports regularly, is well described. Athletes who have initial stages of osteoarthritis require a treatment that improves their clinical symptoms and improves functional functions for as long as possible. Another objective of treatment is for their daily sports activities; sports activities; intraarticular HA injections are more effective in young patients, especially in the long term, while the results are les promising in athletes with advanced osteoarthritis. Reducing the viscoelasticity of synovial fluid, the transmission of mechanical force to the cartilage increases susceptibility to mechanical damage. Therefore the restoration of normal joint homeostasis is the reason for the administration of hyaluronic acid in the joints , in addition to seeking a physiological healing process and, if possible, complete; secondly, to shorten the recovery time, especially in athletes who are not going to limit their activity. The currently evidence that exists regarding the efficacy and safety of viscosupplementation in athletes is limited, hence the present investigation arises from the understanding that there are no protocols that demonstrate the benefits of knee joint infiltration using hyaluronic acid plus sorbitol in athlete patients, so in order to determine the safety and efficacy of this treatment, the following research question is proposed:

RESEARCH QUESTION

Is there a clinical and functional difference in the short and medium term in patients with knee pain due to overuse associated with sports treated by infiltration with hyaluronic acid with sorbitol?

Hypothesis

Athletes with sports-related overuse knee pain have Good clinical and functional results in the short and medium term through joint infiltration of hyaluronic acid with sorbitol.

Null Hypothesis

Athletes with knee pain due to sports-related overuse do not have Good clinical and functional results in the short and medium term through joint infiltration of hyaluronic acid with sorbitol.

Objectives

General Objective

To evaluate safety and efficacy of hyaluronic acid with sorbitol in athletes with overuse knee pain by comparing functional outcomes at short, medium and long term after treatment.

Specific Objectives

- To assess the safety and efficacy of hyaluronic acid with sorbitol in patients with sports-associated knee pain.
- To compare the clinical and functional results of patients with sport-associated knee pain after before and after treatment.

METHODS

Study Design

This research will be a cohort study, prospective and unidirectional direction.

Selection Criteria

- Patients with knee pain for more than 3 months
- Patients between 30 and 55 years old
- Patients without a history of previous knee joint surgery.
- Patients without chronic-degenerative diseases such as diabetes, hypertension, rheumatoid arthritis or other autoimmune diseases.
- Patients who perform impact social sports at least 3 times a week for more than 1 hour in the last 3 months prior to treatment.
- Patients without a history of allergies to non-steroidal anti-inflammatory drugs.
- Patients with no history of infection in or around the knee.

EXCLUSION CRITERIA

- Patients who cannot be categorized as social athletes.
- Patients with an associated sports injury that limits their sports practice.
- Patients who have a treatment associated with knee pain independent of that established in the study protocol.

ELIMITATION CRITERIA

- Patients who suffer from an injury or illness during the study that may limit their sports activity or who require an analgesic or anti-inflammatory treatment other than that established in the protocol.
- Patients who personally want to leave the study.
- Patients who did not have complete follow-up during the study.
- Patients who present an allergic or infectious reaction related to hyaluronic acid or prolotherapy or sepsis and antisepsis methods for infiltration.
- Patient with an allergic reaction to non-steroidal anti-inflammatory drugs.

VARIABLES

Variable	Operational Definition	Dimension	Variable type	Instrument	Indicator
Age	Time of life of any person	Without categories	Quantitative Discrete	Interview	Years
Gender	Biological and physiological characteristics that differentiate a man from a woman	Female Male	Qualitative Nominal	Interview	Gender
Body Mass Index	Score calculated by weight and height of a person.	Normal Overweight Obesity	Quantitative Discrete	Measuring tape Weighing machine	Weight in kg / Height in square meters
Affected Knee	Anatomic Knee side	Left	Qualitative	Physical Exploration	Left

		Right	Nominal		Right
Athlete	Person who practice any type of sport	Social Amateur Professional	Qualitative Nominal	Interview	Have a sports activity for more than 3 months, 3 times a week over 60 minutes per session
Score KOOS	Scores that evaluate functional and osteoarthrosis around the knee	Symptoms Joint Stiffness Pain Regular activities Sports activities Quality of life	Quantitative Discrete	Interview Physical Exam	Percentage 0-100%
Score IKDC	International Knee Documentation Committee	Symptoms Regular Activities Sports Activities	Quantitative Discrete	Interview Physical exam	Percentage 0-100%
Visco supplementation	Intraarticular joint injection of high weight molecular hyaluronic acid with sorbitol	Mono dose Multi dose	Qualitative Nominal	Hyaluronic acid 2ml plus sorbitol 2 dose per knee	Yes = Knee joint infiltration No= Did not apply
Training sports technique	Coaching for adequate techniques of certain sports	Manual technique Instrumented	Qualitative Nominal	Personalized coaching techniques	Achievement survey

	activities			Or Information brochure	

Research Universe

General Population who does sports activities and have knee overuse syndrome between June of 2022 and October 2022.

Sample Size

It will be a non-probability sampling where will be chosen participants who meet selection criteria over the enrolling time which will be for 5 months. The lower limit will be 60 participants and the higher limit will be 120 participants.

Sample size formula: n(sample), z (confidence level), p (probability to occur the studied event), q (probability to didn't occur the studied event) and e (maximum accepted estimated error)

$$n = \frac{Z2 * p*q}{e2}$$

Study Design

Research enrolling and diffusion will be initiated after authorization of the ethics and investigation committee. All participants with knee pain related to sports will be accepted for a physical evaluation. All participants will be interviewed about physical activities, sports, injuries, and knee pain. Once they have been categorized as athletes with knee overuse pain syndrome and have met the selection criteria, then will be invited to the research. For this, the participants must be agreed and sign the informed consent Appendix 1 and 2.

Before treatment Group

To participants who initiate the study research will be applied the KOOS and IKDC scores, the results will be recorder in the collection data sheet. Appendix 2. Participants will be explored by physical exam focus on knee pathology, and also an echography knee scan

looking for non-overuse pain injuries. Coaching for sports activities will be explain for each patient in order to improve its own training techniques adding stretching exercises for previous and after training.

After treatment Group

After KOOS and IKDC scores were recorder two dose of Hyaluronic Acid plus sorbitol will applied. Technique: On the examination table, the patient will lie down at supine position and the area of the knees to be infiltrated will be discovered. Asepsis of the knee region will be performed using an iodine and alcohol solution, the remaining synovial fluid in the joint will be extracted with a 10cc syringe then 4 milliliters of 80 mg of hyaluronic acid plus 160 mg of sorbitol will be applied (Synolis VA Aptissen S. A.) at the sub quadricipital level with a 22G x 32mm sterile needle. At the end of the infiltration, the needle will be removed, and the injection site will be covered with a small sticky-band, which can be thrown away after 20 minutes. It will be recommended do not made any kind of sports activity following the next 72 hours and applied ice therapy 3 times per day for over 20 minutes. Scores recorder data will be made at 15 days, then at 3 and 6 months.

Once the enrolling phase of the trial be concluded, statistical analysis will be made with Excel Office software for Windows, IBM SPSS and Prisma.

Statistical analysis

Recorder data of the functional scores will be evaluated before and after treatment, also at 15 days, 3 and 6 months after hyaluronic acid supplementation.

Data analysis will be made by means standard deviation for numeric variables, also t-test for parametric and Wilcoxon Mann Whitney for non-parametric variables, a standard error of 95% is allowed. Differences in time will be calculated and group compared by Anova test. Variable correlation and association measures with relative risk and attributable risk with Fisher's test will be made with an confidence interval of 95%.

Ethical Implications

This research project will be developed after approvement of the ethics and research Institutional committee.

This research study will be according to principles of ethics by the Helsinki Declaration (2000) following three principles of ethics: beneficence, justice and respect for people.

All the declared principles will be followed in relation to the guide of good clinical practice.

This study research will follow the ethical codes established by the 18ª worldwide medical assembly, protection principle of the participants in the Nuremberg Code (1947), Belmont inform (1979), OMS guidelines and CIOMS (2002) guides for human biomedical research. Also following the NOM 012 of biomedical research health department.

Organization

Human Resources: Principal Research, co-author, medical assistant. Statesian

Economic burden: Noneconomic profit will be obtained by the principal author and coauthor. It will be no economic benefit will be for any participant.

Physical Resources:

Medical office: In this area medical assistant will collect the score records, physical examination, sonographic evaluation, coaching sports hygiene techniques, and stretching exercises.

Request Funds: This Study research will be sponsored by Aptissen

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APPENDIX 1

2000 IKDC SUBJECTIVE KNEE EVALUATION FORM

Your Full Name_____

Today's Date: _____/_____/_____ (Day / Month / Year) Date of Injury: _____/_____/_____ (Day / Month / Year)

SYMPTOMS*:

*Grade symptoms at the highest activity level at which you think you could function without significant symptoms, even if you are not actually performing activities at this level.

1. What is the highest level of activity that you can perform without significant knee pain?

   4❑Very strenuous activities like jumping or pivoting as in basketball or soccer
   3❑Strenuous activities like heavy physical work, skiing or tennis
   2❑Moderate activities like moderate physical work, running or jogging
   1❑Light activities like walking, housework or yard work
   0❑Unable to perform any of the above activities due to knee pain

2. During the past 4 weeks, or since your injury, how often have you had pain?

	10	9	8	7	6	5	4	3	2	1	0	
Never	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	Constant

3. If you have pain, how severe is it?

	10	9	8	7	6	5	4	3	2	1	0	
No pain	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	Worst pain imaginable

4. During the past 4 weeks, or since your injury, how stiff or swollen was your knee?

   4❑Not at all
   3❑Mildly
   2❑Moderately
   1❑Very
   0❑Extremely

5. What is the highest level of activity you can perform without significant swelling in your knee?

   4❑Very strenuous activities like jumping or pivoting as in basketball or soccer
   3❑Strenuous activities like heavy physical work, skiing or tennis
   2❑Moderate activities like moderate physical work, running or jogging
   1❑Light activities like walking, housework, or yard work
   0❑Unable to perform any of the above activities due to knee swelling

6. During the past 4 weeks, or since your injury, did your knee lock or catch?

   0❑Yes 1❑No

7. What is the highest level of activity you can perform without significant giving way in your knee?
   4❑Very strenuous activities like jumping or pivoting as in basketball or soccer
   3❑Strenuous activities like heavy physical work, skiing or tennis
   2❑Moderate activities like moderate physical work, running or jogging
   1❑Light activities like walking, housework or yard work
   0❑Unable to perform any of the above activities due to giving way of the knee

SPORTS ACTIVITIES:

8. What is the highest level of activity you can participate in on a regular basis?

4❑ Very strenuous activities like jumping or pivoting as in basketball or soccer
3❑ Strenuous activities like heavy physical work, skiing or tennis
2❑ Moderate activities like moderate physical work, running or jogging
1❑ Light activities like walking, housework or yard work
0❑ Unable to perform any of the above activities due to knee

9. How does your knee affect your ability to:

		Not difficult at all	Minimally difficult	Moderately Difficult	Extremely difficult	Unable to do
a.	Go up stairs	4❑	3❑	2❑	1❑	0❑
b.	Go down stairs	4❑	3❑	2❑	1❑	0❑
c.	Kneel on the front of your knee	4❑	3❑	2❑	1❑	0❑
d.	Squat	4❑	3❑	2❑	1❑	0❑
e.	Sit with your knee bent	4❑	3❑	2❑	1❑	0❑
f.	Rise from a chair	4❑	3❑	2❑	1❑	0❑
g.	Run straight ahead	4❑	3❑	2❑	1❑	0❑
h.	Jump and land on your involved leg	4❑	3❑	2❑	1❑	0❑
i.	Stop and start quickly	4❑	3❑	2❑	1❑	0❑

FUNCTION:

10. How would you rate the function of your knee on a scale of 0 to 10 with 10 being normal, excellent function and 0 being the inability to perform any of your usual daily activities which may include sports?

FUNCTION PRIOR TO YOUR KNEE INJURY:

Couldn't perform daily activities	0 ❑	1 ❑	2 ❑	3 ❑	4 ❑	5 ❑	6 ❑	7 ❑	8 ❑	9 ❑	10 ❑	No limitation in daily activities

CURRENT FUNCTION OF YOUR KNEE:

Cannot perform daily activities	0 ❑	1 ❑	2 ❑	3 ❑	4 ❑	5 ❑	6 ❑	7 ❑	8 ❑	9 ❑	10 ❑	No limitation in daily activities

APPENDIX 2

Knee Injury and Osteoarthritis Outcome Score (KOOS)

Pain

P1 How often is your knee painful?	☐ Never	☐ Monthly	☐ Weekly	☐ Daily	☐ Always

What degree of pain have you experienced the last week when…?

P2 Twisting/pivoting on your knee	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Extreme
P3 Straightening knee fully	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Extreme
P4 Bending knee fully	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Extreme
P5 Walking on flat surface	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Extreme
P6 Going up or down stairs	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Extreme
P7 At night while in bed	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Extreme
P8 Sitting or lying	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Extreme
P9 Standing upright	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Extreme

Symptoms

Sy1 How severe is your knee stiffness after first wakening in the morning?	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Extreme
Sy2 How severe is your knee stiffness after sitting, lying, or resting later in the day?	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Extreme
Sy3 Do you have swelling in your knee?	☐ Never	☐ Rarely	☐ Sometimes	☐ Often	☐ Always
Sy4 Do you feel grinding, hear clicking or any other type of noise when your knee moves?	☐ Never	☐ Rarely	☐ Sometimes	☐ Often	☐ Always
Sy5 Does your knee catch or hang up when moving?	☐ Never	☐ Rarely	☐ Sometimes	☐ Often	☐ Always
Sy6 Can you straighten your knee fully?	☐ Always	☐ Often	☐ Sometimes	☐ Rarely	☐ Never
Sy7 Can you bend your knee fully?	☐ Always	☐ Often	☐ Sometimes	☐ Rarely	☐ Never

Activities of daily living

What difficulty have you experienced the last week…?

A1 Descending	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Extreme
A2 Ascending stairs	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Extreme
A3 Rising from sitting	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Extreme
A4 Standing	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Extreme
A5 Bending to floor/picking up an object	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Extreme
A6 Walking on flat surface	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Extreme
A7 Getting in/out of car	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Extreme
A8 Going shopping	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Extreme
A9 Putting on socks/stockings	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Extreme
A10 Rising from bed	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Extreme
A11 Taking off socks/stockings	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Extreme
A12 Lying in bed (turning over, maintaining knee position)	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Extreme
A13 Getting in/out of bath	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Extreme
A14 Sitting	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Extreme
A15 Getting on/off toilet	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Extreme
A16 Heavy domestic duties (shovelling, scrubbing floors, etc)	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Extreme
A17 Light domestic duties (cooking, dusting, etc)	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Extreme

Sport and recreation function

What difficulty have you experienced the last week…?

Sp1 Squatting	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Extreme
Sp2 Running	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Extreme
Sp3 Jumping	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Extreme
Sp4 Turning/twisting on your injured knee	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Extreme
Sp5 Kneeling	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Extreme

Knee-related quality of life

Q1 How often are you aware of your knee problems?	☐ Never	☐ Monthly	☐ Weekly	☐ Daily	☐ Always
Q2 Have you modified your lifestyle to avoid potentially damaging activities to your knee?	☐ Not at all	☐ Mildly	☐ Moderately	☐ Severely	☐ Totally
Q3 How troubled are you with lack of confidence in your knee?	☐ Not at all	☐ Mildly	☐ Moderately	☐ Severely	☐ Totally
Q4 In general, how much difficulty do you have with your knee?	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Extreme

APENDIX 3: Data collection sheet

Date sheet colection

Safety and efficacy of hyaluronic acid plus sorbitol in sports man with overuse knee pain.

1.- Participant indetification cardex

Date:_____

Participant ID:_____ Age_____

Gender: Male_____ Female_____

Afected Side_____Right___ Left_____ Both_____

Weight_____Kgs High_____cms BMI:_____

2.- Sports Activities:

Activity:_____ Elapsed Time since begin this sport_____

Frecuency

_____days per week _____minutes per day

3.- Treatment:

INFORMED CONSENT FORM

Research title: **Safety and efficacy of sodium hyaluronate plus sorbitol in athlete patients with knee pain due to overuse.**

ClinicalTrials.gov: NCT05450458

Date: 01/12/2023

Informed Consent Letter for Knee Joint Infiltration and Inclusion in Research Protocol: Safety and efficacy of sodium hyaluronate plus sorbitol in athlete patients with knee pain due to overuse.

ClinicalTrials.gov: NCT05450458

This letter constitutes the free and voluntary decision made by a patient, where they accept the diagnostic and/or therapeutic actions suggested by their doctor.

Date of Issuance:_____

Institution: Instituto de Seguridad Social del Estado de México y Municipios.

Location: Hospital Regional Tlalnepantla

Diagnosis_____
____

Under this letter, I authorize that I:_____ be included in the medical research protocol called: Hyaluronic Acid in Overuse Knee Pain, in which I will undergo: JOINT INFILTRATION OF ONE OR BOTH KNEES IN 2 DOSES USING HIGH MOLECULAR WEIGHT SODIUM HYALURONATE SOLUTION (2 MDALTONS) PLUS POLYOL (SORBITOL) SYNOLIS.

This biological implant consists of a sterile viscoelastic isotonic solution of sodium hyaluronate indicated to improve the symptoms of knee pain and mobility in patients with osteoarthritis. This product is indicated as a non-surgical treatment option for knee injuries.

Treatment risks: Infrequent risks have been reported, including the presence of knee edema, increased synovial fluid, skin redness, and temporary local pain. Other adverse effects may include an immunological allergic reaction to the components, triggering anaphylactic shock, septic arthritis, and even death.

Benefits: The expected benefits of this treatment are to temporarily improve knee pain and function during medium and high-impact sports activities, even with elevated BMI.

Contraindications: This synthetic implant cannot be applied to pregnant patients, breastfeeding individuals, persons under 18 years old, or patients with a history of knee or peripheral tissue infection.

The procedure will be carried out using sterile technique, consisting of cleaning the area to be infiltrated with alcohol antiseptic solution. Infiltration with a 22G x 32mm needle at the lateral infra-patellar level of the patella. Placement of a sterile dressing with adhesive bandage which can be removed 20 minutes after application. It is recommended not to perform physical or high-impact sports activities for the following 48 hours.

I will undergo an evaluation with two questionnaires (IKDC and KOOS scores) that I should fill out with the utmost accuracy on the day of the infiltration, at 15 days, 3 months, and 6 months.

With prior authorization and understanding that the procedure and all related details have been explained to me, I give my explicit consent authorizing the use of my results for the research protocol.

_____ _____

Full Name and Signature of Patient Name and Signature of Treating Physician

_____ _____

WITNESS 1 WITNESS 2

Appendix: **Informed Assent to participate in the Research Protocol.**

Research Name: **Safety and efficacy of sodium hyaluronate plus sorbitol in athlete patients with knee pain due to overuse.**

Principal Investigator: xxxxxxxxxxxxxxxxxxxx

Co-Investigator: xxxxxxxxxxxxxxxxxxxxxxxxxx

Institutional Site: xxxxxxxxxxxxxxxxxxxxxxxxxxx

The objective of this research is to understand the efficacy, safety, and clinical benefits of Sodium Hyaluronate plus Sorbitol, in patients with early osteoarthritis secondary to knee overuse syndrome in athletes.

This research project has the following characteristics:

1. Description of the research: It intends to compare a control group against the study group where participants for each group will be randomly (by chance) selected.

Study Group: This group will receive 2doses of sodium hyaluronate plus sorbitol in the affected knee.

2. Risks and discomforts: There may be no clinical difference in their symptoms and they may continue with pain or functional limitation that partially or totally impedes sports activity. In the study group: anaphylaxis to sodium hyaluronate components may occur, knee redness, edema, and temporary residual pain.

3. Expected benefits: No benefit will be obtained by integrating into this study; however, their results will be useful for international medical scientific development.

4. Compensation in case of damage: If any adverse effect related to the applied treatment is presented, follow-up and treatment will be provided for the effects caused by the infiltration.

5. Economic Compensation: No economic remuneration exists for integrating into this study. The decision to integrate into this research is entirely voluntary and there is the possibility of withdrawing from it at any time without losing any benefits that might be obtained. Medical evaluations, visco-supplementation therapy, or physiotherapy will be at no cost.

6. Protection of personal data: The researchers will have access to medical history and clinical records while safeguarding the protection and confidentiality of personal data. The patient's identity will not be exposed in any results publication.

7. Information update: During the study, participants will be informed of new information that might be relevant to their decision to continue being part of the study.

8. Research duration and data collection: Information related to symptoms and lifestyle will be requested for a period of 6 months after participating in this research. Contact can be in a medical consultation area, by video call, phone call, or email. An emergency phone number will be provided in case additional information or evaluation is needed beyond the scheduled.

9. Number of patients: This research intends to involve approximately 70 participants.

I voluntarily accept to participate in this clinical research trial.

Yes No

Participant Name:_____ Signature:_____ Date: _____

Witness:_____ Signature:_____ Date: _____

Person obtaining consent:_____ Signature: _____