Universitat de Girona
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HYALURONIC ACID AND PLATELET-RICH PLASMA INTRAARTICULAR INJECTIONS IN YOUNG HIGH-INTENSITY ATHLETES WITH EARLY KNEE OSTEOARTHRITIS

FINAL GRADE PROJECT
January 2015

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I would like to thank Dr. Daniel Castillo, my final grade project tutor, who helped me and encouraged me in everything. This is also your project.

I would also like to thank all my family and Oriol C. for all the support received; as well as Àngels Puigdollers, Joan Garcia and Elda Balliu for their contributions, that enrich the project.

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1. ABBREVIATIONS

ACL Anterior Cruciate Ligament

BLOKS Boston Leeds Osteoarthritis Knee Score

BMI Body Mass Index

BMLs Bone Marrow Lesions

ECM Extracellular Matrix

GFs Growth Factors

HA Hyaluronic Acid

IA Intraarticular

ICRS International Cartilage Repair Society

MRI Magnetic Resonance Imaging

MSCs Mesenchymal Stem Cells

OA Osteoarthritis

PRP Platelet-Rich Plasma

WORMS Whole-Organ Magnetic Resonance imaging Score

2. ABSTRACT

Background Knee osteoarthritis is a major cause of physical disability worldwide; in fact, because there is no cure. With the purpose of reversing the degenerative process that osteoarthritis causes, and therefore, heal it; the criteria to diagnose early-stage osteoarthritis has been suggested, so patients at risk of developing it and responders to certain treatments will be identified. For these profile patients, in which high-intensity athletes are included, intraarticular hyaluronic acid and platelet-rich plasma injections may offer the possibility to reverse, or at least, halt osteoarthritis degeneration.

Objective The purpose of the project is to determine whether reverse progression of osteoarthritis, or at least, cessation of further degeneration is possible by using minimally invasive procedures, including HA and PRP intraarticular injections

Design A triple-blinded, randomized, placebo-controlled clinical trial. Designed as multicenter, based at the hospital Santa Caterina in Salt.

Participants Young high-intensity athletes diagnosed with early osteoarthritis by *Criteria for early osteoarthritis* of the Articular Cartilage Committee of ESSKA.

Key words Early knee osteoarthritis; Athletes; Hyaluronic acid; Platelet-rich plasma; Intraarticular injection

3. INTRODUCTION

3.1. Background

Osteoarthritis (OA) is the most common joint disease and a major cause of physical disability and impaired quality of life worldwide, especially consuming an important amount of health resources (1). It is because of its hallmark symptom, which is pain, that lower extremity OA is well-assumed to be a leading cause of reduced mobility on daily living in older adults (2), specially the knee, as it is the joint mostly affected (3,4).

Approximately, 6% of people aged over 30 have radiological signs of OA, increasing up to 40% in people aged over 70. A quarter of these people, cannot perform activities in daily life (5). In reference to smaller regions, in Spain, the EPISER study estimated the prevalence of symptomatic knee osteoarthritis at 10,6% in people over 20, affecting more women than men (14% versus 5,2%). According to the study, the prevalence of being between 20 to 50 years old and having symptomatic knee osteoarthritis is 0,9% of the Spanish population, approximately (4).

All in all, the incidence of knee OA is unknown as there are no cohort studies done to date. However, it is already anticipated among experts that because of the aging population and increasing obesity, the incidence of knee OA will ascend and, therefore, it will become a capital problem for health systems worldwide (3).

Despite the fact that knee osteoarthritis is an important cause of physical disability, experts in this field recognize that it is diagnosed late in the disease progress, and as a consequence, conventional non-surgical treatments are capable of relieving symptoms and improve patients' quality of life, but at the expense of being ineffective in modifying the degenerative process that the cartilage suffers. It is for that reason that a lot of effort has been invested in this issue during the last decade, with the intent of clearly identifying an early stage, in which there might be the possibility to reverse the degeneration or, at least halt the progression, a completely lost capacity in the later phases of osteoarthritis. Furthermore, having a new description of an initial stage will allow clinicians to detect those patients likely to progress through the disease and also will allow investigators to homogenise their study population, what has been impossible in these early stages of osteoarthritis until now (6).

Hence, in 2011 the Articular Cartilage Committee of the European Society of Sports Traumatology, Knee Surgery and Arthroscopy (ESSKA) proposed a new definition to

consider an early stage of knee OA, based on the already known criteria of the American College of Rheumatologist, which included a combination of clinical and radiological findings to diagnose established osteoarthritis.

Whereas knee osteoarthritis is not only a cartilage defect, but also involving synovial membrane, the subchondral bone, ligaments, menisci, capsule and periarticular structures, such as muscles (7), the new definition includes some of their alterations. Therefore, a patient is diagnosed as having early OA when meeting three of the following criteria (8) (see ANNEX I and ANNEX II):

" 1. Knee pain at least two episodes of pain more than 10 days in the last year
2. Standard radiographic Kellgren-Lawrance grade 0 or I or II (osteophytes only) in standing weight-bearing position with knees in approximately 20º of flexion and the feet in 5º of external rotation. The radiographs should be done bilaterally from a posteroanterior view in the frontal plane.
3. At least one of the two following structural criteria:
    - Arthroscopic findings of cartilage lesion following the ICRS classification: ICRS grade I-IV in at least two compartments or grade II_IV in one compartment with at least surrounding softening and swelling of the cartilage
    - MRI findings demonstrating articular cartilage degeneration and/or meniscal degenerations, and/or subchondral bone marrow lesions (BMLs). Minimum two of the following scores should be fulfilled:
        a. Cartilage morphology scores grade 3 or higher (WORMS grades 3-6): minimally multiple areas of partial thickness defects with intermittent areas of normal thickness to diffuse full thickness loss in region (more than 75%; grade 6).
        b. Cartilage score 1: minimally grade 2 (BLOKS grade 2 and 3): 10-75% of cartilage loss in a region (medial, lateral, patellofemoral) to more than 75% cartilage loss in a region.
        c. Meniscal tears: grade 3 or higher (BLOKS grade 3-4): from displaced tears or partial resection (grade 3) to complete maceration, destruction, resection (grade 4).
        d. BMLs, typically scored as BMLs size: minimally WORMS grade 2, i.e., 25% or higher BMLs in any one compartment. "

To better understand what exactly happens in this early stage of osteoarthritis, it has to be considered that the cartilage is involved in strictly regulated conditions and low

homeostatic turnover. This condition would limit extremely the ability to self-repair when degradation processes occur due to biomechanical or biochemical changes (7,9).

After a cartilage injury is suffered in an early stage, the extracellular matrix (ECM) becomes altered by losing proteoglycans and increasing its water content, resulting in the disruption of collagen network and, thus, fibrillation of the cartilage surface (10). Firstly, compensatory response, mediated by growth factors (GFs) (11), is carried out by a proliferation chondrocytes in clusters, which increase the synthesis of ECM components (7), being able to maintain the integrity of the cartilage. However, this attempt to repair fails and leads to chondrocytes hypertrophy (12) and catabolic processes (9), producing mainly tissue-destructive enzymes (aggrecanases and matrix metalloproteinases), increasing apoptotic death chondrocytes and, finally, deficient synthesis of ECM components. As a result, there is cartilage degeneration with a decrease in its thickness (13).
Parallelly, or even before the degeneration of the cartilage (14), the subchondral bone is being remodelated specially beneath regions of articular cartilage damage. A progressive increase in subchondral plate and subarticular spongiosa thickness, also with osteophytes formation are the chief changes (15). Moreover, in recent studies, this structure has been positioned as the primary cause that might produce symptoms, as it is well-vascularised and innerved (16).

Although articular cartilage and subchondral bone are the two most important structures related to the onset of early osteoarthritis, other knee structures may be affected, as mentioned above. In this way, meniscus, synovate membrane, ligaments and muscle injuries lead to joint instability and, therefore, more degenerative cartilage progression (7).
Recognizing the biochemical changes that these structures suffer may be important because early diagnosis of the disease and the application of more specific treatments could be a solution to reverse the degenerative process.

Regarding the etiology of knee osteoarthritis, it is recognized as a complex process and it is an ongoing research issue (13,17). In fact, it is already known that multiple factors interplay and increase the risk of osteoarthritis, but it is not completely understood how (13). So, to understand them, first it needs to be assumed that OA is a result of exercise stress applied in a context of systemic susceptibility, in which the main risk factor of osteoarthritis is age (12). Actually, it is well established that there are age-related

changes which cause alterations in chondrocyte and matrix functions and structure, reducing the ability to synthesize and repair the matrix. All of this is due to a decreased sensitivity to GFs signalling, thus decreasing the capability to regeneration (12,17). Also, females are associated with a higher risk of suffering OA, being more predisposed to severity and progression than men, especially after menopause (18).

However, age and gender work in combination with other factors, such as genetics which has a high heritability component up to 40% (19), or biomechanical disorders; both to intensify and, thus, accelerate the changes that the age per se cause. Other risk factors like diet or smoking are still in controversial, as to whether they may or not be factors that could contribute to OA progression (20).

Special interest is required for osteoarthritis when talking about age and related to biomechanical alterations. In young patients, knee osteoarthritis is principally a consequence of non-optimal biomechanics conditions of the joint that eventually can produce a higher mechanical demand than what the knee is capable of sustaining and repairing. This finally overcomes the knee tolerance and will make it susceptible to early cartilage degeneration. Focusing on these several biomechanical factors, altered overloading plays an important role since many clinical conditions can result on it, and actually it is the main cause for this excessive mechanic demand (17).

Affecting focally in the joint, malalignment is a condition that shifts from normal load distribution, which is passing slightly through the medial compartment, to abnormal transmission of mechanical forces (13,17). So in a varus and valgus malalignment, loads are being increased in the medial and lateral knee compartments, respectively, affecting the articular cartilage and the subchondral bone below. This increases the risk not for incidence of OA, but progression (17). In fact, four and five more times for medial and lateral compartment progression, respectively, was found in those people with varus and valgus malalignment. Moreover, progression occurs with greater intensity in advanced stages of the disease (21).

Other local factors that contribute to the degeneration of cartilage are joint instability or laxity. On one hand, muscle strength, represented mainly by the quadriceps, as it is a provider of dynamic stability to the joint, absorption of limb loading and deceleration during ambulation; its deficit at baseline, consequently destabilizes and overloads the

knee, resulting in a predisposition to greater cartilage degeneration (13,22). Conversely, OA may cause muscle weakness due to the joint disuse in order to avoid pain (13).
On the other hand, rupture of anterior cruciate ligament (ACL) is highly associated with the future development of osteoarthritis. Because of the loss of stability function that the ligament has, knee load is redistributed to a more peripheral location and, consequently, overloads parts of the articular cartilage (17). The importance of ACL rupture lies in the early onset of the degeneration, as precocious as 10 to 12 years after the initial injury. So, given the fact that this injury is mostly affecting teenagers and adults aged less than 30, osteoarthritis might occur when they are between 30-45 years of age (23). *Lohmander et al.* reported radiographic changes in 82% of the female soccer players, whilst a 51% met the criteria for radiographic knee OA, at a 12 year follow-up (24).

Markedly predisposition is given when combined ACL rupture with meniscal injuries (24). Since, meniscus have an essential role in load transmission in the knee, any loss or tear of the tissue may permanently alter the biomechanical environment of the joint, as well as the biological (17). For that, degeneration consequences occur as a result of erroneous loads transmission. Nevertheless, it has been demonstrated also, that OA may change the normal structure of the meniscus and, again, producing a non-functional tissue, which finally creates a vicious circle (13).

By affecting more diffusely the knee, the body mass index (BMI) seems to have a role in knee osteoarthritis progression, as more weight means more knee load and, thus, increases the possibility of clinical and radiological OA progression, in addition to the greater severity of symptoms (20). Actually, by increasing 5 units of BMI, there is a 35% higher risk of knee osteoarthritis (25), and by reducing weight, the risk decreases up to 50% (13).

Finally, and needing to be highlighted, is the increased risk of osteoarthritis due to excessive intensity in sport (13), understood as long-duration exercise, high stress, high repetition or high joint impact (26). Although it is still a controversial issue, several studies report the higher association between elite-level athletes and predisposition to OA development when compared to the aged-matched general population, because of the biomechanical overwork that the knee has to sustain and, also, related to the type of sport (26–28). *Tveit et al*. reported that, when adjusted per age, the risk of development knee OA was 64% higher in former athletes than in the control group (29). Nevertheless, risk for osteoarthritis is greater if there is a history of previous knee injury (ACL rupture

or meniscus tear) or malalignment, providing it from susceptibility to early cartilage degeneration (26) and, thus, practising sport would determine a constant overloading in a knee that already has risk factors to develop osteoarthritis.
Furthermore, this issue requires much importance, for the reason that if it is thought that high-intensity sports are a predisposing factor for osteoarthritis, as well as knee injury, we must recognize that we are facing a risk patient profile who can have signs of emerging joint disease and also eventually a higher risk of developing established osteoarthritis; bearing in mind that they are very young and they might have motivation to continue playing despite pain, what maybe adding more insult to the knee (30). In conclusion, we believe that high-intensity sport is a companion and potentiating factor of others that have already been explained, which increases the huge aggression these can cause to the cartilage.

Focusing on current treatments, knee OA is limited to a healing perspective and its end-stage is usually treated with invasive joint replacement. However, if surgical treatment is not contemplated at an early stage of knee OA because there are no clear lesions and no other anomalies to be surgically repaired, non-surgical treatment would be the first choice (31). This conservative management aims to reduce symptoms and to improve knee functionality and, thus, maintain patients' quality of life.

There is a wide range of therapies used to achieve this goal, which include non-pharmacological support (physical therapy, dietary supplements and exercise), pharmacological therapies, such as analgesic drugs (paracetamol, NSAIDs or, in the worst cases, opioids) or slow-acting drugs (glucosamine, chondroitin sulphate and diacerein) and, also, minimally invasive therapies, that consist of intraarticular (IA) injection of different substances (corticoids, HA, PRP and stem cells). Actually, all those treatments in different degrees of efficiency, have demonstrated to relieve osteoarthritis symptoms (31), which are pain (typically worst during and after weight-bearing activities), stiffness (after a period of inactivity), discomfort and impaired functionality (loss of movement) (9).

Nevertheless, in a continuously evolving world, in which there is an emerging interest in regenerative therapies, new treatments are being developed; and among these, there are also therapies for the joint articular surface which are being investigated (8). Specifically, when setting the target of regeneration, IA injection treatments appear to be

a possible response (31). Hyaluronic acid (HA), platelet-rich plasma (PRP) and stem cells are up-to-date therapies in regenerative research in osteoarthritis.

HA, also called hyaluronan, is the oldest therapy between these three (31). HA is a glycosaminoglycan, produced from rooster combs as well as via bacterial fermentation, providing enhance viscosity and elasticity of the synovial fluid and, also, lubrication and shock absorbency in the knee joint (31,32). It can be found as a component of the cartilage matrix, forming complexes with proteoglycans called *aggrecan* (31). In the early osteoarthritic knee, aggrecanases break the HA-proteoglycan binding and, as the synovial membrane is inflamed, HA flows through it (32), thus decreasing its concentration up to 33-50% (31). It is thought that a knee IA infiltration of HA can restore temporally the lubricating and shock-absorbing effects of the synovial fluid, and as a consequence, it may improve clinical symptoms (32). But, actually, when based on evidence there is controversy, as to whether it is effective or not, especially when talking of high-molecular-weight and low-molecular-weight HA. Among published metaanalysis, some conclude beneficial effect for injections HA, while others report minimal effect or no effect (33–35). In addition, in recent years, based only on this positive effectiveness, several authors have sensed that hyaluronan might have disease modifying effects by reducing inflammation, protecting of the cartilage erosion and promoting more HA production (32) when facing early osteoarthritis, so it might have an effect on reversing progression. Further studies are needed to affirm these results, especially in young people and early stages of OA, because there is no literature which refers this. In fact, if reversion was demonstrated, IAHA would be a safe treatment for OA degenerative defects, since it has already been demonstrated that side effects rarely occur (34).

PRP is a preparation obtained from autologous blood after its centrifugation. It results in a sample of platelets with a higher concentration compared to basal blood, in which there are a-granules containing growth factors (GFs) (31). Thereby, platelets undergo degranulation and release the GFs (32). As explained above, GFs have an important function in promoting the first compensatory response after cartilage injury occurs in initial stages of OA (7), and that is the reason for the increasing interest in PRP as a therapy for early OA. Concretely, it is thought that injecting IA PRP will promote articular renovation, by increasing cell proliferation, cartilage and bone remodelling, angiogenesis and antiinflamation (36). In fact, several studies have reported better results in relieving symptoms with IA PRP, than what is seen with HA (37). *Kon et al.* reported, in two studies, significant improvements at 6 and 12 months, after three

injections at 3-week intervals. Even though, there was effect persistency compared to the basal level, especially in those with no clear lesions, overall worsening was seen at a 2 year follow-up. The main duration of clinical effect was 9 months (38,39). *Jang et al.*, meanwhile, brought similar conclusions. Clinical betterment was reported, but decreasing had effect at 8.8 months. It was observed that better results were obtained in younger people (40). Finally, in a systematic review short-term benefits are described for injected PRP in all the studies, but lessening effects at 6 months (41). As a conclusion, PRP is promising for the relive of symptoms, in safety conditions (38), but there is still no evidence that PRP might reverse OA degeneration. More research is needed, particularly in young patients and early stages of OA, when better results have been seen (42).

Finally, stem cells are still a wide field in where research is investing lots of funds. Adults mesenchymal stem cells (MSCs) have emerged as a cell type potentially used as a conservative therapy for early OA therapy (31). Not many studies have been carried out in this early-stage osteoarthritis, but positive results in reliving symptoms, articular cartilage regeneration and safety were seen in two case reports (43,44). In a metaanalysis reviewing various studies with stem cells, it was concluded that although optimal doses of MSCs is not well established, it is an encouraging therapy for cartilage regeneration (45). Further studies are required to evaluate this biological treatment that seems to be a possible future option to treat early OA (31).
To sum up, although IA injections of HA, PRP or MSCs are safe, minimal approach and so, a possible treatment for early OA, much more research is required to provide better results and more hope in treating and healing osteoarthritis (31).

Other extremely novel therapies are being developed for reversing OA progression, such as fibroblast growth factor-18, inhibitors of ADAMTS and, also, bifosfonates. Since, OA is an imbalance between anabolic and catabolic pathways, these newel approaches would increase anabolism or inhibit catabolism. Also, as there is controversy on whether OA might have a subchondral bone onset, bifosfonates are an up-to-date research issue (31). Overall, there is long way go with research.

As a conclusion, if there is already an early stage diagnosis of osteoarthritis, in which several risk factors might be involved to the onset and progression of this knee articular degeneration and in which biochemical and biomechanical changes occur, what should be clear is that treatment might be done during this precocious stage in the attempt to reverse the degeneration or, at least halt it (6,8,17,31); especially, if we are thinking of

young patients who still have a long way to go and in whom both, symptomatic and regenerative therapies, seem to have had a better response.

3.2. Justification

Given that osteoarthritis prevalence in the population continues to increase, seems that we are facing a burden disease and, mainly, for the years that come.

But with the increasing interest in healing this disease, there are two conditions in which intraarticular treatments seem that could have an important role: young age and early stage of the disease.

When looking for a profile of patients with these characteristics, high intensity athletes seem to meet both of them. So then, taking into account that in an early stage of knee osteoarthritis in athletes, symptoms might be minimal, usually increasing after long periods of effort (9); a more ambitious treatment target should be followed, which consists on reversing the disease, meaning regenerating the cartilage, or at least, halt its further progression.

As far as it is known, there is no prevention of osteoarthritis, but preventing further progression when the disease has already appeared. Then, in high-intensity athletes with early knee osteoarthritis, the unique risk factors in which might be changes are the BMI, muscular strength and lesions, as has already explained above. But conversely, several athletes may have a high BMI that cannot be reduced, may have already been training muscular strength and cannot avoid the inherent risk of injuries during training sessions and competitions; therefore, accepting that the early diagnosis is the only way to potentially treat and reverse the degeneration process of osteoarthritis. After that, intraarticular treatments appear to demonstrate this regenerative effect on the articular defects.

The aim of this study is to demonstrate that hyaluronic acid or platelet-rich plasma may have an important role in reversing or, at least, halting the diseases. Both conditions are favourable: young people diagnosed with early knee osteoarthritis.

Although it is little known about cartilage regeneration, it is an ongoing research issue worldwide; since by preventing those emerging cases of early osteoarthritis from progressing towards an advanced stage, we will be avoiding the potential physical disability that osteoarthritis cause, especially in those younger cases when there is still long way to go. And perhaps we will be preventing a major increase in the incidence of osteoarthritis and, therefore, preventing the growth of a major global health problem.

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5. QUESTION

Are hyaluronic acid and platelet-rich plasma infiltrations more effective treatments in reversing the progression of early knee osteoarthritis when compared to saline infiltrations, in young high-intensity athletes?

6. HYPOTHESIS

Main hypothesis

In young high-intensity athletes undergoing minimally invasive procedures, including intraarticular hyaluronic or platelet-rich plasma infiltrations, differences in reversing knee osteoarthritis degeneration process will be detected, in respect to those treated with saline injections. HA and PRP infiltrations will demonstrate, at least, the same effect.

Secondary hypothesis

- HA and PRP infiltrations improve the clinical short-term outcomes, such as pain, stiffness or discomfort when compared to placebo.

7. OBJECTIVE

Primary objective

The aim of this project is to assess whether the regeneration of the articular defects in osteoarthritis, or at least cessation of further degeneration is possible by using minimally invasive procedures, including HA and PRP intraarticular injections, in young high-intensity athletes between 25 and 55 years of age. We aim to compare both treatments with a placebo controlled-group.

Secondary objective

- To determine the clinical short-term outcomes of both treatments in decreasing the main symptoms, including pain, stiffness or discomfort.

8. METHODOLOGY

8.1. Study design

This study has been designed as a triple-blinded, randomized, placebo-controlled clinical trial with three groups receiving three different lines of treatment (one group used as placebo controls). It will be carried out by a multidisciplinary team integrating sports medicine doctors, traumatologists, radiologists and hospital pharmacy, in reference hospitals, but based in Hospital Santa Caterina in Salt.

8.2. Participants

The study population is based on young high-intensity athletes diagnosed with early osteoarthritis. *Criteria for early osteoarthritis* of the Articular Cartilage Committee of ESSKA (see ANNEX I) will be used for the diagnosis, in which all patients will undergo clinical examination and imaging evaluations, including knee radiographs and knee magnetic resonance imaging (MRI).

8.3. Inclusion criteria

- Active high-intensity athletes, defined as > 10hours/week and >7 METS/training session
- Either gender, aged 25 to 55 years
- Meeting the diagnosis criteria of early osteoarthritis (see ANNEX I).

8.4. Exclusion criteria

- Active cancer or autoimmune disease
- Other rheumatic diseases
- Ongoing infections (specially, bacteraemia or local knee infections)
- Status of immune suppression
- Bleeding disorders, patients on therapy with anticoagulants or inhibitors of platelet aggregation
- Patients with haemoglobin values <11g/dL and platelet values <150.000/µL
- Acute injured athletes or inactive athletes
- Athletes that have already been infiltrated during the last year

8.5. Sample selection

A consecutive non-probabilistic sampling will be used. The sample recruitment will take place in Units specialized in Sports Medicine or Traumatology in reference hospitals, for a year (12 months). Patients will seek medical attention and those likely to meet

inclusion criteria will be given an information sheet describing the study and inviting them to join (see ANNEX III). If patients are interested, they will be contacted with a trial doctor who will review the study planning and will obtain informed consent (see ANNEX IV).

8.6. Sample size

For calculating the sample size of our project, Sample Size and Power Calculator GRANMO was used. Accepting an alpha risk of 0.05 and a beta risk of 0.2 in a two-sided test, 60 subjects are necessary in each group, so in total 180, to find as statistically significant a proportion difference, expected to be of 0.02 in the placebo-controlled group and 0.20 in both groups, HA injection and PRP injection. A drop-out rate of 10% has been anticipated.

It is known, from the *Consell Català de l'Esport*, that 3400 athletes are recognized as elite or high-performance athletes. Based on that, and knowing that those athletes are mostly concentrated in Barcelona, we consider executing a multicenter study, in order to recruit as many athletes in the shortest time possible. In fact, many athletes not being considered of these levels would be meeting the inclusion criteria mentioned before, so that we expect to start from a larger population.

8.7. Variables

Having into consideration the purpose of the study, variables are described as:

8.7.1 Independent variables

Being allocated to one of the three treatment groups of intraarticular infiltration: saline (control group), hyaluronic acid or PRP.

The independent variable is considered to be nominal qualitative.

- **Platelet-rich plasma preparation**

  Every treatment cycle will require a previous blood collection. Preparations of PRP will be obtained using ORTHO$^{PRAS®}$ 40ml PRP Concentration System KIT (Proteal®). This kit contains all the elements to extraction, procession and activate-anticoagulation of the samples, except for the centrifuge.

  A single treatment cycle consist on the following steps: A) We collect 40mL of venous blood, in 4 tubs of 10 mL. B) A 6mL aliquot anticoagulant citrate dextrose 3,2% is added to the blood to prevent coagulation. C) After that, blood tubs are centrifuged with the Omnigrafter II® centrifuge at 280g for 15 minutes, in which after centrifugation a concentration suspended plasma is

extracted. Then, this plasma is centrifuged again at 680g for 20 more minutes, when finally is obtained a total of 8 mL of platelet pellet, which is extracted carefully to avoid leukocyte aspiration. D) The 8 ml-unit leukocyte-reduced PRP is divided into 4 smalls units of 2 ml each. One unit is sent to the laboratory for a quality test, 1 unit is used for the first injection and the other two are stored at -20ºC, until they will be used for the 2nd and 3rd dose of the treatment cycle. E) Before the injection, 10% of Ca-chloride is added to the 2 ml unit to activate platelets. F) A syringe is loaded and the injection of 2 mL PRP is done 1h after the blood collection, with a supralateral patellar approach in supine, which seems to be the most accurate way, and in the most affected knee (46) . Sterile conditions are required during the procedure. G) After the infiltration, strips are used.

The 2nd and 3rd dose will be defrost and prepared the same way, but starting from E. After the infiltration, patients will be permitted to do their daily life activities, but they will be limited to practice sport for 2 days and they will not be able to take any analgesia treatment. From there, training sessions and competitions will be permitted and they need to be, all along the follow-up at the intensity that athletes commented us they usually did at the beginning of the study.

- **Hyaluronic acid preparation**

  Every treatment cycle will require a previous blood collection and the first infiltration will be also done 1 hour after the blood collection, in order to blind patients.

  Hyaluronic acid will be bought to KELA PHARMA N.V. HYALGAN 20mg/ml solution for injection will be used. To achieve blinding, Kela Pharma L.V will provide us of little bottles of 2mL and our hospital pharmacy will prepare the syringe that will be the same as PRP preparation.

  The same conditions as PRP group when infiltration and after it will be required for this group of patients.

- **Placebo preparation**

  Every treatment cycle will require a previous blood collection and the first infiltration will be also done 1 hour after the blood collection, in order to blind patients. Saline solution NaCl 0,9% will be used in this group. The hospital pharmacy will prepare the same syringe as PRP and HA infiltrations, with 2

mL of saline solution. The same conditions as PRP group when infiltration and after it will be required for this group of patients.

8.7.2 Dependent variable

The outcome variable in this study is the regeneration of the articular defects in osteoarthritis, or at least cessation of further degeneration. This dependent variable is considered to be nominal dichotomous qualitative.

According to the background of the project, diagnosis of early osteoarthritis includes meeting minimally two of four scores in MRI, in addition to the clinical and radiographic criteria. However, there are no references on what might think to be improvement.

Therefore, the current project will take as a reference the scores of the MRI findings included in the *Criteria for early osteoarthritis* to evaluate the dependent variable. The following definitions will be used to consider improvement or not:

- Improvement: a decrease of a degree or more, in at least two of the scores in MRI.
- Non-improvement: non-decrease any degree in any score, or a decrease of only one degree in only one of the scores in MRI.

Secondary outcome

A secondary outcome variable in this study is decreasing the main symptoms, such as pain, stiffness or discomfort. This variable is considered to be nominal dichotomous qualitative.

In accordance to what has been explained, early osteoarthritis may have minimum symptoms and, in addition, rarely differentiated. So Visual Analogue Scale (VAS) will be used as a global predictor of the clinical patients status (see ANNEX V).

8.7.3 Covariables

- Age: in years. Continuous quantitative variable.
- Sex: male or female. Nominal qualitative variable.
- BMI: in kg/m^2. Continuous quantitative variable.
- Malalignment (normal, varus or valgus). Nominal qualitative variable.
- History of knee injuries (any kind). Nominal qualitative variable.
- Total training and competing time: in hours. Continuous quantitative variable.

- METS/training session: it will be calculated using the mean heart rate during training sessions. A mean heart rate will be taken every 15 days and, then, a finally mean per patient will be calculated. Continuous quantitative variable.
- Type of sport (contact or non-contact). Nominal dichotomous qualitative variable.

All the continuous variables will be discretized in order to facilitate the statistical analysis.

8.8. Intervention

8.8.1 Randomization methods

Participants agreed to be randomized using the random number generator. Treatment assignments will be done sequentially with a letter (A, B or C) within opaque envelopes.

8.8.2 Blinding degree

This project will be triple-blinded, since participants, doctors and radiologists (those who will infiltrate and assess RMI findings) and assessors (those collecting data) will ignore the intervention assignments. Participants will not be informed until the project is finished. The hospital pharmacy department will be the only one that will know whose patient belongs to each group.

8.8.3 Progress of subjects throughout study

Patients will start their participation when coming the first day. By then, a physical examination, a clinical evaluation (VAS score) and blood collection will be done to each patient, although blood will be used only for the PRP group. Radiographies done when patients are diagnosed will be used to evaluate the axial alignment of the knees. By the same day, 1 hour later, patients will receive the first knee infiltration of the first treatment cycle. The following doses will be done 7 days and 14 days after the first one, respectively. By the 3rd month, athletes will come to do clinical evaluation (except for those that preferably wishing to do so by phone).

A half year after the beginning, the second treatment cycle will start. Another treatment cycle is needed to enhance the durability of the treatment effect, since it is demonstrated that effect decrease between 6 to 9 months (39,40,42). Same evaluations will be done in addition of a MRI evaluation, but at expense of the

physical one, and monitoring will be at the 9th month. Finally, another clinical evaluation will be done at 1-year follow-up and we will wait until the 18th month to revaluate clinically and, at last, take a second MRI. Patients' participation will finish by then.

Here is a schedule of the 18-month follow-up:

	1st W*	2nd W	3th W	3th M*	6th M	6th M + 1W	6th M + 2W	9th M	12th M	18th M
PHYSICAL EXAMINATION	Prior to 1st dose treatment									
BLOOD TEST	Prior to 1st dose treatment				Prior to 1st dose treatment					
TREATMENT	1ST TREATMENT CYCLE 1st dose 2nd dose 3rd dose				2ND TREATMENT CYCLE 1st dose 2nd dose 3rd dose					
CLINICAL EVALUATION	Prior to 1st dose treatment				Prior to 1st dose treatment					
IMAGING (MRI) EVALUATION					Prior to 1st dose treatment					

*** W=week / M=Month.**

8.9. Methods of data collection

For data collection, a database will be created, in order to connected and facilitate the data between hospitals. Specially, radiologists will be informed that the study is being carried out. It is important due to the fact that there is an important part of the inclusion criteria in which they are implicated.

Some data (age, sex, diagnosis of early osteoarthritis, history of knee injury) will be collected from the electronic medical records and they will be transferred to the study database. The other information will be obtained from:

- Basic data and clinical report: doctors will obtain the specific data related to type of sport, hours of training/competition, METS/training session. BMI will be obtained in the physical examination. In addition, to evaluate pain, the VAS scale will be used.
- Radiologist report: radiographies used to diagnose the participants will be also used to measure the axial alignment of the knees. Moreover, RMI will be used to obtain the information about the changes in the articular structures, which they are in fact the outcomes. Radiologists will do this report. Each radiologist will receive all RMI of all patients, and so there will need to be an agreement when cataloguing patients in status after treatment.

All data, except for the clinical symptoms, METS/training session and RMI findings will be collected the first day; and these three data will be obtained in accordance with the progress through the study that was explained above.

9. STATYSTICAL ANALISIS

For the nominal qualitative variables, the results will be expressed as percentages (proportions), presented for each group and globally.

Considering the bivariate analysis, the homogeneity between groups will be proved using Pearson's chi-square test. In addition, for the second outcome, as it will be also taken as a nominal qualitative variable, the same statistical test will be used.

Finally, a multivariate analysis will be performed adjusting covariables that have already demonstrated possible confusion in our study and, also, for those in the literature that could explain a relation between our independent and dependent variables. Considering, though, that our variables are nominal qualitative a logistic regression model will be used.

Statistical analysis will be performed using SPSS for Windows.

10. ETHICAL ASPECTS

This project will be evaluated by *La Agencia Española del Medicamento* (AEMPS) and also the Clinical Research Ethical Committee (Comitè Ètic d'Investigació Clínica, CEIC) of the Hospital Santa Caterina in Salt. It will assess if this project complies the criteria required for being approved.

The project will be executed in accordance with the principles of the Helsinki Declaration and according the Medical Research Involving Human Subjects Act (last revision in 64th WMA General Assembly, Fortaleza, Brazil, October 2013). It will be considered the Spanish Organic Law *LEY 14/2007, de 3 de julio, de Investigación biomédica.*

Confidential data will be treated as such according to the Spanish Organic Law *15/1999, de 13 de diciembre, de Protección de Datos de Carácter Personal.* Besides, in accordance to article 5 and 6 of the above mentioned law, all patients will be informed with the information sheet (ANNEX III) and will be asked to sign the informed consent (ANNEX IV). All data will be managed anonymously.

Finally, although our idea of working with a trademark, our principles respond to the intention of maintaining the greatest objectivity and impartiality regarding the outcomes of the study. We declare no conflicts of interest.

11. LIMITATIONS OF THE STUDY

Some limitations in this project must be considered:

- In relation to the field work (phase 2), a limiting condition could be the loss of some follow-ups, since monitoring has been planned in 10 visits during 18 months. However, in our intent to reduce these losses, patients will be asked whether those days when there is only clinical evaluation using the VAS score, they want better to be phoned instead of coming to the hospital, and so they could respond that way. If patients accepted it, in the very first day they would be given a copy of the VAS scale and they could bring it home.

- Intraarticular injections are operative-dependent techniques, so differences between groups could be consequences of the procedure. In an attempt to solve the possible disparity, it has been planned some training sessions during the coordination phase, in which only one professional per hospital will learn the exact technique to do the infiltration.

- Our sample size is limited, so that could not be representative of the population. We would recommend that further studies must be done in greater population.

- Another limitation is the assessment only of the short-term outcomes that are only during 18 months. Taking into account that osteoarthritis is a chronic disease, we would recommend further studies to assess also the long-term outcomes; such as the need to more treatment cycles or the progression towards more advanced stages of the disease, instead of halt it until patients are older.

- The treatments used in this study are more expensive than others used in osteoarthritis, so this has had an effect on the budget. Therefore, maybe if the hyaluronic acid's trademark (KELA PHARMA N.V.) was in accordance with our principles of objectivity and impartiality, we could reach an agreement to obtain finance for the project. We could ask also for a grant in the *Instituto de Salut Carlos III*, if needed.

12. WORK PLAN

Investigators: Georgina Gener (GG), Daniel Castillo (DC)

Collaborators: sports medicine doctors (SPD), traumatologists (T), radiologists specialized in musculoskeletal system (R), hospital pharmacies (HP), statisticians (S)

The project has been designed to be carried out in 5 phases:

1. **Coordinating phase** (3 months)

   All the investigators and collaborators will be involved.

   A meeting will be organized in which all the team will review the study planning and the data collection methods will be set up. In addition, a training period in intraarticular injection for traumatologists and sports medicine doctors will take place then. Only one professional per hospital will do the infiltrations.

   Every 6 months, a coordination meeting will be held and data quality controls will be made, in order to evaluate the established schedules, the correct functionality of the project as well as the consistency of the collecting data.

2. **Field work** (30 months)

   All the investigators, SPD, T, HP and R will be involved.

   Recruitment will take 1 year approximately, taking into account inclusion and exclusion criteria mentioned above. In each patient recruited: A) patients will be asked to voluntarily participate in the study and, if they agree, after reading the information sheet, they will be asked to sign the informed consent; B) first treatment cycle starts. On the first day, patients first will undergo a physical examination, blood collection and clinical examination (with the VAS score) and, then, the first treatment dose. After that, patients should follow the established protocol; C) second treatment cycle starts on the 6th month. Patients undergo an imaging evaluation (MRI), blood collection and clinical examination, just before they are given the dose. Clinical examination and MRI results will be recorded in the database. Again, patients should follow the established protocol; D) one and a half years after the beginning of the process, patients will undergo the second imaging evaluation (MRI), the results of which will be entered in the database. The study finishes for that patient; E) Investigators thank the patients for participating in the study. Patients are also asked whether they want to be sent a copy of the results when they are published.

3. **Data extraction and processing database** (12 months)
   The statistician will be implicated in this phase.

   All data collected will be entered in a created database. Collection will be accomplished every 6 months, together with the method data quality controls. Periodically, data analysis will also be performed in order to sense its evolution and revise whether statistical differences appear between groups.

4. **Data analysis** (3 months)
   All investigators and the statistician will be involved.

   All data collected will be processed. The analysis will be performed using the pertinent statistical test already explained.

5. **Interpretation, publication and dissemination of the results** (3 months)
   All the team will be part of this last phase.

   A final report with the evaluation and interpretation of all outcomes will be drafted, with a previous discussion and agreement of the all team.

13. TIMELINE

The schedule of the project, in which 5 phases are set up over 42 months, is distributed as follows:

	TIME							
	2016		2017		2018		2019	
PHASE	**Jan-Jun**	**Jul-Des**	**Jan-Jun**	**Jul-Des**	**Jan-Jun**	**Jul-Des**	**Jan-Jun**	**PERSONAL**
Coordination phase	■							All the team
Field work		■	■	■	■	■		GG, DC, SMD, HP, T, R
Data extraction and processing database		■		■		■		S
Data analysis							■	GG, DC, S
Interpretation, publication and dissemination of the results							■	All the team

14. AVAILABLE MEANS TO CARRY OUT THE PROJECT

Hospital Santa Caterina will provide those necessary means to carry out the study, except for the treatments and the statistician, which will be borne by the project. All units, including Sports Medicine, Traumatology, Radiology and hospital pharmacy will be coordinated in order to progress together in the study and according to the established program. The same coordination conditions will be required in the other reference hospitals which participate in the project, where their respective services will provide all means, except for those mentioned above for Hospital Santa Caterina. Also, there will be created a network among all hospitals, to regulate and organize all the activities done during the project.

As it was commented previously, means could be also financed for the trademark that provides us the hyaluronic acid, and therefore, budget won't be so burden for the project.

15. BUDGET

		PROPOSED PRICE		
		Quantity	**Price**	**Cost**
Personal costs	Statistician	1		1.700€
Goods and services	▪ ORTHO$^{PRAS®}$ 40ml PRP Concentration System KIT (Proteal®)	120	450€	54.000€
	▪ Hyalgan 20mg/mL	24 boxes (5 bottles)	180€	4.320€
	▪ Saline serum	60	0,50€	30€
	▪ RMI	360	120€	36.000€
	▪ Syringes	10 box (100 syringes)	7,45€	74,5€
	▪ Blood collection tubs (EDTA tubes)	20 box (50 tubs)	4€	80€
Insurance		1	3.000€	3.000€
Travel and subsistence arrangements	▪ Inscription to *Congreso Nacional de la Federación de Medicina del Deporte*	2	400€	800€
	▪ Cost of the trip	2	200€	400€
Publication fees		1	1.500€	1.500€
TOTAL				101.904,5 €

16. ANNEX

16.1. ANNEX I. Classification of early osteoarthritis

Early OA		
Three criteria		
1	Knee pain	At least two episodes of pain for 10 days in the last year
2	Standard radiographs	Kellgren-Lawrence grade 0 or I or II (osteophytes only)
3	At least one	
	Arthroscopy	ICRS score grade I-IV in at least two compartments or grade II-IV in one compartment with surrounding softening and swelling
	MRI	At least two Cartilage morphology WORMS score 3-6 Cartilage BLOKS grade 2 and 3 Meniscus BLOKS grade 3 and 4 BMLs WORMS 2 and 3

Reference:
Luyten FP, Denti M, Filardo G, Kon E, Engebretsen L. Definition and classification of early osteoarthritis of the knee. Knee Surgery, Sport Traumatol Arthrosc [Internet]. 2012 Mar [cited 2014 Nov 4];20(3):401–6. Available from: http://link.springer.com/article/10.1007/s00167-011-1743-2

16.2. ANNEX II. Scores included in the criteria of early osteoarthritis

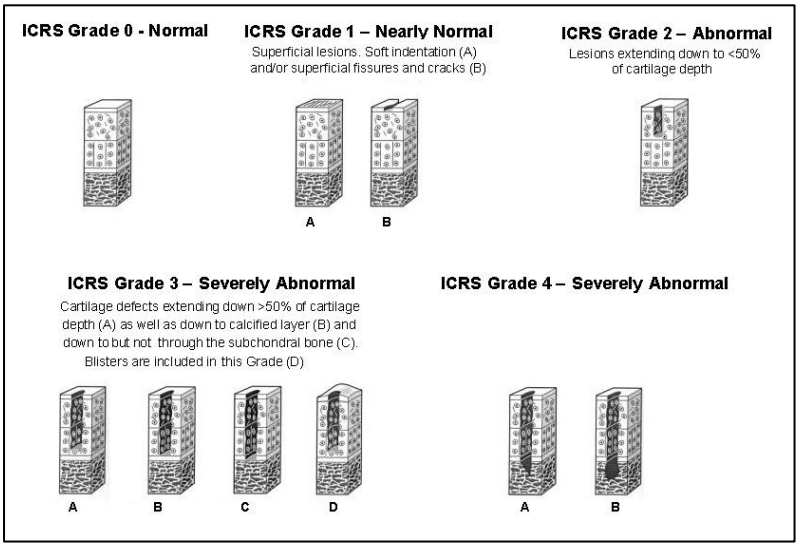
The ESSKA (European Society of Sports Traumathology, Knee Surgery and Arthroscopy) Cartilage Committee early osteoarthritis classification is based on 6 classifications:

- **Kellgren and Lawrence radiography OA classification**

Grade 0	No changes
Grade 1	Doubtful narrowing of the joint space and possible osteophytic lipping
Grade 2	Definite osteophytes and possible narrowing of the joint space
Grade 3	Moderate multiple osteophytes, definite narrowing of the joint space and some sclerosis, and possible deformity of the bone ends
Grade 4	Large osteophytes, mark narrowing of the joint space, severe sclerosis, and definite deformity of the bone ends

Reference:
Altman R, Asch E, Bloch D, Bole G, Borenstein D, Brandt K et al. Development of criteria for the classification and reporting of osteoarthritis. Classification of osteoarthritis of the knee. Diagnostic and therapeutic criteria committee of the American Rheumatism Association. Arthritis Rheu; 1986; 8:1039–1049

- **ICRS – Articular cartilage injury classification**



Reference:

The ICRS Clinical Cartilage Injury Evaluation system-2000. [Internet]. 2000 Jan 27-30; Available from: www.cartilage.org/_files/contentmanagement/ICRS_evaluation.pdf

- **Cartilage morphology (WORMS score)**

  Eight-point scale for scoring articular cartilage signal and morphology. A fat-suppressed T2 MRI sequence was used. Scores were defined as given:

  0 = normal thickness and signal

  1 = Normal thickness but increased signal on T2-weighted images

  2 = partial thickness focal defect <1cm in greatest width

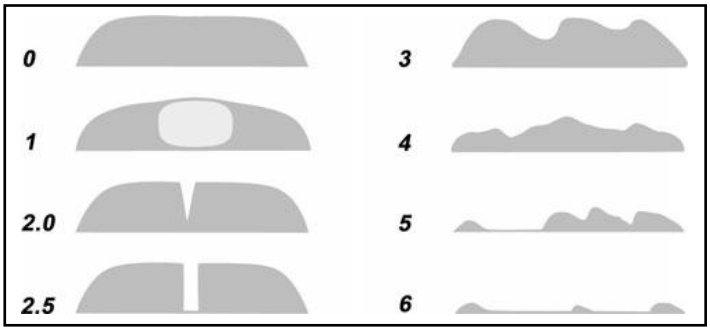
  2.5 = full thickness focal defect <1cm in greatest width

3 = multiple areas of partial-thickness (Grade 2.0) defects intermixed with areas of normal thickness, or a Grade 2.0 defect wider than 1 cm but <75% of the region

4=diffuse (≥75% of the region) partial-thickness loss

5=multiple areas of full thickness loss (grade 2.5) or a grade 2.5 lesion wider than 1 cm but <75% of the region

6=diffuse (≥75% of the region) full-thickness loss.



Reference:
Peterfy CG, Guermazi A, Zaim S, Tirman PF, Miaux Y, White D et al. Whole-organ magnetic resonance imaging score (WORMS) of the knee in osteoarthritis. Osteoarthr Cartil. 2004; (3):177–190

- **Cartilage BLOKS score: *delineation of grading for cartilage score 1***

Size of any cartilage loss (including partial and full thickness loss) as a % of surface area as related to the size of each individual region	% full thickness cartilage loss of the region
0: none	0: none
1: <10% of region of cartilage surface area	1: <10% of region of cartilage surface area
2: 10-75% of region of cartilage surface area	2: 10-75% of region of cartilage surface area
3: ≥ 75% of region of cartilage surface area	3: ≥ 75% of region of cartilage surface area

Reference:
Peterfy CG, Guermazi A, Zaim S, Tirman PF, Miaux Y, White D et al. Whole-organ magnetic resonance imaging score (WORMS) of the knee in osteoarthritis. Osteoarthr Cartil. 2004; (3):177–190

- **Meniscus tear (BLOKS score) medial meniscus**

Grade 0	intact
Grade 1	minor radial tear or parrot-beak tear
Grade 2	non-displaced tear or prior surgical repair
Grade 3	displaced tear or partial resection
Grade 4	complete maceration/destruction/resection

Reference:
Lynch JA, Roemer FW, Nevitt MC, Felson DT, Niu J, Eaton CB et al. Comparison of BLOKS and WORMS scoring systems part I. Cross sectional comparison of methods to assess cartilage morphology, meniscal damage and bone marrow lesions on knee MRI: data from the osteoarthritis initiative. Osteoarthr Cartil; 2010; 11:1393–1401

- **Bone Marrow Lesions (WORMS grading)**

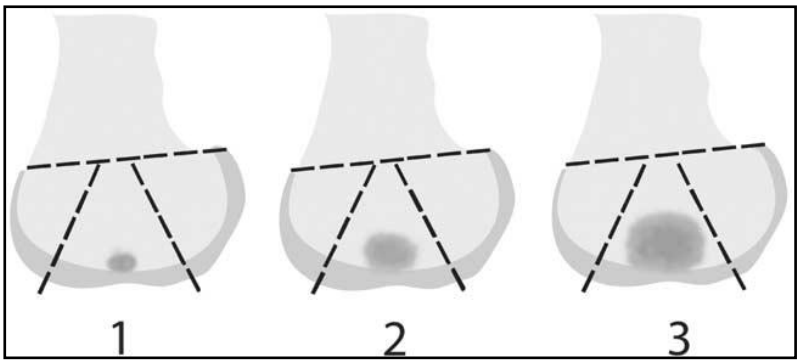
  Subarticular marrow abnormality score. This score is based on the extent of regional marrow involvement by areas of free water signal with ill-defined margins. A fat-suppressed T2-weighted MRI sequence was used.

  0 = none

  1 = <25% of the region

  2 = 25% to 50% of the region

  3 = >50% of the region.



Reference:
Peterfy CG, Guermazi A, Zaim S, Tirman PF, Miaux Y, White D et al. Whole-organ magnetic resonance imaging score (WORMS) of the knee in osteoarthritis. Osteoarthr Cartil. 2004; (3):177–190

16.3. ANNEX III. Information sheet

FULL D'INFORMACIÓ AL PARTICIPANT

Títol del projecte:

INJECCIONS INTRAARTICULARS D'ÀCID HIALURÒNIC I PLASMA
RIC EN PLAQUETES EN ESPORTISTES JOVES D'ALTA INTENSITAT
AMB OSTEOARTRITIS PRECOÇ DE GENOLL

Agraïm el seu interès pel que fa a la seva col·laboració en l'estudi que estem duent a terme des de la Unitat de Medicina de l'Esport de l'Hospital Santa Caterina de Salt.

El convidem a participar en un estudi d'investigació. Abans de decidir si vol participar o no, és important que entengui les principals característiques de l'estudi, per què es realitza i els possibles beneficis i incomoditats que li pot comportar.
L'investigador principal de l'estudi o un dels seus col·laboradors, l'informarà de les característiques de l'estudi i podrà fer-li totes les preguntes que consideri oportunes. Prengui's el temps que consideri necessari per llegir amb deteniment aquesta informació que li facilitem per escrit i per pensar-s'ho.

Quina és la finalitat de l'estudi?

L'objectiu de l'estudi és el d'avaluar l'efectivitat de dos tractaments (àcid hialurònic i plasma ric en plaquetes) injectats intraarticularment per revertir o, al menys, frenar la degeneració del cartílag en estadis inicials de l'osteoartritis de genoll o, altrament coneguda, artrosi de genoll.

Actualment, l'osteoartritis es diagnostica tard en la seva evolució com a malaltia, de manera que no existeixen tractaments per revertir o, com a mínim, frenar-ne el progrés. L'existència d'una nova definició d'un estadi primerenc de la malaltia ha portat a la possibilitat de tractar-la de forma precoç i, per tant, contribuir a la possibilitat de restablir la degeneració que és causada al cartílag.

En què consisteix l'estudi?

L'estudi consisteix en un assaig clínic aleatoritzat a triple cec. No se sap si aquests tractaments, donats en estadis precoços, podrien ajudar a revertir o, com a mínim, frenar la malaltia. Per saber-ho, s'han de comparar ambdues tècniques i respecte un grup control, a qui se li injectarà sèrum. Això vol dir que es faran tres grups i perquè siguin el màxim d'iguals, seran fets de forma aleatòria. Llavors, els resultats es compararan entre els grups.

Donat que l'estudi és triple cec, ni vostè, ni el metge que l'infiltrarà, ni l'analista de dades saben a quin grup de tractament pertany.
Cada tractament consta de dos cicles de 3 injeccions, separades per una setmana cada una, i visites de control que poden incloure la pràctica de ressonància magnètica o no.

En què consistirà la seva participació en l'estudi?
Si vostè accepta participar-hi, entrarà a formar part d'un assaig clínic aleatoritzat.
El primer dia del cicle de tractament se li extraurà sang per fer una analítica, se li farà una exploració completa de l'aparell locomotor i un seguit de preguntes, a més de la primera injecció. Caldran visites successives, al llarg de tot l'estudi, per fer el segon cicle de tractament, dues ressonàncies de control i visites de protocol.
Per poder dur a terme aquest estudi, necessitem que signi la següent autorització segons la qual vostè entén i accepta les condicions ja explicades.

Quins són els beneficis potencials de la seva participació?
Els beneficis que pot obtenir de formar part d'aquest estudi són la possibilitat de ser tractat amb un fàrmac que, donat de forma precoç, creiem que podria frenar el procés degeneratiu que provoca l'artrosi i, a part, la possible millora dels símptomes.

Quins són els riscos i/o incomoditats potencials de la seva participació?
Els riscos són els derivats de la injecció intraarticular: sagnat, sensació de "botiment" transitori al genoll. Les infiltracions es fan en un mitjà estèril. De tota manera, existeix un risc molt baix d'infecció articular. Pel que fa a les incomoditats, les que derivin de venir a cada visita o tractament.

Quins són els seus drets?
Voluntarietat:
La seva participació en aquest estudi és totalment voluntària. Si decideix deixar l'estudi en el seu decurs, no se'l penalitzarà ni repercutirà en la seva atenció mèdica. Les seves dades, llavors, seran inutilitzades.

Secret professional i confidencialitat :
La seva participació en l'estudi és totalment confidencial i anònima. Totes les dades de l'estudi són estrictament confidencials, i només hi tindran accés els investigadors i personal autoritzat per garantir la qualitat i l'anàlisi de les dades, tal com obliga la Llei Orgànica 15 /1999 de Protecció de Dades de Caràcter Personal.

Publicació:

Es podran publicar els resultats de l'estudi, tal com assenyala l'art. 38.1 RD 223/2004. Així mateix si vostè vol, li farem arribar una còpia dels resultats un cop publicats.

A qui puc dirigir-me per demanar més informació?

Si té qualsevol dubte, algun suggeriment o necessita més informació, l'atendrem pel que sigui. Visiti'ns, truqui al telèfon de la Unitat (972 186 922) o enviï un correu a medicina.esportiva@ias.scs.es

Moltes gràcies,

Unitat de Medicina de l'Esport de l'Hospital Santa Caterina de Salt

16.4. ANNEX IV. Informed consent

FULL D'INFORMACIÓ AL PARTICIPANT

Títol del projecte:

INJECCIONS INTRAARTICULARS D'ÀCID HIALURÒNIC I PLASMA RIC EN PLAQUETES EN ESPORTISTES JOVES D'ALTA INTENSITAT AMB OSTEOARTRITIS PRECOÇ DE GENOLL

Declaro que he estat correctament informat pel membre responsable de l'equip investigador; sobre els objectius de l'estudi, els beneficis i riscos o incomoditats potencials de la meva participació; sobre la voluntarietat de l'estudi i de la possible retirada i eliminació del les meves dades; així com, també, he estat informat de l'ús de caire científic que es farà de les meves dades personals.
Tanmateix, he rebut una còpia d'aquest mateix document.

Jo (Nom i cognoms) _____

He llegit la nota informativa que m'han entregat.
He pogut realitzar les preguntes sobre l'estudi.
He rebut suficient informació sobre l'estudi.

He parlat amb (nom de l'investigador) _____

Entenc que la meva participació és voluntària.
Entenc que puc retirar-me de l'estudi:

1a. Quan vulgui.
2a. Sense haver de donar explicacions.
3a. Sense que això repercuteixi en la meva atenció mèdica.

Dono la meva conformitat per participar a l'estudi.

Firma del pacient Firma de l'investigador

_____ _____

Salt, ... de .....de 20....

16.5. ANNEX V. Visual Analogue Scale (VAS) for clinical outcomes

This visual scale will be used to follow patients clinical outcomes.