Analgesic Outcomes of Chondromalacia Patella Treated with and without the Preventive Intra-Articular Injection of Corticosteroid

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Abstract: From September 2013 to September 2014 we were collected 58 patients afflicted by chondromalacia patella femoral knee disease, diagnosed with MRI examination, 24 of these patients underwent an injection with hyaluronic acid (HA) (Cross-Linked 3.6 to 6 MDalton), the other 24 patients received the same therapy, but preceded by the intra-articular injection of corticosteroids (CS) (methylprednisolone acetate 40 mg / 1 ml). Patients were evaluated at different time point (1, 3, and 6 months) performing disability and pain with Rivermead Mobility Index (RMI), Cincinnati Knee Rating Scale (CKRS) and Visual Analogue Scale (VAS) measures. This study discloses the effectiveness of the infiltration of CS before performing the treatment with intra-articular injection of HA in patients with chondromalacia of the knee. Moreover demonstrating that this therapeutic approach relieves pain faster, since after one month post-treatment, and relief is last longer.

Keywords: Chondromalacia, hyaluronic acid, corticosteroids, patella.

1. INTRODUCTION

Chondromalacia is a condition where the cartilage deteriorates and softens. The patellofemoral joint is one of the most commonly compartments affected by this disease. Approximately 5% of patients with osteoarthritis (OA) of the knee have symptomatic patellofemoral arthritis in the absence of tibiofemoral arthritis [1]. The patella’s posterior surface is covered with a layer of smooth cartilage, which the base of the femur normally glides effortlessly against when the knee is bent.

Chondromalacia patella results from degeneration of cartilage due to poor alignment of the kneecap (patella) as it slides over the lower end of the thighbone (femur) [2]. This process is sometimes referred to as patellofemoral syndrome. The cartilage is altered because a mechanical and/or traumatic injury involving the knee joint. Direct trauma is obviously due to the subchondral bone edema and qualitative alteration of the cartilage, but certainly often the cause is not traumatic [3]. The condition may result from acute injury to the patella or chronic friction between the patella and a groove in the femur through which it passes during knee flexion. When the patellar femoral components are not well positioned in the space, they work badly during movement. This alteration of the dynamic relationships induces friction between the articular surfaces and, therefore, it is due to chondral wear [4].

This condition is common among young, athletics individuals, but may also occur in older adults who have arthritis of the knee.

The cartilage under the kneecap is a natural shock absorber, and overuse, injury, and many other factors can cause increased deterioration and breakdown of the cartilage. The cartilage is no longer smooth and therefore the movement and the use are painful.

Patients with chondromalacia patella disease frequently have abnormal patellar "tracking" toward the lateral (outer) side of the femur [5]. This slightly off-kilter pathway allows the undersurface of the patella to grate along the femur, inducing chronic inflammation and pain. Certain individuals are predisposed to develop chondromalacia patella: females, knock-kneed or flat-footed runners, moreover those with an unusually shaped patella undersurface.

Improper kneecap movement may result from [6-8]:

- Misalignment between the femur and patella;
- Muscle imbalance between the adductors and abductors;
- Repeated mechanical stress such as running, jumping, skiing;
- Trauma to the kneecap, such as a dislocation or fracture, has been linked to patellofemoral pain syndrome;
- Knee surgery, particularly repair to the anterior cruciate ligament using your own patellar tendon as a graft, increases the risk of patellofemoral pain.
The diagnosis is carried out with clinical and instrumental processes. The symptoms, the observation of the movement of the knee, and the positioning concur in diagnosing the patellar syndrome. The patient has pain when he squats, runs, climbs or stairs. The suffering reduces sports performance and normal activities, as walking fast.

Axial radiographs of the patellofemoral joint ("sunrise" views) are useful for demonstrating the general morphology of the patella, including the different Wiberg types based on the lengths of the medial and lateral facets, as well as the size of the patella with respect to the trochlea. Techniques described by Merchant [9] and Laurin [10] are the two most widely used.

The use of MRI is important indeed, Edema of the superolateral aspect of Hoffa's fat pad (SHFPE) is the more frequent finding in patellofemoral disorders than involvement of other fat pads [11].

The patient comes to the physician asking to suddenly improve joint function and reduce suffering. Surgery was excluded as the initial approach [12]. In the absence of cartilage damage, pain at the front of the knee due to overuse can be managed with a combination of RICE (rest, ice, compression, and elevation), anti-inflammatory medications, and physiotherapy. Joint injections can be a relevant approach to the treatment of knee pain, swelling, inflammation, and arthritis. They tend to be more effective and have fewer side effects than oral medication.

There are two main types of injections for the treatment of knee pain [13, 14]:

1. CS Injections: They help relieve knee pain and inflammation. They are often combined with local anaesthetic. The local anaesthetic part of the injection provides instant pain relief and the cortisone part provides longer term relief of inflammation which consequently reduces pain. Steroid injections for knee pain are usually given when other treatments, such as medication and physical therapy, are not working.

2. HA Injections: Hyaluronan is present in high concentrations in connective tissues, such as skin, cartilage but the largest single reservoir is the synovial fluid (SF) of the diarthrodial joints. HA confers exceptional visco-elasticity and lubricating properties to SF. Injecting a viscous fluid in the knee joint is, therefore, a method for reducing the friction of the articular components and improves the sliding of the joint surfaces [15].

2. MATERIALS AND METHODS

Informed consent was obtained from all patients prior to the inclusion in the study. As this study was a standard of care assessment, local ethics committee authorization was not required. The study was performed in accordance with the ethical standards of the 1964 Declaration of Helsinki as revised in 2000. Between September 2013 and September 2014, at the Department of Orthopedics and Traumatology of the San Giacomo Apostolo Hospital in Castelfranco Veneto (Italy), intra-articular knee injection was performed for 58 patients using two different therapeutic approaches: injection of HA (Cross-Linked 3.6 to 6 MDalton) (Group A) and injection of HA (Cross-Linked 3.6 to 6 MDalton) preceded by an injection of CS performed methylprednisolone acetate 40 mg / 1 ml) one week before.

The group A consisted of 24 patients (9 males and 15 female), with a mean age of 49 years (range 35 - 58), instead the group B consisted of 24 patients (10 males and 14 female), with a mean age of 50 years (range 36 - 60).

Inclusion criteria were: aged between 35 and 60 years, persistent anterior knee pain lasting at least 4 months prior to screening, X-ray showing no fracture or osteoarthritis, MRI findings of chondromalacia moderate, chondromalacia patella, and/or femoral condyle, failed previous physical therapy intervention, pain/crepitus with patellar grind, >5 out of 10 on a Visual Analogue Scale (VAS), Rivermead Mobility Index (RMI) <11, Cincinnati Knee Rating Scale (CKRS) <90.

Exclusion criteria were: any form of inflammatory arthritis (e.g. rheumatoid arthritis, gout, pseudogout, lupus, etc), serious progressive medical conditions (such as cancer, AIDS, end-stage renal disease, cardiac disease, or neurological disease), pregnant or breast feeding, body mass index > 40, history of recent injuries of the knee (less than one year), oral steroid medications, intra-articular (knee joint) steroid in the past, any prior use of viscosupplements, prior surgery in the knees, clinical and radiographic evidence of hip disease, history of fractures of the lower limbs, presence of knee/patellofemoral joint effusion, patellar tendinitis, patellofemoral joint space narrowing as noted on Merchant/sunrise x-ray, significant patellar mal-tracking as noted on merchant view x-ray,
diagnosis of tibiofemoral osteoarthritis (Kellgren Lawrence grade osteoarthritis of II, III or IV), cruciate/collateral knee ligament instability, meniscus injury, and currently enrolled in another experimental clinical trials.

The same protocol was used for both groups, and moreover the joint injections were performed by the same operator. Previously the skin was washed with povidone-iodine solution, and than, with the patient in supine position a 21 gauge needle was inserted facing the superolateral margin of the patella. Following, the patella was pulled laterally and a needle was advanced under the patella. After the injection of the medication, both needle and syringe were withdrawn. Finally the skin was cleansed, and a bandage was applied over the needle-puncture site. The accuracy of the procedure was determined by ultrasonography joint.

No excessive weight-bearing physical activity should take place for one to two days following injection.

Clinical follow-up was performed at 1, 3 and 6 months from HA joint injections (baseline). All evaluations were performed by a physician who was unaware of the treatment used. The level of knee pain was assessed using the VAS with a score from 0 to 10 cm. Specific data on knee joint function were gathered during clinical check-up employing the RMI and the CKRS. The RMI is a measure of disability related to bodily mobility (Figure 1). It demonstrates the patient's ability to move her or his own body. It does not measure the effective use of a wheelchair or the mobility when aided by someone else. It includes 15 items related to bed mobility, transfers, walking, stair use, and running. The RMI is presented in a questionnaire format with the examiner required to make one observation (standing unsupported >10s). All items are rated in a yes/no format with positive responses scoring a 1 for a maximal RMI score of 15 [16].

CKRS is a symptom rating scale that includes a functional assessment based on 6 abilities important for everyday life and sport: walking, using stairs, squatting and kneeling, straight running, jumping and landing, hard twists, cuts, and pivots. It based on a total of 100 possible points; each question of the

Figure 1: Topic and questions of Rivermead Mobility Index.
assessment is awarded a certain number of points based on how it is answered (Figure 2). In the CKRS, patients are asked to rate the overall condition of the knee by circling a number on a scale from 1 to 10. Under the number 2 is the term “poor,” defined as “I have significant limitations that affect activities of daily living,” whereas under the number 10 are the terms “normal/excellent” [17].

A Paired t-test for comparisons, a Normality Test (Shapiro-Wilk) or a Wilcoxon Signed Rank Test were used when required. Analysis of data was done using the MedCalc (version 12) and SigmaPlot (version 12.3) statistical packages. The p-value <0.05 was considered statistically significant.

3. RESULTS

The two groups of patients analyzed in this study presented similar values of weight, sex and VAS status. All patients had no systemic or local side effects, only one patient of group A and two patient of group B developed a skin hematoma at the injection site. Intra-articular injection therapy showed no improvement in 2 patients in the group A and in 1 patient in the group B. All 3 patients underwent arthroscopic surgery that showed degeneration of the posterior horn of the medial meniscus in 2 patients, and a hypertrophic medial synovial plica in the knee of another patient (injuries were not detected on MRI and clinical exams).
The level of knee suffer was assessed using the VAS 0–10 cm (rest, movement), the mean of two group ± standard deviation was represented in Figure 3. All groups had good analgesia, but after 1 month the VAS assessment was significantly lower in patient of group B (p < 0.009), while the 3rd and 6th month values overlap. This demonstrated that the therapy preceded by an injection of CS relieves pain faster, since after one month post-treatment, and relief is last longer.

The ability to improve daily activities was assessed with RMI. The results obtained during the first month disclosed a significant progress in the patient's ability, belonging to group B, to move her or his own body (Figure 4). The mean values measured in group A are of 10.25, instead the mean values of the group B are of 12.83 with a value statistically significant in the group B (p<0.001) (Table 1). In the 3rd and 6th month values are excellent in both groups, resulting rather similar.

Table 1. The Mean Values ± S.D. of the Scales (VAS, RMI, and CKRS) assessed in this Study

<table>
<thead>
<tr>
<th>Months</th>
<th>VAS</th>
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<th>CKRS</th>
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<td>Group A</td>
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<td>0</td>
<td>7.3</td>
<td>0.9</td>
<td>7.5</td>
<td>1.1</td>
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<td>2.3</td>
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<tr>
<td>1</td>
<td>4.7</td>
<td>1.5</td>
<td>3.3</td>
<td>1.7</td>
<td>10.3</td>
<td>1.8</td>
</tr>
<tr>
<td>3</td>
<td>3.3</td>
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<td>1.7</td>
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<tr>
<td>6</td>
<td>3.4</td>
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<td>3.3</td>
<td>1.6</td>
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</table>

The CKRS showed a significant improvement in function and quality in the joint of the group B (Figure 5) since the first month to the third month. In fact mean values of the group B exceed by 13 points in the first month and 7 points in the 3rd month, with a statistical significance of p <0.001 and p <0.034 respectively.

The three indices of health evaluation of the patients, who have undergone these two treatments, showed a significant improvement of walking performance, mobility and well-being in the group B, already after one month.

Figure 3: Visual Analogue Scale measure. The vertical histograms refer to the VAS value in blue are represented the group A and in grey the group B at different time point (0 month is referred to as basal values, and 1, 3, and 6 months). 24 patients per group were analyzed and data are expressed as means ± S.D. at one month Group B presented a statistically difference compared to Group A (Normality Test, Shapiro- Wilk, p = 0.009).

Figure 4: Rivermead Mobility Index measure. The vertical histograms refer to the RMI value in blue are represented the group A and in grey the group B at different time point (0 month is referred to as basal values, and 1, 3, and 6 months). 24 patients per group were analyzed and data are expressed as means ± S.D. at one month Group B presented a statistically difference compared to Group A (Normality Test, Shapiro- Wilk, p<0.001).
Figure 5: Cincinnati Knee Rating Scale measure. The vertical histograms refer to the CKRS value in blue are represented the group A and in grey the group B at different time point (0 month is referred to as basal values, and 1, 3, and 6 months). 24 patients per group were analyzed and data are expressed as means ± S.D. At the first and third months Group B presented a statistically difference compared to Group A (Wilcoxon Signed Rank Test, p<0.001 and p = 0.034, respectively).

4. DISCUSSION

Chondromalacia of the knee, defined as cartilaginous softening and fibrillation of bone cartilage, is one of the possible causes of patellofemoral pain syndrome (PFPS). Chondromalacia is characterized by a slow and progressive deterioration of articular cartilage. Its incidence is prevalent in society and is a major cause of disability [18], moreover it is a precursor of the osteoarthritis. It can, perhaps, be regarded as an early senescence (the changes in the inter-vertebral discs that begin during the second decade of life are often so described) but much more must be learn about the chemistry of proteins and polysaccharides involved in this disease, before such an idea can be accepted. The articular cartilage of the patella is entailed earlier and more constantly than almost any other joint surface [19]. The process often begins during the second decade of life, and by the age of thirty nearly everyone is affected. It is, however, in only a few individuals that the changes cause symptoms, and in fewer still that they progress to osteoarthritis.

Symptoms of chondromalacia include pain, crepitus (popping and cracking), decreased function and occasionally swelling. Pain is the most common symptom and is what usually causes people to see their physician. Activities such as running, jumping, stairs, hiking, squats and lunges will exacerbate the condition. People will also notice that sitting in one position for a period of time (driving, riding in a plane or a car) will also bring on their symptoms.

This disease can be documented by magnetic (MRI) scans [20, 21]. The treatment of this disease is usually non-operative. According to the EULAR recommendations [22], the management of the pathology requires a combination of nonpharmacological (education, weight reduction, exercise and mechanical support) and pharmacological treatment modalities.

Therapeutic joint injections for pain management have been used for many years and are usually performed to treat inflammatory conditions such as osteoarthritis. The success rate and clinical improvement depends greatly on the overall condition of the joint and the medication administered during the injection, as well as the accurate placement of the needle tip into the joint. The drugs that are most frequently used and may relieve patients’ symptoms are CS, HA, and anesthetics [23, 24].

CS reduces the inflammatory reaction by limiting the capillary dilation and permeability of the vascular structures. These compounds restrict the accumulation of polymorphonuclear, leukocytes and macrophages, and reduce the release of vasoactive kinins. Furthermore, CS may inhibit the release of arachidonic acid from phospholipids, thereby reducing the formation of prostaglandins, which contribute to the inflammatory process [25].

HA is an organic polysaccharide that induces normalization of the viscoelasticity of the synovial liquid and activation of the tissue regeneration of the articular cartilage. In the cartilage, HA plays an important structural role in the matrix, forming an aggregation center for aggrecan, a large chondroitin sulfate proteoglycan that retains its macromolecular assembly in the matrix due to specific HA-protein interactions [26]. Cartilage homeostasis and modulation of cartilage metabolism is maintained by the interaction of HA with the CD44 receptor on chondrocytes (CD44 variant isoform), suggesting that disruption of these interactions may promote matrix remodeling [27, 28]. This receptor is also present in the osteocyte plasma,
basolateral membrane, and the cytoplasmic processes of active osteoblasts. The interaction of the CD44 receptor with HA restricts osteoblast-mediated osteoclastogenesis [29, 30].

Many clinical trials using different HA formulations have shown that HA is more active than placebo in reducing arthritic pain [31, 32]. Lately Migliore et al. showed that the infiltration with HA significantly improves the quality and joint function, and decrease the painful symptoms in osteoarthritis [33].

In a literature review conducted by Brzusek and Petron [34] identified randomized, placebo-controlled trials involving the use of hyaluronans, HA and sodium hyaluronate plus hylan G-F 20 (a cross-linked HA derivative) were both associated with significant improvements in pain and physical function in patients (mostly adults aged over 40 years) with chondropathy knee both regimens were most effective between 5 and 13 weeks after injection, but improvements were also observed at 14-26 weeks and sometimes even longer; both were well tolerated with a low incidence of side effects.

The 2006 Cochrane review summarised the results of 76 randomised controlled trials comparing HA and various other treatment modalities [35]. The authors concluded that viscosupplementation is an effective treatment for knee osteoarthritis (OA) with beneficial effects on pain, function, and global assessment, especially at the 5- to 13-week post-injection period. Although the sample size restriction may preclude any definitive comment on the safety of the products, no major safety issues were detected.

A recent multicenter study in China [36] show that the single 6-mL intra-articular injection of hylan G-F 20 (cross-linked HA, 6000 kDa) could significantly reduce pain and improve function in patients with primary knee OA. The beneficial effect could be sustained for up to 6 months. The VAS scores increased again by the 1-year follow-up visit, but the values were still significantly lower than the pre-injection levels. The 5-point Likert scale also revealed that about 75% of patients had reduced pain at 3 months, 62% at 6 months, and the percentage remained decreased at 50% at the 1-year follow-up visit. The American College of Rheumatology subcommittee recommends chorticosteroid injections as an effective method of decreasing pain [37].

From randomized controlled trials there is evidence that intra-articular injections of CS are effective, but their benefit over placebo may be relatively short-lived, up to four weeks. Recently, the short-term effect was also highlighted in a systematic review by Hepper et al. [38] and in a meta-analysis by Bannuru et al. [39]. One more recent study also demonstrated that injections of CS resulted more effective than placebo on Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) total subscale scores at four weeks [40]. Moreover, some studies suggest a possible benefit of up to 26 weeks [41, 42]. On the other hand, in the 2006 Cochrane Review, emphasized that there was a lack of evidence for efficacy in functional improvement (e.g., stiffness, walking distance, and quality of life) at any time point with IA CS injections [43].

In the literature data, it is evident that the intra-articular CS injections act immediately and for a short period of time, while the intra-articular injections with HA begin to have a clinical outcome after several weeks. With our study, we demonstrated that the synergistic action of both drugs accelerates and enhances the quality of the clinical outcome. Also the result of pain reduction and quality improvement in time overlapping joints remain the use of HA without CS. The pain symptom is rapidly reduced in group B in the first month (p<0.009) of control and it improves the quality and quantity of daily activities performed by the patient as measured by MRI (p<0.001). Joint function measured with the CORSA is better on the 1st (p<0.001) and the 3rd month (p<0.034). The anti-inflammatory and analgesic CS, allowing better performance lubricant action of HA being able to make more effective and better joint movement.

The CS, in fact, helps the action of HA and this is related to its anti-inflammatory action.

CS has both anti-inflammatory and immuno-suppressive effect, but their mechanism of action is complex. CS act directly on nuclear steroid receptors and interrupt the inflammatory and immune cascade at several levels. By this means, they reduce vascular permeability and inhibit accumulation of inflammatory cells, phagocytosis, production of neutrophil superoxide, metalloprotease, and metalloprotease activator, and prevent the synthesis and secretion of several inflammatory mediators such as prostaglandin and leukotrienes [44, 45]. The clinical anti-inflammatory reflections of these actions are decreases in erythema, swelling, heat, and tenderness of the inflamed joints and an increase in relative viscosity with an increase in HA concentration [46, 47]. HA will act as a synovium
and cartilage devoid of substances that can slow or degrade its components.

5. CONCLUSIONS

The current literature and our experience indicate that intra-articular HA injections for knee chondromalacia are safe and have positive effects in patients. After all, the patient should have resolution of symptoms and good functional results in a short time and for a long period of time.

Chondromalacia is characterized by inflammation and softening of the cartilage, therefore the modification of the structure induce a reduction of the efficacy and the capability of HA to induce benefit in the patient.

The hyaluronic acid requires inflammation free area to carry out its physical and biological properties; otherwise it will be degraded.

Injection with CS has the function of relieving the pain soon, furthermore presents an anti-inflammatory action, leading the arrangement of the cartilage to receive HA.

Our study showed that the use of intra-articular injection of CS at the first cycle infiltrative with HA:

1) Quickly reduces the pain;
2) Enhances the mechanical action of HA;
3) Extends the period of good results.

REFERENCES


DOI: http://dx.doi.org/10.20941/2311-0317.2015.03.02.2

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