



Hyaluronic Acid Intra-Articular Injections for Treating Idiopathic Patello-Femoral Chondropathy in Adolescents

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Abstract

Background: Anterior knee pain attributed to idiopathic patellofemoral chondropathy (PFC) is a frequent cause of consultation of children and adolescents. Current treatment is often disappointing but the natural evolution is usually favorable in a few years. To date the effectiveness of intra-articular articular hyaluronic acid (IA-HA) injections for relieving anterior knee pain in adolescent has never been studied.

Objective: The aim of the present paper is to report data on safety and efficacy of IA-HA injections in children and adolescents suffering from idiopathic PFC.

Patients and methods: Case series. Sixteen patients referred for anterior knee pain diagnosed as PFC, aged 10 to 16, without major anatomical abnormality of the knee or other identifiable cause of knee pain, in who conservative treatments for at least 3 months failed, were treated with IA-HA injection between September 2016 and May 2019. Treatment consisted in 1 IA injection of a cross-linked HA+mannitol. The injected dose depended on the child's weight (1 ml if weight < 45 kg and 2 ml if weight ≥ 45 kg). Clinical data and patients' self-assessment of efficacy and safety were analyzed retrospectively.

Results: The series included 16 girls (mean age 13.4 years, mean symptom duration 20.2 months). All had to stop practicing sports because of knee pain. Before IA-HA injection 13 patients have had rehabilitation and 7 were taking

pain killers every day. Twenty-two knees were injected. Eight patients had one course of injections, 7 had 2 courses (mean time interval 11.4 months, range 7 to 14) and 1 had 3 courses at 1 year-interval. Patients assessed treatment efficacy as excellent in 9 cases, very good in 4, moderate in 2 and poor in 1. The painful knee was completely "forgotten" in 9 adolescents. Improvement occurred between the 4th and 6th week post-injection. All patients whose pain started less than 12 months ago were completely relieved. All but one patient returned to sport within 3 months after injection. There was no safety concern.

Conclusion: This small case series suggests that IA-HA injection is a valuable and safe option to relieve anterior knee pain durably in children and adolescents with idiopathic PFC. Further controlled trials are warranted to confirm these promising findings.

Keywords: Adolescent; Hyaluronic acid; Intra-articular injection; Knee; Patellofemoral chondropathy

Introduction

Anterior knee pain, attributed to patello-femoral chondropathy (PFC) is a common cause of consultation of children and adolescents, frequently leading them to shut down sport for many months. Much more common in the girl than in the boy, the origin remains poorly understood and is often attributed to mechanical disorders (i.e. sequelae of dislocation or subluxation, articular hypermobility, chronic instability of the patella, trochlea dysplasia, patella alta, sports

overwork) [1]. However, in a significant number of cases there is no detectable cause, and a psychological component is evoked. What is the most surprising in adolescents' anterior knee pain is the usual discrepancy between the pain intensity and the lack of objective data at clinical examination and imaging [1, 2]. Management of adolescents with patellar chondropathy is difficult. To date there is no specific treatment that is universally accepted as a standard of care. It includes rehabilitation (stretching and isometric strengthening), patella stabilizing braces and insoles aimed to decrease foot hyperpronation [1, 3, 4]. The current pharmacological treatment is only symptomatic, usually limited to analgesics such as paracetamol or non-steroidal anti-inflammatory drugs (e.g. ibuprofen).

Intra-articular (IA) injections of hyaluronic acid (HA) have been successfully used for more than 20 years for treating pain related to knee osteoarthritis (OA) [5-9], including chondromalacia patella [10]. Because HA has a direct effect on joint nociceptors [11] and an excellent efficacy-safety ratio [9], it makes sense to use it in PFC, a condition in which the conventional medical treatment is often disappointing. Indeed, one out of the multiple hypotheses that might explain the unpredictable effectiveness of conventional therapies, is that the primary source of pain might be the joint soft tissue nociceptors (i.e. synovium and capsule) [12, 13] on which HA has been shown to be active [11]. Furthermore, anterior knee pain in adolescence has been identified as a possible predictor of knee OA. A histological study on patellar chondropathy in 83 adolescents (98 knees) with anterior knee pain, showed histological lesions similar to that found at the early stages of knee osteoarthritis. However these lesions showed far more potential for repair than does osteoarthritis [14]. This finding raises the question as to whether the pathophysiology of PFC may have, at least in part, similarities to that of OA [15, 16] and legitimize the use of HA injections in adolescents suffering from idiopathic anterior knee pain in who conventional treatment failed. Based on our clinical experience, we drew the hypothesis that IA-HA injections is well tolerated and effective to relieve anterior knee pain in young patients suffering from PFC without major anatomical abnormality.

Patients and Methods

The present paper reports data from a case series followed in daily clinical practice, where outcomes were analyzed retrospectively. All patients were seen in a single public hospital and were referred to the pediatric rheumatology department, between September 2016 and May 2019, for anterior knee pain diagnosed as patello-femoral chondropathy (PFC). Among them, only cases meeting the following criteria were included in the present case report: 1) patients aged 10 to 16; 2) anterior knee pain since more than 3 months, 3) lack of major anatomical abnormality of the knee (i.e. trochlea dysplasia, patella alta, patello-femoral dislocation); 4) absence of other identifiable cause of knee pain (i.e. meniscus tear, tendinopathy, Osgood-Schlatter disease, Sinding-Larsen-Johanssen disease, inflammatory arthritis); 5) failure of well

conducted conservative treatments for at least 3 months (rehabilitation and analgesics). This retrospective data analysis was approved by the scientific and ethics committee of the North Franche-Comté Hospital, Trevenans, France.

The diagnosis of PFC was based on clinical questioning: anterior knee pain that had been evolving for more than 3 months that worsened with activities increasing the stress on the patello-femoral joint (squatting, going up and down stairs, and running, sitting legs bent). The physical examination assessed the presence or absence of synovial effusion, quadriceps strength and patella mobility. The patellar glide, grind and tilt tests were performed as part of the routine evaluation of patients with anterior knee pain, since positive results have been shown to be consistent with the diagnosis of PFC [17]. X-ray examination of both knees (standing anteroposterior extended view, lateral view, skyline view of the patella) was performed in all patients for assessment of patella anatomy and positioning and for eliminating other etiologies of knee pain (i.e. osteochondritis dissecans, bone tumor). CT-scan, MRI and blood tests were performed only when diagnosis remained uncertain, especially for eliminating mild architectural abnormalities (e.g. trochlea dysplasia), inflammatory arthritis (i.e. juvenile idiopathic arthritis) or synovial tumor.

Treatment Procedure

Patients included in this analysis underwent 1 to 3 courses of intra-articular (IA) HA injection, performed by a single rheumatologist (TC). One course consisted in 1 IA injection of a cross-linked HA viscosupplement, combining HA 16 mg/ml and mannitol 35 mg/ml (HANOX-M-XL, HAPPYMINI®, Labrha SAS, France) depending on the child's weight (1 ml if weight < 45 kg and 2 ml if weight ≥ 45 kg). HANOX-M-XL has been successfully used in knee, hip, ankle and trapezio-metacarpal OA) [18-21] without any safety concern. During knee injection, patients were supine with their legs extended. Skin local anesthesia was performed using a lidocain patch (EMLA®, Aspen Pharma, France) placed 1 hour before the injection. Skin disinfection was performed using an antiseptic solution (iodine povidone, Betadine®, Mylan medical SAS). Intra-articular injection was achieved using a 23 to 25 Gauges needle, with a length of 25 to 30 mm, according to the child's corpulence. As recommended, intra-articular injection was achieved using a lateral mid-patellar approach [22]. After the injection, children were advised to rest until the next morning (no running, no jumping) and not resume sport until 15 days later. A follow-up visit was scheduled 3 and 6 months after the injection. A follow-up visit was scheduled 3 and 6 months after the injection. However, parents were asked to return earlier with their child if pain returned to baseline.

Case Report

Sixteen patients fulfilled the above criteria. All were girls, whom mean age (range) at the time of HA treatment was 13.4 years (11 to 16). Anterior knee pain was bilateral in 9

children. The mean symptom duration before injection was 20.2 months (6 to 72). Thirteen had stopped school sporting activities. Among the 14 patients who were practicing weekly one or more sports (1 soccer, 5 dance, 3 basketball, 3 gymnastic, 4 swimming, 2 horse riding), all had to stop practicing their favourite sport. Regarding knee pain management, 13 patients underwent rehabilitation sessions, 7 were taking pain killers regularly (4 ibuprofen and 3 paracetamol), 4 wore orthopaedic insoles and 6 used knee braces. One child was treated with chondroitin sulphate for 9 months. One received 1 corticosteroid IA injection 7 months before viscosupplementation.

Twenty-two knees were injected. Eight patients had one course of injections: 4 received 1 ml per course and 4 received 2 ml per course. Seven received 2 courses of treatment (mean time interval 11.4 months, range 7 to 14). Three courses of 1 ml injection, at 1 year-interval, were achieved in one child.

The last time they were seen, patients and parents assessed treatment efficacy as excellent in 9 cases (absence of pain, very good in 4 (mild and infrequent pain), moderate in 2 (mild improvement) and poor in 1. The painful knee was completely "forgotten" in 9 young girls. Improvement occurred between the 4th and 6th week post-injection in all the children who were improved. The only one patient who did not resume sport activity was the one who had suffered for 6 years. All patients whose pain started less than 12 months ago were completely relieved. The 8 patients who were playing a competitive sport took it back within 3 months after injection. Short and long term tolerability of the treatment was good in all patients. Only 2 children reported mild knee pain the very next hours after injection that resolved spontaneously within 24 hours.

Discussion

Most of patients in this short case series experienced a significant decrease in pain and disability compared to baseline and returned to sport a few weeks after IA-HA injection. Obviously, the interpretation of the present data is limited by the retrospective nature and the lack of standardization of their acquisition, the small sample size, the subjectivity of the measured variables and the lack of comparator. Further randomized controlled trials with larger sample sizes and longer follow-ups are naturally warranted to confirm or infirm these promising results. However, the fact that about 80% of patients were satisfied with the treatment, despite a long history of knee pain (mean time 2.5 years), strongly suggests that IA-HA injection is a new valuable option in the treatment of adolescent PFC. In our small sample, all but one children return to sport the very next months after HA injection. It is important to underline that only patients with idiopathic anterior knee pain, that is to say without major anatomical patello-femoral abnormality (such as patella malalignment, trochlea dysplasia, patella alta), or history of trauma/dislocation, have been treated. It is not possible to extrapolate our results to other etiologies of knee pain.

The mechanisms by which HA relieves pain is still not fully understood. For a long time, it has been believed that the viscous nature of HA was the main reason of its analgesic effects, thanks to the ability of the HA macromolecule to "mechanically" protect nerve endings. Since then, numerous studies have demonstrated that HA acts through multiple mechanisms involving interactions between HA and nociceptors [11], inhibition of pro-inflammatory cytokines (i.e. IL-1 β , TNF α) [11, 23], modulation of the plasminogen/plasminogen activator inhibitor (PA/PAI) system [24], inhibition of the cyclo-oxygenase 2 (COX-2) expression [25], binding bradykinin through electrostatic interaction, decrease of synovial-fluid levels of glutamate and aspartate [26] and reduction of mechanical sensitivity of stretch-activated ion channel. Most of these properties are mediated through HA binding to cell surface receptors, including cluster determinant 44 (CD44) and receptor for hyaluronate-mediated motility (RHAMM) [11]. All the patellofemoral tissues that possess sensory innervations can be a potential source of anterior knee pain, making specific diagnosis difficult [27]. There are many free nerve endings in the patellar tendon, the retinacular tissue, the fat pad and the synovium. Furthermore elevated pressure in the patella can also be associated with pain, since the subchondral underlying bone has the potential to generate pain when overloaded by overlying cartilage deficiency [27]. The higher frequency of PFC in girls than in boys can be explained in part by a thinner patellar cartilage that might expose bone to higher mechanical pressure [28]. It also has been demonstrated that patients with patellofemoral pain exhibit elevated bone metabolic activity at the patellofemoral joint, suggesting that anterior knee pain may be related to abnormal bone metabolic activity at the patellofemoral joint [28, 29]. Hyaluronic acid that is claimed to restore a physiological joint homeostasis [30] might act through complex and multiple mechanisms of action on the different joint tissues. As the precise mechanism of pain in PFC is unknown we can only make assumptions about how IA-HA causes pain reduction. Two potential mechanisms of action are possible. The biomechanical one, by directly enhancing the viscoelasticity and lubrication of synovial fluid, is unlikely. It has never been shown that synovial fluid was altered in young patients with knee pain. The physiologic one is more probable. HA may penetrate synovium and cartilage tissues and suppress gene expression of inflammatory mediators and matrix metalloproteases [31], resulting long-term improvement in pain.

Lastly, with regard to the particular structure of the used viscosupplement HANOX-M-XL (high viscoelastic properties due to its cross linked structure, presence of mannitol that exhibits anti-inflammatory and anti-oedematous properties) [32, 33] the present results must be extrapolated with caution to other HA visco supplements (Table 1).

Patient No	Age	Sex	Duration (Months)	X-rays			Rehab	Uni-bilateral	Sport	Treatment			Results		
				CT Scan	MRI	ml				No of courses	Interval				
												Yes		No	1 ml
												No		No	2 courses
1	12	F	20	Yes	No	1 ml	2 courses	11 months	Forgotten Knee						
2	16	F	42	Yes	Yes	Bilateral	Dance	2 ml	1 course	-	Very Good				
				Yes											
				Yes											
3	12.5	F	12	Yes	No	Unilateral	Gymnastic	2 ml	2 courses	12 months	Forgotten Knee				
				No											
				Yes											
4	13	F	12	Yes	Yes	Unilateral	Dance, Soccer	1 ml	1 course	-	Forgotten Knee				
				No											
				No											
5	13	F	24	Yes	Yes	Bilateral	Basketball	1ml	3 courses	12 Months	Very Good				
				Yes											
				Yes											
6	13,5	F	14	Yes	Yes	Bilateral	Gymnastic	1ml	3 courses	12 months	Very Good				
				No											
				Yes											
7	14	F	36	Yes	Yes	Bilateral	Basketball	1ml	2 courses	11 months	Forgotten Knee				
				No											
				Yes											
8	13	F	18	Yes	Yes	Unilateral	Swimming, Horse riding	2ml	1 course	-	Very Good				
				Yes											
				Yes											
9	14,5	F	12	Yes	No	Bilateral	No	1ml	1 course	-	Forgotten Knee				
				No											
				Yes											
10	16	F	72	Yes	Yes	Unilateral	Swimming	2ml	2 courses	7 months	Failure				
				Yes											
				Yes											
11	12	F	6	Yes	Yes	Unilateral	Dance	1ml	1 course	-	Forgotten Knee				
				No											
				No											
12	4	F	8	Yes	No	Bilateral	Gymnastic, Swimming	2ml	1 course	-	Forgotten Knee				
				No											
				Yes											
13	14	F	14	Yes	Yes	Unilateral	Horse riding	1ml	2 courses	11 months	Moderate				
				No											
				Yes											
14	12,5	F	12	Yes	Yes	Bilateral	Swimming, Dance	2ml	2 courses	13 months	Forgotten Knee				
				Yes											
				Yes											
15	11	F	7	Yes	Yes	Unilateral	No	2ml	2 courses	14 months	Forgotten Knee				
				No											
				No											
16	13.5	F	14	Yes	Yes	Bilateral	Basketball	1ml	1 course	-	Moderate				
				No											
				Yes											

Table 1: patient's main characteristics.

Conclusion

At our knowledge this case series is the first report ever published on IA-HA injection for idiopathic PFC in children and adolescents. It suggests that a single IA injection of cross-linked HA combined with mannitol may be helpful and safe in relieving anterior knee pain over a period of 6 to 12 months, and allows resumption of sports in most children. These preliminary observational data are sufficient to consider the design of a randomized placebo-controlled trial to confirm or refute these promising results.

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Author Contributions

Analyzed the data : AL, JCB
Wrote the first draft of the manuscript : AL, TC.
Contributed to the writing of the manuscript : AG;JCB.

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