Rev Soc Esp Dolor
2017; 24(2): 74-84

DOI: 10.20986/resed.2016.3485/2016

Effectiveness of hyaluronic acid intra-articular injections in treating knee osteoarthritis: results of a series of cases treated in a Pain Unit

M. D. Rodrigo Royo[1], J. C. Quero López[1], R. M. Aparicio Abiol[1], P. Cía Blasco[1], P. Baltanás Rubio[1] and M. P. Acín Lázaro[2]

[1]Unidad del Dolor. Hospital Universitario Lozano Blesa. [2]Servicio de Anestesiología. Hospital Royo Villanova. Zaragoza

Rodrigo Royo MD, Quero López JC, Aparicio Abiol RM, Cía Blasco P, Baltanás Rubio P y Acín Lázaro MP. Effectiveness of hyaluronic acid intra-articular injections in treating knee osteoarthritis: results of a series of cases treated in a Pain Unit. Rev Soc Esp Dolor 2017;24(2):74-84.

ABSTRACT

Objective: To evaluate the results of treating knee osteoarthritis with a single intra-articular injection of hyaluronic acid in terms of pain reduction, joint function improvement and duration of effects.

Method: Patients with clinical and radiological diagnosis of osteoarthritis at different stages of evolution in one or both knees were treated at the Pain Unit of a tertiary hospital. Socio-demographic and clinical characteristics provided by the patient following the usual clinical practice were prospectively collected. Pain at rest, walking, climbing up and down stairs, morning stiffness, time walking as well as sleep time/quality were recorded pre- and post-treatment. At post-treatment visit the degree and duration of improvement experienced, as well as investigator assessment, were also recorded. The treatment consisted of a single intra-articular injection of hyaluronic acid, with the possibility of a booster.

Results: A total of 29 patients (52 knees) were included. Both knees were treated in 23 individuals (n = 46) and only one knee in the remaining 6. 92.3 % were osteoarthritic joints with an evolution > 12 months, with clinical grade of 4-5 in 61.6 % (n = 32) and a radiological grade (Kellgren & Lawrence) of III-IV in 67.7 % (n = 35), so 55.8 % of cases were classified as severe by investigators. There was a significant improvement in all parameters of pain and function considered ($p < 0.001$). Walking time increased by over 100 % and 67.3% of patients defined their quality of sleep as normal, compared to 38.5 % at baseline. Improvement was evaluated by the investigator as good or very good in 73.1 % of cases.

Conclusions: Our study confirms the effectiveness of a single hyaluronic acid injection to reduce symptoms in patients with knee osteoarthritis with different grades of severity, with results that last between 6 and 12 months and which are especially significant in patients with mild to moderate osteoarthritis.

Key words: Knee osteoarthritis, hyaluronic acid,

RESUMEN

Objetivo: Valorar los resultados del tratamiento de la artrosis de rodilla mediante una inyección intrarticular de ácido hialurónico en lo que se refiere a reducción del dolor, mejoría de la función articular y duración de los efectos.

Método: Pacientes con diagnóstico clínico y radiológico de artrosis en diferentes fases de evolución en una o ambas rodillas, tratados en la Unidad del Dolor de un hospital de tercer nivel. Se recogió prospectivamente la información facilitada por el paciente siguiendo la práctica clínica habitual: características sociodemográficas y clínicas. Se realizaron valoraciones pre y postratamiento del dolor en reposo, a la deambulación y al subir/bajar escaleras, rigidez matutina, tiempo caminando y las horas/calidad del descanso nocturno. En la visita postratamiento se registraron, además, el grado de mejoría experimentada, duración de la misma y la satisfacción del investigador. El tratamiento consistió en una única inyección de ácido hialurónico por vía intrarticular, con posibilidad de una dosis de recuerdo.

Received: 27-06-16.
Accepted: 04-07-16.

Correspondence: María Dolores Rodrigo Royo
mdrodrigo@salud.aragon.es

Resultados: Se incluyeron 29 pacientes (52 rodillas); en 23 se trataron ambas rodillas (n = 46) y en 6 una rodilla. El 92,3 % corresponden a articulaciones artrósicas con un tiempo de evolución > 12 meses, con grado clínico 4-5 en el 61,6 % de las rodillas tratadas (n = 32) y grado radiológico III-IV de Kellgren y Lawrence en el 67,7 % (n = 35), por lo que un 55,8 % de los casos fueron calificados como severos por los investigadores. Hubo una mejoría significativa en todos los parámetros de dolor y funcionalidad considerados (p < 0,001). El tiempo caminando se incrementó en más del 100 % y el 67,3 % de los pacientes definieron su calidad de sueño como normal, frente al 38,5 % inicial. La mejoría fue valorada por el investigador como buena o muy buena en el 73,1 % de los casos.

Conclusiones: Nuestro trabajo confirma la eficacia de una única inyección de ácido hialurónico para reducir la sintomatología en pacientes con gonartrosis en diferentes grados de severidad, con resultados que se mantienen entre 6 y 12 meses y son especialmente significativos en aquellos con artrosis leve y moderada.

Palabras clave: Gonartrosis, ácido hialurónico.

TABLE I
RISK FACTORS IN OSTEOARTHRITIS

Modifiable	*Partially modifiable*	*Non modifiable*
Obesity	Estrogen deficiency	Sex
Joint injury	Osteoporosis	Age
Occupational	Vitamins C, E and D	Race
Nutritional	C-reactive protein	Genetic predisposition
Structural misalignment		
Muscular weakness		

INTRODUCTION

Osteoarthritis is a chronic, degenerative joint disease, characterized by focal areas of articular cartilage loss in the synovial joints, associated with bone hypertrophy (osteophytes and subchondral bone sclerosis) and thickening of the capsule (1) accompanied by pain, rigidity and loss of functionality.

The most frequent location is the knee, and symptomatic osteoarthritis of this joint is estimated to affect 24% of the general population's (1). This is due to a number of factors, the most important being the biomechanical requirements that this joint is subjected to (2,3).

The etiology of osteoarthritis is multifactorial and includes a variety of risk factors that interact to cause the disease (4). Some of these are modifiable to a greater or lesser extent, while others are not (Table I) (5-18).

Every population combines a different set of risk factors, so it is essential for every country to have representative prevalence studies. In Spain, according to recent studies, osteoarthritis affects 11.72% of the general population (19), slightly higher results than the 2-6% registered in Framingham (20), 6.6% in Greece (21) or 5.4% in Italy (22).

From the age of 45 onwards, the risk of developing osteoarthritis increases substantially with every decade of life (23), so, bearing in mind the increase in life expectancy, it is to be expected that the arthritic population will grow in coming years (24). For example, in recent studies carried out in Spain, the prevalence of knee osteoarthritis among the population aged 60-90 reached up to 71% according to series (25,26).

The main goals in treating osteoarthritis are reducing pain, improving joint function and limiting functional deterioration. The secondary goal focuses on reducing the disease's progression and improving muscular strength, with the aim of preserving patients' independence and quality of life (27).

Despite this disease's enormous impact, effective, non-surgical therapeutic options are very limited. The current treatment guidelines (28-30) recommend starting with the use of non-drug measures, such as patient education, weight loss and physical therapy. However, it is commonly accepted that proper management of knee osteoarthritis requires a combination of non-pharmacological and pharmacological treatments, such as paracetamol, non-steroidal anti-inflammatory drugs or selective COX 2 inhibitors.

One alternative to oral medication for pain in patients with a poor response to analgesics and/or anti-inflammatory drugs or with contra-indications against them, is the use of intra-articular (IA) therapy (31). IA treatment is not only of special interest for pain relief, but also in achieving an improvement in patients' quality of life, which can postpone surgery (32). At present, hyaluronic acid (HA) and corticosteroids (CS) are being used. CS infiltrations have been used for the last 60 years as conservative management of OA and its use is recommended in several consensus documents (28-30). In an extensive review of the Cochrane Database (33), the authors concluded that CS infiltrations are effective, but their results, though rapid at the outset, are relatively short-lived (1-3 weeks).

HA is a component of synovial fluid and in patients with OA its concentration and molecular weight in this fluid are diminished, leading to the proposal that its use as a treatment for OA could be beneficial. Since Balazs et al. began working with HA (34), this compound has been used with increasing frequency as a non-surgical alternative in OA and its use is recommended by several scientific societies (35-37). HA is a key molecule in joint biomechanics, because treatment with exogenous HA helps restore the synovial fluid's elastic and viscous properties, giving rise to pain reduction and functional improvement. Additionally, several studies have confirmed that HA interacts with mediators of inflammation and matrix turnover in articular cells, reduces chondrocyte apoptosis and exerts a biosynthetic-chondroprotective effect (38-42).

However, the characteristics of patients with the greatest probabilities of benefitting from this treatment are not clearly defined, nor the number of IA injections to administer nor the time that should elapse between two series. This is compounded by the fact that the different HAs available have different physical-chemical characteristics and, therefore, the same clinical effect cannot be expected (43-45). The objective of this study is to evaluate the results of treating knee osteoarthritis with IA infiltration of HA, in terms of pain reduction, improving knee joint function and recording the time elapsed until re-injecttion, in a series of patients treated in the Pain Unit of a tertiary hospital, according to standard clinical practice.

METHOD

Study design

Observational, prospective, single-center study with patients treated by the Pain Unit team of the Hospital Clínico Universitario Lozano Blesa in Zaragoza. The study included patients of both sexes, aged older than 18, with knee OA according to clinical diagnosis of the American College of Rheumatology (ACR) (37) and radiological diagnosis according to Kellgren and Lawrence (K&L) (46) in one or both knees, of more than 6 months' evolution, with normal coagulation and without contra-indications for HA treatment, in the investigator's opinion.

Information provided by patients was collected according to standard clinical practice: socio-demographic and clinical characteristics. Pre-and post-treatment evaluations were carried out regarding pain intensity at rest, during ambulation and climbing up/down stairs, functionality according to the ability to go up and down stairs, the time and distance they are able to walk, morning stiffness (yes/no), and hours/quality of sleep. The post-treatament visit also recorded the degree of improvement experienced, its duration and the investigator's satisfaction with the treatment. Patients were asked to return 6 and 12 months following treatment for evaluation, with instructions to bring visits forward if they returned to baseline pain levels.

Measuring tools used were:

– *Clinical grading criteria:* clinical grade was assessed with 5 items, taking into account all the clinical parameters evaluated and observed, which we summarize as:
  - *Grade 1. Mild.* No pain at rest. Mild pain with movement, allowing them to walk without limitation and climb up and down stairs.
  - *Grade 2. Moderate.* No pain at rest. Moderate pain with movement, allowing subjects to walk more than 1 km, climb stairs normally and go down with support (handrail).
  - *Grade 3. Intense.* Mild pain at rest, increasing with movement, allowing subjects to walk 500 to 1,000 metros. They can go up and down stairs but supported by the handrail and with occasional difficulty sleeping.
  - *Grade 4. Severe.* Moderate to intense pain at rest, which increases with movement, making sleep difficult and preventing them from walking more than 500 meters. They can go up stairs using the handrail but cannot go down.
  - *Grade 5. Very Severe.* Very intense pain, both at rest and in movement, interfering significantly with sleep and preventing them from leaving home. Inability to climb up or down stairs.
– *Pain intensity:* Visual analog scale (VAS) (0-10 cm) for pain intensity at rest, in movement and when going up and down stairs.
– *Stairs and walking:* evaluation of patients' ability to climb up and down stairs and walk used the criteria of the KSS Overall Function Subscale (46) (Table II).
– *Sleep:* sleep evaluation used the MOS sleep scale (47), which is given to patients and interpreted according to the score obtained with normal, poor, bad, maximum interference.

  This tool comprises 12 items that explore the impact caused by a disease or a treatment on sleep structure. It examines how external stimuli affect the amount of sleep, sudden awakenings, snoring, somnolence, disturbed sleep, etc. It produces an overall sleep interference score that ranges between 0 and 100. A score of 0 represents no interference with sleep and 100 the maximum interference possible. Each attribute is scored independently, also from lesser to greater impact upon it (the higher the score, the greater

TABLE II
KSS OVERALL FUNCTION SUBSCALE FOR STAIRS AND WALKING

Stairs	*Score*	*Walking*	*Score*
Climb up/down normally	50	No limit	50
Climb up normally/down with handrail	40	> 1.000 m	40
Climb up/down with handrail	30	500 m – 1.000 m	30
Climb with handrail/ unable to climb down	15	< 500 m	20
Unable to climb up or down	0	Cannot leave home	10
		Disabled	0

the negative impact), except for adequacy and optimal sleep, where a lower score means a worse qualification, and amount of sleep, which are hours slept per day (Table III).

– *Grade of improvement:* in the assessing the improvement achieved with the treatment, the investigator carried this out according to the variations in all these parameters before and after the treatment mentioned. Accordingly, overall improvement has been allocated according to the following percentages:
  • Improvement between 100 and 80 %: Very good result.
  • Improvement between 80 and 50 %: good result.
  • Improvement between 50 and 10 %: modest result.
  • No improvement or below 10 %: zero result..
– *Treatment:* the treatment consisted of administering an IA injection of HA of an average molecular weight (Adant One®, Tedec-Meiji Farma, S.A.). In the case of patients with bilateral osteoarthritis, both knees were injected. Patients with an initially positive response to the treatment, but who returned to baseline pain levels, were offered the possibility of another injection.

  The procedure was carried out in one of the rooms of the Pain Unit set up for this kind of minimally invasive treatment. It consisted of preparing the patient with intravenous cannulation, disinfecting the area by cleansing, preparing a sterile field and subcutaneous, percutaneous button with local anesthetic (lidocaine 2%). The approach for HA administration was intra-rticular, lateral, external and infra-patellar.

  During the study, oral analgesic treatment was allowed to be taken (NSAIDs and/or weak opioid) if necessary. All patients had signed informed consent for the procedure.

  Ethical considerations: the project was authorized by the Comité Ético de Investigación of Aragon and patients freely gave their prior consent to take part in the study. Data confidentiality was managed according to the recommendations of the Personal Data Protection Act 15/1999, of 13 December.
– *Statistical analysis:* for quantitative variables, normality of data was first analyzed using the Kolmogorov-Smirnoff test. For descriptive statistics, mean and standard deviation were calculated in the normal and median variables together with the interquartile range for non-normal data. Percentages were used for qualitative variables. Pre-post tests (Wilcoxon or t paired tests) were conducted for matched measurements in quantitative variables (VAS at rest, walking, climbing up / down stairs, time walking) and pre-post tests (McNemar) for qualitative variables in the sleep hours/quality parameter. A multivariate logistic regression analysis was carried out on factors that could influence the response, using clinical response as the dependent variable and including variables with a statistical relation to the clinical response ($p < 0.05$) as independent variables in the bivariate analysis. Regression was constructed by a procedure of successive steps, including control of confusion and collinearity factors. Data analysis was carried out with the program SPSS V14 (SPSS INC, CHICAGO, IL) .

RESULTS

Between March 2013 and March 2015, a total of 562 knees, belonging to 29 patients with OA in different grades of evolution, were included and treated with HA

TABLE III
MOS SLEEP SURVEY

MOS Sleep Survey
(Sleep Scale from the Medical Outcomes Study)

1. **How long did it usually take for you to fall asleep during the past 4 weeks?** (tick one):
   - ☐ 1 .....0-15 minutes
   - ☐ 2 .....16-30 minutes
   - ☐ 3 .....31-45 minutes
   - ☐ 4 .....46-60 minutes
   - ☐ 5 .....More than 60 minutes

2. **On average, how many hours did you sleep each night during the past 4 weeks?** Write in number of hours per night ☐☐

How often during the past 4 weeks did you...?		*All of the time*	*Most of the time*	*A good bit of the time*	*Some of the time*	*A little of the time*	*None of the time*
3	feel that your sleep was not quiet (moving restlessly, feeling tense, speaking, etc., while sleeping)?	1	2	3	4	5	6
4	get enough sleep to feel rested upon waking in the morning?	1	2	3	4	5	6
5	awaken short of breath or with a headache?	1	2	3	4	5	6
6	feel drowsy or sleepy during the day?	1	2	3	4	5	6
7	have trouble falling asleep?	1	2	3	4	5	6
8	awaken during your sleep time and have trouble falling asleep again?	1	2	3	4	5	6
9	have trouble staying awake during the day?	1	2	3	4	5	6
10	snore during your sleep?	1	2	3	4	5	6
11	take naps (5 minutes or longer) during the day?	1	2	3	4	5	6
12	get the amount of sleep you needed?	1	2	3	4	5	6

NOTE: Transcribe on a follow-up sheet the answers corresponding to the responses for each item.

injection. 23 patients were treated for both knees (total: 46) and the remaining 6 for one knee. Mean age was 72.6 (range 46 to 89 years old), 85% older than 60, and mean weight was 79.8 kg. Of the total number of patients, 23 (79.3%) were women. In 92.3%, treatment was for arthritic joints with over 12 months' evolution and major symptoms, with clinical grade 4-5 in 61% of knees treated (n = 32) and radiological grade III-IV in 67.7% (n = 35), so 55.8% of cases were qualified by investigators as severe.

Table IV summarizes socio-demographic and clinical characteristics.

Pre-and post-treatment evaluations were carried out. Prior to the study's initiation, patients reported mild-moderate pain at rest (mean 3.3), but not in the case of pain when walking and on stairs, which was moderate-severe (mean 7.7 and 8.6, respectively). Additionally, 86.5% of the knees suffered from morning stiffness and the time walking without pain was limited (median 5 minutes, with an interquartile range of 3 to 15 minutes). Sleep quality was qualified as poor due to symptoms in 48.1% of patients (Table V).

Post-treatment evaluation showed major changes in all parameters regarding the baseline situation, with significant improvement in the measurements of pain and functionality considered (Tables V and VI). Walking time increased by more than 100%, and 67.3% of patients defined their sleep quality as normal, compared with the baseline 38.5%. The improvement was evaluated by investigators as good or very good in 73.1% of cases (n = 38) (Table VII).

TABLA IV
BASELINE CHARACTERISTICS OF PATIENTS

Socio-demographic characteristics (n = 29 patients)	
Age (years), mean (SD)	73,0 (11.9)
Sex n (%)	
Man	6 (20.7)
Woman	23 (79.3)
Weight (kg), mean (SD)	79,8 (15.7)
Clinical characteristics (n = 52 knees)	
Radiological grading (Kellgren & Lawrence) n (%)	
II	17 (32.7)
III	12 (23,1)
IV	23 (44.2)
Clinical grading n (%)	
1	1 (1.9)
2	6 (11.5)
3	13 (25.0)
4	24 (46.2)
5	8 (15.4)
Diagnosis n (%)	
Mild	6 (11.5)
Moderate	17 (32.6)
Severe	29 (55.8)
Time of evolution	
6-12 months	4 (7.7)
> 12 months	48 (92.3)

When comparing the values of VAS (mean ± SD) and walking time (minutes) among patients with grade II-III-IV, no differences were found in the responses among the three groups in the variables of pain at rest ($p = 0.313$) and walking time ($p = 0,207$); in the case of variables in pain with walking and stairs, patients with grade IV had a smaller reduction in VAS than the other 2 groups ($p = 0.008$ and $p = 0.024$, respectively) (Table VIII). Similarly, when the response was analyzed according to clinical grade, patients with a mild-moderate grade also showed a better response than patients with a severe grade. To verify the variables associated with good clinical response to the treatment, a multivariate analysis was conducted by logistic regression, including as independent variables: radiological grade (IV versus the rest), clinical grade (4 + 5 versus 2 + 3), clinical diagnosis (severe versus moderate and mild), initial VAS walking and climbing up stairs and pain-free walking time at baseline, which are the variables that had shown statistical relation to the clinical response in the bivariate analysis (values of $p \leq 0.1$). The regression was constructed by the procedure of successive stages, including control of confusion and colinearity factors. The analysis indicates that the treatment's failure is associated essentially with a clinical diagnosis of severe, OR = 9.90 (95% CI = 1.15 -83.33; $p = 0.037$).

In a second logistic regression analysis to relate clinical variables with re-injection risk, only carried out in the patient group where there was a good initial response, two variables were included: radiological grade (IV versus the rest) and response time (6 months or less compared with over 6 months). In the regression, both variables proved to be risk factors independent of re-injection: response duration of 6 months or less has OR = 34.48 (95% CI = 3.56 -333.33); $p = 0.002$) and a K&L grade of IV has OR = 11.00 (95% CI = 1.14 - 100.01; $p = 0.038$).

A total of 6 patients with bilateral ailment (n = 12) were withdrawn from the study due to lack of effectiveness and were referred to the Orthopedic Surgery and Traumatology Service. In these cases, clinical diagnosis was severe in 91.7% and 75.0% had radiographic lesions compatible with K&L grade IV.

At the end of the study, the treatment's effect continued in 42.3% of cases, while 34.6% received a second injection, with a mean time up to re-injection of 7.2 months.

As regards safety, no related adverse events were recorded, confirming the treatment's excellent safety profile.

TABLE V
CLINICAL EVOLUTION

		Pre-treatment	*Post-treatment*	*Change (%)*	*P*
Pain in VAS, mean (SD)	*Rest*	3.2 (2.5)	1.2 (2.2)	-51.6 (52.5)	< 0.001*
	Ambulation	7.7 (1.5)	3.8 (2.9)	-54.2 (32.3)	< 0.001*
	Stairs	8.6 (1.3)	5.3 (2.8)	-40.6 (28.2)	< 0.001*
Time walking (minutes)		5 (3-15)	25 (14-45)	100 (50-337)	< 0.001*
Morning stiffness (present)		45 (86.5 %)	24 (46.2 %)		< 0.001**
Sleep quality	*Normal*	20 (38.5)	35 (67.3)		
	Poor	7 (13.5)	9 (17.3)		
	Bad	25 (48.1)	8 (15.4)		< 0.001**

*Wilcoxon / t paired test. **Mc Nemar.

TABLE VI
CHANGES IN PRE- AND POST-TREATMENT FUNCTIONALITY: CLIMBING UP/DOWN STAIRS AND DISTANCE WALKED (n = 52)

Climbing up/down stairs			*Distance walked*		
	Pre-treatment (%)	*Post-treatment (%)*		*Pre-treatment (%)*	*Post-treatment (%)*
Climb up / down normally	0 (0)	1 (1.9)	Without limit	0 (0)	10 (19.2)
Climb up normally / down with handrail	0 (0)	15 (28.8)	> 1.000 m	3 (5.7)	8 (15.4)
Climb up / down with handrail	3 (5.8)	14 (26.9)	500 m-1.000 m	7 (13.5)	8 (15.4)
Climb up with handrail / unable to climb down	13 (25.0)	10 (19.2)	< 500 m	13 (25.0)	14 (26.9)
Unable to climb up or down	36 (69.2)	12 (23.1)	Cannot leave home	29 (55.8)	12 (23.1)
			Disabled	0 (0)	0 (0)

TABLE VII
REASEARCHER'S EVALUATION OF IMPROVEMENT AND ITS DURATION

Improvement	*n (%)*	*Duration (months)*					*Re-injection*
		No improv.	*< 6 m*	*6 m*	*> 6 m*	*12 m*	
Zero	10 (19.2)	10	-	-	-	-	0 (0.0)
Modest (< 50 %)	4 (7.7)	-	3	1	-	-	2 (50.0)
Good (≥ 50 ≤ 80 %)	18 (34.6)	-	-	7	11	-	9 (50.0)
Very good (≥ 80 %)	20 (38.5)	-	2	3	14	1	7 (35.0)
Total	52 (100)	10 (19.2)	5 (9.6)	11 (21.1)	25 (48.1)	1 (1.9)	18 (34.6)

TABLE VIII
RESPONSE TO TREATMENT IN THE VAS AND TIME WALKING ACCORDING TO RADIOLOGICAL GRADING, EXPRESSED AS % OF CHANGE

	Grade II n = 17	*Grade III n = 12*	*Grade IV n = 23*	*p**
Pain				
Rest	-48.7 (47.9)	-66.7 (49.2)	-45.9 (57.9)	0.313
Ambulation	-64.0 (30.0)	-68.9 (27.9)	-39.3 (30.8)	0.008
Stairs	-52.6 (26.5)	-50.05 (24.96)	-26.89 (25.8)	0.024
Time walking	432 (935.0)	252.78 (139.4)	202 (217.0)	0.207

*Wilcoxon.

DISCUSSION

Pain Units try to provide an effective solution to patients in pain, both acute and chronic, of different types, origins and etiologies. They are generally conditions that lead to situations of disability, with considerable deterioration in the quality of life of patients who suffer them. In a recent study carried out in these units (48), OA was the main cause of chronic pain in 50.5% of cases, and OA of the knee affected 22.4% of patients. Multidisciplinary treatment of pain is beneficial not only for the patient but for society, and there are now many studies regarding cost/effectiveness, which show that specialized treatment represents a very significant economic saving worth keeping in mind (49).

It is commonly accepted that treatment of OA should be multifactorial, combining non-pharmacological and pharmacological methods. Arthritic patients for whom other therapeutic options have failed are referred to our unit from other specialties, and are evaluated as candidates for IA HA injection. This is a minimally invasive treatment that is given in out-patient care and which, in our experience, provides patients with pain relief and improved functionality for an extended period. The number of injections to be given is variable and, though in many cases between 3 and 5 injections are carried out, this is not always possible owing to the patient's characteristics, lifestyle, family constraints, etc., and we opt for a single administration with the possibility of booster injections. To study the effects of a single HA injection we have analyzed patients affected with knee OA in different degrees of evolution subjected to this treatment under the standard conditions of our clinical practice. Most of them had bilateral affection and a major symptoms, with a clinical grade of 4-5 in 61% of knees treated and a radiological grade of III-IV in 67.7%, so the status of 55.8% of cases was considered severe. These patients reported significant pain with mobility and major limitation to functionality, considerably affecting their quality of life. Administration of a single injection of 4.9 ml HA achieved a significant improvement in all pain and functionality parameters considered. Furthermore, time walking increased by more than 100%, and 67.3% of patients reported good quality sleep compared to the baseline 38.5%. As a consequence, the investigator evaluated the effectiveness of the treatment as good or very good in 73.1% of knees treated.

When the results were analyzed according to radiological grade, it was found that, in some of the parameters studied, patients with grade IV OA showed a poorer response than those with grade II-III. Similarly, when the response was analyzed according to clinical grade, patients with mild-moderate grade had a more significant response than patients with a severe grade. The 6 patients who were withdrawn from the study and referred to Orthopedic Surgery owing to lack of response had bilateral affection and severe osteoarthritis, from both a clinical and radiological point of view.

Among the responsive patients, we may identify 2 groups: those who required a second injection (n = 10, 18 knees), with a mean period of 7.2 months up to re-injection (range of 5.1 to 13.3 months), and those whose improvement continued at the end of the study: 95.8% of knees treated reached 6 months and in 83,3% the improvement lasted more than six months.

Our study confirms the results of other works demonstrating that IA HA injections are effective in reducing pain and improving function over an extended period in patients with knee osteoarthritis. The treatment's safety was excellent and we can assert that HA infiltrations are safe and do not represent a risk for patients, in line with the general opinion and contrary to the meta-analysis by Rutjes et al. (50), whose results have been questioned by other investigators and scientific societies (51,52).

The absence of a control group is a limitation for the study. We should bear in mind that a number of systematic reviews and meta-analyses have already shown HA's effectiveness compared with a placebo (53-55) and

compared with other forms of intra-articular intervention, such as corticosteroids, or else the two treatments have been compared both in the short term (56-62) and long term (63). Furthermore, a recent network meta-analysis (64) analyzing the different therapeutic options in comparison with a placebo for treating knee OA, concludes that IA treatments are more effective than oral options, and that HA is the most effective treatment in comparison with oral placebos; additionally, withdrawals due to adverse events are more frequent with oral treatments (paracetamol, NSAIDs, celecoxib) than with IA. As this is now known, the objective of our study has been to analyze the duration of effects of a single HA injection in a series of consecutive cases referred to the unit, many of them severely affected, as well as the treatment's safety. Another possible limitation to take into account has been the duration of patient monitoring, especially those that received a second injection, as repeated administration of HA has been found to have an accumulative effect ("carry over") that prolongs the improvement's duration over time (65).

The results of this work confirm the treatment's effectiveness in patients with OA, both mild and moderate, with results that last from 6 to 12 months. Individuals with severe osteoarthritis have a more variable response, which could be attributed to a more deteriorated baseline situation. Our results coincide with those of a network meta-analysis published after our work ended (66), which concludes by recommending HA as an effective treatment for knee OA and defines patients with K&L grade II-III and older than 60 as those able to obtain the best results with this treatment. Accordingly, we consider it worthwhile for the scientific community's different specialties to continue exploring the study into the characteristics of arthritic patients who can most benefit from this treatment, in order to establish consensual criteria to identify them prospectively.

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