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Safety of intra-articular hip injection of hyaluronic acid products by ultrasound guidance: an open study from ANTIAGE register

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Abstract. – OBJECTIVE: We developed a standardized technique for ultrasound guided intra-articular injection of the hip joint with the purpose of extending routine intra-articular injection of hyaluronans and steroids to the hip, as commonly used in the knee. In this article we report the safety of this technique in an extended series of patients.

PATIENTS AND METHODS: Patients were injected supine with an anterosuperior approach under ultrasound guidance. The Us probe is applied with a target device for biopsy.

RESULTS: The standardised technique was used to inject 1906 patients with 4002 injections of hyaluronan products over a four-year period. The treatment was well tolerated with few, and exclusively local, side effects.

CONCLUSIONS: The administration of hyaluronans under ultrasound-guided intra-articular injection is a safe technique for treatment of rheumatic diseases of the hip.

Key Words:
Intraarticular injection, Hip, Osteoarthritis, Safety, Ultrasound.

Introduction

Intra-articular therapies are widely used. One of the main advantages is that it allows therapeutic agents to be given at their intended site of action. The original reports of intra-articular corticosteroids showed marked improvements in both osteoarthritis and inflammatory arthritis, and today most rheumatologists frequently use intra-articular steroids. More recently trials of intra-articular hyaluronans in knee osteoarthritis (OA) also suggest positive benefits.

OA is the most common cause of joint pain in the adult, particularly among the elderly[1]. It represents a major cause of morbidity, disability and social isolation, especially when the hip and knee are involved. Relief of pain with preservation or restoration of joint motion is the major objective of therapy. The revised American College of Rheumatology (ARA) Guidelines for the management of knee and hip OA[2], include intra-articular therapy (steroids and hyaluronate) as valuable additions to the therapeutic armamentarium for the management of knee OA, such as arthroplasty and surgical joint replacement. Intra-articular hyaluronans (viscosupplementation), are indicated in: (1) patients who have not responded sufficiently to non-invasive, non-operative modalities and who are not candidates for total knee arthroplasty; (2) patients in whom nonsteroidal anti-inflammatory drugs (NSAIDs) are contraindicated (e.g. patients with a history of re-

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nal, hepatic or peptic-ulcer disease); (3) patients intolerant to NSAID therapy; and (4) patients who have failed to respond adequately to NSAIDs and/or corticosteroids. The clinical efficacy of viscosupplementation, in patients with knee OA, has been documented in several randomised, controlled, prospective trials[3-8]. The duration of benefit of intra-articular hyaluronans ranges from months to years.

The management of hip OA is similar to that for the knee though the use of the intra-articular therapies is more difficult. If the problems with administration could be lessened then the intra-articular steroids and viscosupplementation could provide an additional weapon for the therapeutic management of hip disorders. The intra-articular injection of the hip is not as easy as for the knee, mainly due to anatomical features of the joint and the proximity of "sensitive" structures such as the femoral artery and nerves. Even though intra-articular hip injection may be performed "blindly", failure rate is significant. Leopold et al[9] injected fifteen human cadavers (30 hips) and found that neither the anterior nor the lateral injection approach, using published techniques based on anatomic landmarks, were sufficiently reliable to recommend for clinical use without radiographic or sonographic guidance. The anterior approach was successful in only 60% of injections, while the lateral technique was successful in 80% of injections. Moreover, when a slowly-acting viscosupplement is used, the potential local complications may jeopardize the therapeutic benefit[10]. For such reasons, it has been suggested that intra-articular injection of the hip might be performed with an imaging guidance (fluoroscopy, tomography, magnetic resonance imaging or sonography). Fluoroscopic guidance is preferred by some clinicians for hip aspiration and injection, but this technique implies the use of iodine contrast and radiation exposure for patients and physicians as well. Over the last few years, the rapid technological advances in ultrasonography have greatly increased the potential applications of sonographically-guided procedures[11]. Sonographically-guided intralesional injection is used as a rapid and reliable procedure, especially in patients with arthritis, tenosynovitis, and bursitis. After target localization, needle placement can be performed under continuous sonographic monitoring. Sonographic guidance is particularly useful when the lesion is adjacent to anatomic structures that could be seriously damaged by a blind injection[12].

Ultrasound guidance in hip injection represents a safe, inexpensive and radiation-free tool that allows identification and avoidance of vascular and nervous structures and reliable, real-time injection into the articular space[13]. This is important as injection into the joint space is necessary for efficacy and helps reduce the appearance of local reactions.

We have standardized a technique for intra-articular injection of the hip using ultrasound guidance[14-17] with the purpose of extending the use of intra-articular therapies from the knee to the hip. For such reason we also founded the ANTIAGE non lucrative association (National Association for Intra-Articular Therapy of Hip Joint, www.antiagefbf.it), that is made up of physicians specialized in different medical fields such as Internal Medicine, Radiology, Rheumatology, Physical Medicine, Sports Medicine, interested in treating the various hip diseases with ultrasound-guided intra-articular injections. All specialists adhered to set up a national Italian registry of all the ultrasound-guided intra-articular injections performed in accordance with the standardized technique. In this registry are recorded the patients distinguishing characteristics, their different hip diseases, the drugs used, the side effects, the assessment of the treatment effectiveness, the treatment courses and the total number of injections. Objective of this study was to assess safety profile for intra-articular ultrasound-guided hip injection with hyaluronic acid products performed in 9 different rheumatology or orthopaedic centers who administered such therapy following our standardized technique. We report the safety data from four years of activity.

Patients and Methods

Ultrasound guided injection technique: all patients were examined supine with the hip in internal-rotation of 15-20°. A 7 MHz linear or 3.5 MHz convex transducer (ASTRO 256, Hitachi-Esaote, Genoa, Italy) was used together with a sterile bioptical target device. The hip joint was scanned by means of an anterior parasagittal approach, lateral to the femoral vessels. The transducer was aligned with the long axis of the femoral neck, comprising also the acetabulum and the femoral head. Intra-articular (IA) injection was performed by inserting into the biopsy guide a 20 gauge (9 cm) spinal needle with the anterosuperior approach. Then, using biopsy real-time guidance

software, the needle was advanced into the anterior capsular recess, at the level of the femoral head. Once the needle came into contact with the femoral head, the needle was retracted 1mm. Then the treatment was injected into the hip joint and verification of intra-articular placement was evident with the real-time monitoring (direct visualization of viscous fluid or air bubbles) also utilising power Doppler imaging (flow signals in intra-articular recess). The colour Doppler vision allowed us to avoid injecting blood vessels.

Patients Selection

This is a multicentric retrospective study regarding the safety of US-guided Intra-articular injection of hyaluronic acid in hip joint in patients affected by hip osteoarthritis.

Inclusion Criteria

Patients attending to our Ambulatory for hip pain in the years going from 2005 to 2008 that had mono or bilateral symptomatic hip OA according to ARA criteria[18], refractory to therapy, with radiological OA graded II-IV (Kellgren and Lawrence)[19] assessed within the two preceding months. Exclusion criteria included use of anticoagulant therapy (to avoid the possibility of intra-articular or pericapsular haemorrhages). Usually, the absence of articular space at radiological examination represents an exclusion criteria for patients candidates for intra-articular hip injection, as surgical interventions are best suited for such patients. Although a recent review of 80 patients with symptomatic knee OA treated with hyaluronic acid revealed that patients with a complete collapse of joint space or bone loss showed a poor clinical response[20], the absence of articular space at radiological or ultrasound assessment was not considered as an exclusion criteria for the analysis when patients were unable to undergo to surgical intervention or hip arthroplasty. Even if it is not a grade with primary indication to viscosupplementation, in some cases intra-articular treatment may support a temporary, even if small, symptoms' relief. In this cases, ultrasound-guided hip injection was performed as a second line option with the aim of possibly reducing pain and NSAIDs consumption. For such reason, safety data reported in this study include data from IV Kellgren-Lawrence IV grade patients as well. Injections were given according to symptoms and clinical judgment; namely one or two injections every six months according to patients' clinical condition. One 2 ml ampule was used with high molecular weight HA, e.g. Synvisc and Euflexxa; two 2 ml ampule with low or medium molecular weight HA, e.g. Hyalgan, Hyalubrix, Jointex, and Ortoial.

Safety was evaluated by recording adverse events reported during the follow-up period. All patients were evaluated at baseline and at each control visit, performed every 3 months. All patients also received a phone call every 3 months from nurses attending to Rheumatology Units where the study was performed, in order to program next step (control visit or hip injection) and also to screen drop-out from programmed therapy and eventual motivations for dropping out. All patients who decided to withdraw from programmed therapy were interviewed and eventual adverse events (AE) were recorded.

All adverse events/effects were studied and collected in subgroups related to: HA used, radiological grading of osteoarthritis according to Kellegren-Lawrence classification, patients' age, algofunctional Lequesne[21] score at the basal evaluation arranged by low, medium and high grade. A rank testing was performed between different rates of adverse events or side effects occurrence and patient's mentioned subgroups.

Adverse events were recorded by a direct interview of patients that was performed when patients were visited at each control visit. Patients were intensively studied for eventual side effects such as pain or other side effects such as hip joint or other joints swelling, fatigue, fever, dermatological or respiratory affections that may be related to HA injection.

Statistical Analysis

In order to describe patients evaluated in this study, descriptive statistics were reported as appropriate. Mean, range and numerousness were reported for continuous variables, count and proportions were reported for discrete variables. Rates of AEs in different subpopulations were analyzed by a chi-square test. Significant independent variables were selected among some presumed predictive indices using a backward stepwise method. $p < 0.05$ was considered statistically significant.

Results

1906 patients received 4002 injections.Patients' demographics are shown in Table I.

Different hyaluronic acid products and their characteristics are shown in Table II.

Table I. Features of different hyaluronic acid products.

Parameter	Summary statistic	All patients
Number of patients	N	1.906
Gender		
Male	N (%)	1.011 (53)
Female	N (%)	895 (47)
Age	Mean (SD)	63.4 (11.4)
Weight (kg)	Mean (SD)	74.6 (13.5)
Height (cm)	Mean (SD)	167 (9)
Body mass index (kg/m^2)	Mean (SD)	26.5 (3.8)
OA location		
Right hip	%	40.5
Left hip	%	38.2
Bilateral	%	21.3
OA disease severity		
Grade II	(%)	801 (42)
Grade III	(%)	878 (46)
Grade IV	(%)	227 (12)
Ultrasound pattern		
Regular	%	35.4
Irregular	%	64.6

Table III shows the number of patients and the number of injections with each HA product.

Figure 1 summarizes the number of patients per different injections numbers.

No systemic side effects or joint infections were observed in our study. A transient sensation of local heaviness and pain was reported. Generally these reactions lasted from 1 to 4 days. By 63% of patients lasting from few hours to one day, by 17% from one to four days and by 20% from four to ten days. No differences were observed when comparing different rates of side effects in populations receiving different hyaluronic acid products, thus suggesting that, in terms of safety, different products may have similar safety profiles in the selected patients. Rates of painful events arranged by Kellgren-Lawrence radiological score were higher in the 1° and 4° degree as shown in table 4 but no statistical significance was obtained when comparing rates from different groups categorized for Kellgren-Lawrence radiological score. Table V shows that the higher rate of painful events arranged by age was noticed by patients in their fifties (5.17%), while the lower by patients in their seventies (1.33%), but still no significative differences were observed.

Table VI shows that the lower rate of painful events arranged by Lequesne score was displayed in the higher degree of the score, but still no significative differences were observed.

A modest ecchymosis at the site of injection was reported by 6.3% of the injections (264 events)

In all cases direct visualization of needle introduction and progression into the articular space was by on-screen guidance. The visualization of the products injected varied depending on their density and molecular weight. Higher molecular weight products, like Synvisc or Euflexxa, displayed a characteristic ultrasound pattern showing a little hyperechogenic cloud inside the joint whereas lower molecular weigth HA, like Hyalgan, were detected only indirectly through the

Table II. Features of different hyaluronic acid products.

Trade name	Molecular weight	Source	mg/ml
Hyalgan	500-730 KDa	HA extracted from rooster combs	20 mg/2 ml
Hyalubrix	> 1500 KDa	HA produced by fermentation from bacteria	30 mg/2 ml
Jointex	800-1200 KDa	HA produced by fermentation from bacteria	16 mg/2 ml
Synvisc	6000 KDa	HA extracted from rooster combs	16 mg/2 ml
Euflexxa	2.4-3.6 million Da	HA produced by fermentation from bacteria	20 mg/2 ml
Intragel	1 million Da	HA produced by fermentation from bacteria	16 mg/2 ml

Table III. Injections number for each hyaluronic acid product and related painful events (%).

Trade name	Number of patients	Number of injections	Patients with painful events (%)	Injections with painful events (%)	Number of painful events
Hyalgan	168	314	4.1	2.22	7
Hyalubrix	377	862	6.8	3.01	26
Jointex	224	407	4.9	2.7	11
Synvisc	950	2146	8.8	3.58	77
Ortoial	127	205	4.7	2.92	6
Euflexxa	60	68	3.3	2.94	2
Total	1906	4002	7.5	3.2	129

amplification of the articular space. The time taken to complete the procedure varied between 7 and 10 minutes.

None of the reactions caused loss of daily activity or required treatment.

After treatment, four patients (< 0.1%, 1 receiving Synvisc, 1 receiving Euflexxa, 1 receiving Hyalubrix and 1 receiving Jointex) showed a rapid symptomatic worsening with local pain intensification. Pain didn't show any more mechanical characteristics and became continuous, during day and night, and lasted for over 10 days. Due to persisting symptoms, all patients underwent to a magnetic resonance imaging (MRI) of the symptomatic hip, and in each of these patient MRI demonstrated femur head bone oedema. After treatment with intra-muscular Clodronate all patients reported slow but continuous remission of symptoms until complete resolution in two months with *restitutio ad integrum*. It was impossible for us to identify predictor factors such as age, gender or radiological grade or used product that could lead to such event.

Discussion

Published data on viscosupplementation in the OA hip is limited[13]. Recent clinical evidence has shown that intra-articular injection with hyaluronians may be a safe and effective treatment to improve functionality and to reduce pain in patients with hip OA[13].

Our technique uses an anterosuperior access while that of Qvistgaard et al[12] uses an anteroinferior approach. The latter is commonly used for the arthrocentesis. The needle position in the lower part of the joint allows better drainage of the effusion. However, we believe that the anterosuperior approach is better due to positioning the medical

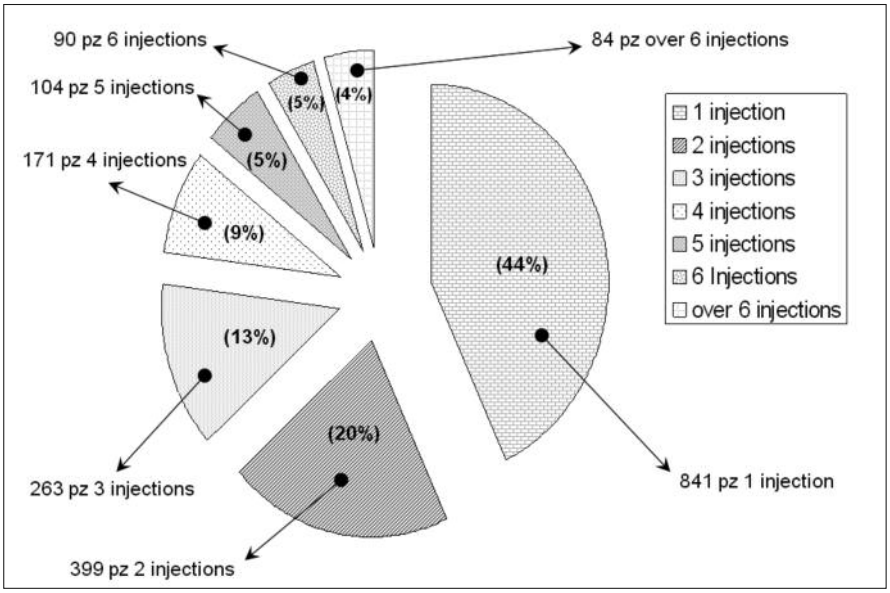

Figure 1. Number of patients and the number of injections with each HA product.

Table IV. Rates of painful events arranged by Kellgren-Lawrence radiological score. Statistical significance was evaluated by ANOVA testing between each group and every other group.

KL radiological scale	Patients number	Injections number	% rate per patients number	% rate per injections number	Cases number	Statistical significance
1°	127	255	11.11	6.84	17	NS
2°	695	1209	8.81	5.48	66	NS
3°	733	1166	4.5	2.89	34	NS
4°	349	425	11.11	8.16	35	NS
Total	**1906**	**4002**		3.61	152	

Table V. Rates of painful events arranged by age groups. Statistical significance was evaluated by ANOVA testing between each group and every other group.

Basal lequesne score	Patients number	Injections number	% rate per patients number	% rate per injections number	Cases number	Statistical significance
Under 40	51	91	8.33	4.91	4	NS
40-49	159	209	6.73	3.27	7	NS
50-59	349	840	10	5.17	43	NS
60-69	455	1016	6.05	2.67	27	NS
70-79	571	1242	2.4	1.33	17	NS
over 80	316	604	2	0.80	5	NS
Total	**1906**	**4002**		2.45	103	

Table VI. Rates of painful events arranged by low, medium and high Lequesne score. Statistical significance was evaluated by ANOVA testing between each group and every other group.

Basal lequesne score	Patients number	Injections number	Patients % rate	Injections % rate	Cases number	Statistical significance
Low (0-5)	791	1557	8.43	3.18	50	NS
Medium (6-10)	498	957	8.25	3.61	35	NS
High (11+)	617	1488	3.56	2	30	NS
Total	**1906**	**4002**		2.73	**115**	

product just above the femoral head which exploits gravity to involve the articular cartilage of the femoral head and acetabulum. With an inferior injection approach the medical product is placed at the base of the femoral head on the femoral neck. We used a bioptic device attached to the probe for simpler, faster and more accurate needle positioning compared with the free-hand US guidance. Specific bioptic guidance software allowed real time monitoring of needle introduction and intra-articular placement producing a good visualization of the needle during the procedure and reducing the time of injection and patients'discomfort as well.

The side effects seen after hip injection are similar to those found in patients treated with knee injections[22,23].

Our four years experience of intra-articular ultrasound-guided treatment of the hip suggests that it can be as safe and reliable as that used for knee diseases, that is commonly performed without image-guidance. The safety data confirm good systemic tolerance, as already documented with knee injection. Differently from fluoroscopic guidance, ultrasound-guidance allows the detection of arteries and veins via colour-Doppler signal and also allows the detection of nerves, granting a more safe needle introduction. Aim of this investigation was to assess safety for image-guidance performed by ultrasound and these data seem to confirm the relevance of ultrasound guidance to recognize and consequently avoid sensitive structures such as vessels and nerves. The most severe adverse event in our cases was Bone Marrow Edema Syndrome (BMES) that was reported in 4 patients, for an evaluated prevalence of 0.1% in our population. BMES

refers to a transient clinical condition with unknown pathogenic mechanisms. Many hypotheses have been previously proposed in order to explain the pathogenesis of the disease. Unfortunately, at now, the etiology of BMES remains obscure[24]. A reflex sympathetic mechanism could be the primary mechanism leading to BMES but further studies are needed to confirm such hypothesis.

The local tolerance was also good, with mild side effects following 2.2% of Hyalgan injections and 3.5% with Synvisc. In the latter the increased percentage of painful events may be due to the higher molecular weight of this product.

Related to Kellgren-Lawrence radiological score the higher number of painful events by patients with 1° and 4° degree may be due to the lack of symptoms in the first group and to the oversensibility of the patients in the second one.

A reduced susceptibility to pain may cause the smaller frequency of painful events in the older population and in the more severe Lequesne score as well.

Patients' daily activities were unaffected by these events. No septic complications were observed. No increased effect of repeated injections or cycles of injections was detected.

The aforementioned data are similar to those already reported in our previous papers[14-17].

No increased effect of repeated injections or cycles of injections was detected.

The injection of 4 ml (2 ampoules at the same time) is well tolerated as 2 ml (1 ampoule). That means the reduction in the number of injections performed and consequently in the occurrence of possible side effects, in the medical expenses and in a sparing of time for the patients and the doctors as well. The results confirm the safety and the precision of the technique. Direct evidence of the needle placement and direct or indirect evidence of the therapeutic fluid inside the joint are very important goals. Ultrasound guidance is more economic and faster in comparison to the computed tomography (CT) or fluoroscopic guidance. Contrary to CT or fluoroscopic techniques ultrasound does not require use of contrast, allowing use in patients intolerant to iodized contrasts. It can be repeated without problems of radiation load to either the operator or the patient.

Moreover, the European Community "Directive 97/43/Euratom" lays down the general principles for protection of individuals in relation to the exposure of patients to radiation as part of their medical diagnosis or treatment. It requires a sufficient net benefit, weighing the total potential therapeutic benefits against the individual detriment that the exposure might cause, taking into account the efficacy, benefits and risks of available alternative techniques having the same objective but involving no or less exposure to ionizing radiation. Existing types of practices involving medical exposure may be reviewed whenever new, important evidence about their efficacy or consequences is acquired. If exposure cannot be justified, it should be prohibited.

Conclusions

We believe that, even if fluoroscopy or CT guidance can, on occasion, be justified, nevertheless for general and repetitive use physicians should use the ultrasound technique that eliminates use of radiation and is cost-saving. The technique has proved well tolerated, despite the advanced age of the patients and the high clinical and radiological degree of disease in some cases. The horizon of loco-regional therapy in rheumatic hip disease appears to be extremely promising. The ultrasound guided hip injection technique can allow to extend to the hip what is commonplace for the knee joint in OA and other rheumatic diseases.

This is not a placebo controlled study and is based upon data on the safety profiles obtained from cohorts of patients undergoing to different hyaluronans injections into hip joint performed with a standardized technique in different Italian centres. Moreover, patients assumed different kinds of pain killers and/or NSAIDs, and at different dosages: for such reason, mild to moderate pain adverse events may have been altered in their perception depending on the type and dosage of pain killer taken.

Conflict of Interest

None declared.

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