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EFFICACY AND SAFETY PROFILE OF INTRA-ARTICULAR ADMINISTRATION OF JOINTEX® IN PATIENTS SUFFERING FROM SYMPTOMATIC HIP OSTEOARTHRITIS: AN OPEN, PROSPECTIVE STUDY WITH A 12-MONTH FOLLOW-UP

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Hip osteoarthritis represents a statistically relevant problem in clinical practice; previous reports showed different efficacy and safety profiles for intra-articular use of hyaluronic acid in hip osteoarthritis-affected patients, and in this sense, to add evidence to this topic, data regarding safety and efficacy of ultrasound-guided viscosupplementation are reported in order to establish whether such a therapeutic tool may represent a valid option. This study investigates the safety and efficacy profiles of ultrasound-guided intra-articular injections of Jointex® in hip osteoarthritis affected patients. This is a prospective multicentric study carried out in public hospitals. Adult outpatients suffering from symptomatic hip OA (Kellgren and Lawrence Grade 2, 3 or 4) were injected with one syringe of 4 ml (2 vials) of Jointex® under ultrasound guidance, repeated after six months; when clinically necessary an adjunctive injection was performed. Patients' characteristics, such as gender, age, weight, height and BMI, smoking habit, unilateral or bilateral hip OA, radiological grade for hip OA following Kellgren-Lawrence grading and duration of disease, were evaluated. Patients were assessed at baseline and at every control visit and injection time for Lequesne index as primary endpoint, pain (evaluated by VAS) and NSAID consumption (number of days patients assumed NSAID in the last month) both as secondary endpoint. A total of 180 patients entered the study, all of whom received at least one IA US-guided injection of Jointex® into the hip joint. A total of 36 drop outs were registered, and both distribution and causes of drop out were recorded. A total of 389 injections were carried out, as 18 patients were affected by bilateral hip OA and 7 patients affected by monolateral hip OA required one more injection for symptomatic relief in respect to other patients. Scores obtained for primary as well as secondary study endpoints reached statistical significance when compared with scores obtained at baseline visit. Lequesne index mean scores obtained at each control visit, when compared with baseline mean value, were significantly different ($p<0.001$ for all control visits *vs* baseline). Similarly, results obtained for secondary endpoints, such as Pain VAS and NSAID consumption, when compared with results obtained at the baseline visit, showed a statistical significance ($p<0.001$ for all control visits *vs* baseline). We also evaluated how many patients reached an improvement in Lequesne algo-functional index of at least 70% at 6- and 12-month control visits: a percentage of 21.23% of patients attending the 6-month control visit showed such improvement, while at the 12-month control the percentage was 20%. No local or systemic infectious adverse events were reported during the

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DISCLOSURE: ALL AUTHORS REPORT NO CONFLICTS OF INTEREST RELEVANT TO THIS ARTICLE.

whole follow-up time. Twenty-seven patients out of 180 reported a transient discomfort in the treated hip for 1-3 days after injection that regressed spontaneously or with paracetamol 1 g two or three times a day. No systemic adverse events were observed. Intra-articular administration of Jointex® in hip OA-affected patients seems to be an efficacious and safe therapeutic option.

Osteoarthritis (OA) is one of the the most prevalent chronic joint disorders worldwide and may cause significant pain and disability (1). Intra-articular hyaluronan therapy has been used to relieve symptoms associated with OA of the knee with a very favorable safety profile (2). Many reviews suggest that viscosupplementation (VS) is an effective treatment for OA of the knee with beneficial effects: on pain, function and patient global assessment (3-8). Viscosupplements are comparable in efficacy to systemic forms of active intervention, with more local reactions but fewer systemic adverse events. In other analyses HA products seem to have more prolonged effects than IA corticosteroids. Little datum exists in literature on the viscosupplementation of hip OA in spite of it being common site of the disease after the knee (9-15). One of the limiting factors for this practice is related to the need of guidance for the injection procedure. Hand-free knee injection is safe and effective; on the contrary, even though hip injection may be performed "blindly", the failure rate is nevertheless significant, and when using viscosupplement, the potential placement just outside the joint may make the therapeutic benefit useless. For such reasons, it has been suggested to perform intra-articular injection of the hip under radiological or ultrasound control. Although several ultrasound guidance techniques were available (16-18), we developed a personal one using an antero-superior approach (12-15). We had reported several observational trials to assess viscosupplementation for the treatment of hip OA with a progressive number of patients and longer follow-up using different HA products. Lastly, a double-blind randomized controlled trial regarding the use of Hyalubrix against local anesthetic in hip OA was carried out, showing a statistically significant difference on improvement of Leqeusne index in the HA treated group (19). Other authors reported data showing that intra-articular (IA) injection of hyaluronic products are safe and effective for the treatment of hip osteoarthritis, but the available casuistry is still limited and often related to a short follow-up (19-22). Among viscosupplements, Jointex® is a CE-marked medication, a sterile viscoelastic solution of sodium hyaluronate for injection into the joint cavity available in European countries. This hyaluronate contains a highly purified sodium hyaluronate 800-1.200 KD, (8 mg/ml) produced by fermentation from bacteria in Switzerland. Neither the fermentation nor the purification process involves animal proteins. It is registered as a medication in Italy, Poland, Czech Republic and Slovakia with indication for all painful joints due to osteoarthritic or traumatic processes. In order to increase the burden of clinical data on the use of HA in hip OA we carried out this observational study, the aim of which is to assess the safety and efficacy of administering Jointex® (Chiesi SpA 800-1.200 KD, 8 mg/ml) to painful hip OA in a large cohort of patients for a 12-month follow-up.

MATERIALS AND METHODS

Study design

The present cohort study was open, multicentric and prospective; patients referring to our Rheumatology Units from 2007 to 2009 were considered possibly eligible for the study. All patients were required to sign a written informed consent before starting treatment. Patients were considered eligible for the study if: male and female of an age of at least 40 years, affected by symptomatic hip OA according to ARA criteria (23) with radiographic grade II and III according to Kellgren and Lawrence (KL) (24). Data regarding KL grading were accepted only if deduced from radiographs taken within two months before patient enrollment. Patients showing a IV KL grade were included in the study only if total hip replacement or arthroplasty represented unfeasible options due to comorbodities. In such patients intra-articular ultrasound-guided injection of the hip was performed with the aim of reducing pain and reducing NSAID and pain killer consumption. The patients had to have duration of hip OA for at least 1 year and no previous intra-articular injection.

Patients were not included in the study if: undergoing a concomitant anti-coagulant therapy, in order to avoid

hemorrhagic complications due to injection, patients with KL grading IV, except for patients who were unable to undergo surgical replacement of hip joint (patients KL IV grade that resulted not admissible to total hip replacement were eventually included in the study if other inclusion and exclusion criteria were met), concomitant steroid therapy, significant rheumatologic associated disease (e.g. connective tissue diseases), any previous history of hyaluronan therapy.

All outpatients referring to our clinics complaining of hip OA were studied and if inclusion criteria were met the patients were included in the study after giving informed consent.

Each patient was treated with one injection of 4 ml of Jointex® at baseline and then every six months. One or two additional injections were carried out at the 3rd and/or 9th month if clinically necessary in order to further reduce pain/disability only in patients who did not show a reduction in pain VAS and/or Lequesne index lasting until the 3rd month after the previous injection. Each patient underwent a control visit performed 3 months after the first injection and was newly injected at 6 months. At 9 months and at 12 months new control visits were performed.

During each visit, the patient was evaluated using:

1) Lequesne index (25);

2) measure of individual hip OA pain in the previous week on a 100 mm visual analogue scale (pain VAS);

3) a NSAID consumption score: Consumption of NSAIDs was measured as the number of days a month the patient had used NSAIDs during the previous month.

During the whole study period, adverse events were monitored by registering those reported by the patient at each clinical control. All Adverse Events (AEs) were recorded and categorized as local or systemic, transient or persistent, and mild, moderate or severe in terms of induced invalidity. The primary endpoint of this study was the evaluation of Lequesne index in patients affected by hip osteoarthritis undergoing intra-articular ultrasound-guided injection of Jointex® and a 12 month follow-up. Secondary endpoints were recording NSAID consumption and Pain VAS for all patients included in the study.

Injection technique

Patients underwent hip injection under control of ultrasound as described previously (13). Briefly, the patient was examined supine with the hip in internal-rotation of 15-20°. A 3.5 MHz convex transducer (Star 256, Hitachi-Esaote, Genoa, Italy) was used with a sterile biopsy guide attached. 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, including the acetabolum and the femoral head.

Intra-articular (IA) injection was performed by inserting a 20-gauge (11 cm) spinal needle through the biopsy guide, using an anterosuperior approach. Then, with a 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 by 1 mm. The hyaluronan preparation was then injected into the hip joint and verification of intra-articular placement was evident with real-time monitoring (direct visualization of viscous fluid) also utilizing power doppler imaging (flow signals in intra-articular recess). The colour Doppler vision allowed us to avoid injecting blood vessels.

Statistics

For both Lequesne index and Pain VAS, the analysis of variance for repeated measures was performed. To compare values at months 3, 6, 9 and 12 *vs* baseline values, we performed *t*-tests of within-subject contrasts.

Relatively to NSAID consumption, the non-parametric Wilcoxon test for related samples was performed to evaluate the significance of the variation that occurred between baseline and each visit after the first injection and the significance of the variation that occurred during the treatment period (12 months). The Bonferroni correction for multiple comparisons was used.

RESULTS

Patient population

A total of 180 patients were enrolled the study. All of them received at least one IA US-guided injection of Jointex® into the hip joint. The patients' characteristics, such as gender, age, weight, height and BMI, smoking habit, unilateral or bilateral hip OA, radiological grade for hip OA following Kellgren-Lawrence grading and duration of disease, are shown in Table I. The numbers of patients reaching 3, 6, 9 and 12 months control visits are shown in Table II.

A total of 36 drop outs were registered, and both distribution and causes of drop out are reported in Table II. A total of 389 injections was performed, as 18 patients were affected by bilateral hip OA, and 7 patients affected by monolateral hip OA required one extra injection to obtain a satisfying symptomatic relief. Scores obtained for primary as well as secondary study endpoints reached statistical significance when compared with scores obtained at

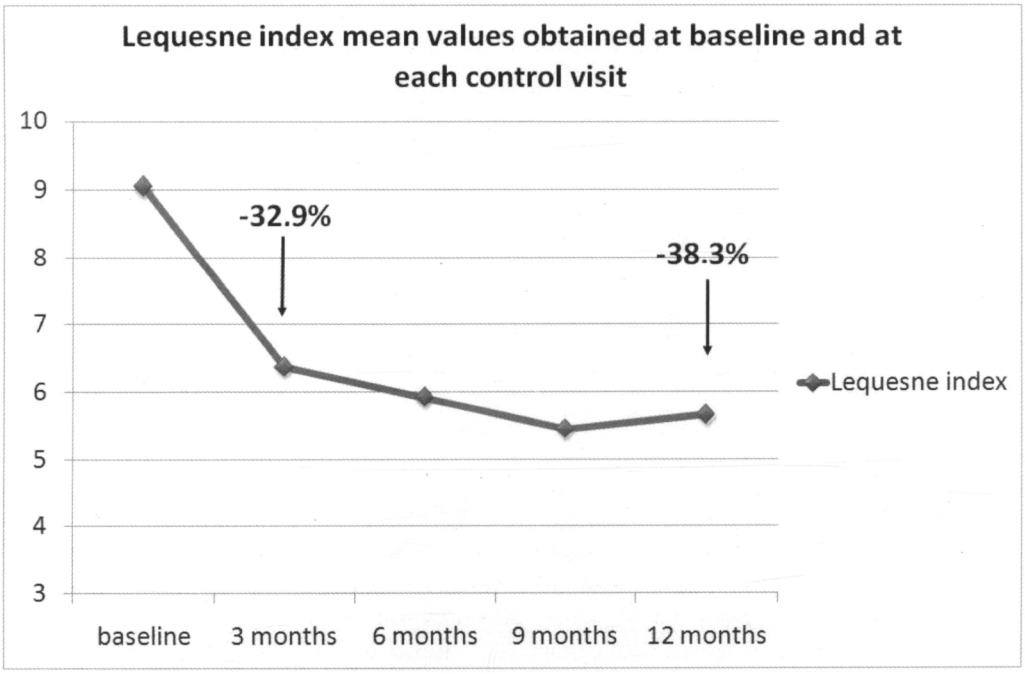

Fig. 1. *Lequesne index mean values obtained at each control visit. P<0.001 when compared with baseline for each value obtained at control visit. Entity of reduction in respect to baseline value in Lequesne index mean scores are also reported for 3-month control visit and 12-month control visit. Such reduction was persistent for all study duration.*

baseline visit, as shown in Table III.

Efficacy Data

Primary endpoint

Scores obtained for primary study endpoint reached statistical significance when compared with scores obtained at baseline visit. In facts Lequesne index mean scores obtained at each control visit (6.08±0.87, 5.59±1.0, 5.46±0.94, 5.59±1.0 respectively at 3, 6, 9 and 12 months), when compared with baseline mean value (9.05±1.78), were significantly different ($p<0.001$) (Fig. 1). Mean Lequesne value decreased 32.9% and 38.3% respectively at 3 and 12 month when compared to baseline. We also evaluated how many patients reached an improvement in Lequesne algo-funcional index of at least 70% at the 6 and 12 month control visits: 21.23% of the patients attending the 6-month control visit showed such improvement and at the 12-month control visit the percentage was 20% for patients not lost to follow-up (Fig. 2).

Secondary endpoint

Scores obtained for secondary endpoints reached statistical significance ($p<0.001$) at each time point when compared with scores obtained at the baseline visit. Results obtained for Pain VAS and NSAID consumption, when compared with results obtained at the baseline visit, showed a statistical significance ($p<0.001$) (Fig. 2, Table III). Namely, mean Pain score decreased by 30.2% and 37.9% respectively at 3 and 12 months when compared to baseline; the average days/month consuming NSAIDs decreased 42.3% and 63.8%, respectively, at 6 and 12 months compared to baseline.

Safety data

No systemic adverse events were observed. No local infectious adverse events were reported during the whole follow-up time. Twenty-seven patients out of 180 (15%) reported a transient mild discomfort in the treated hip for 1-3 days after injection that regressed spontaneously or with paracetamol 1 g two or three times a day.

DISCUSSION

In the last 15 years rigorous clinical studies

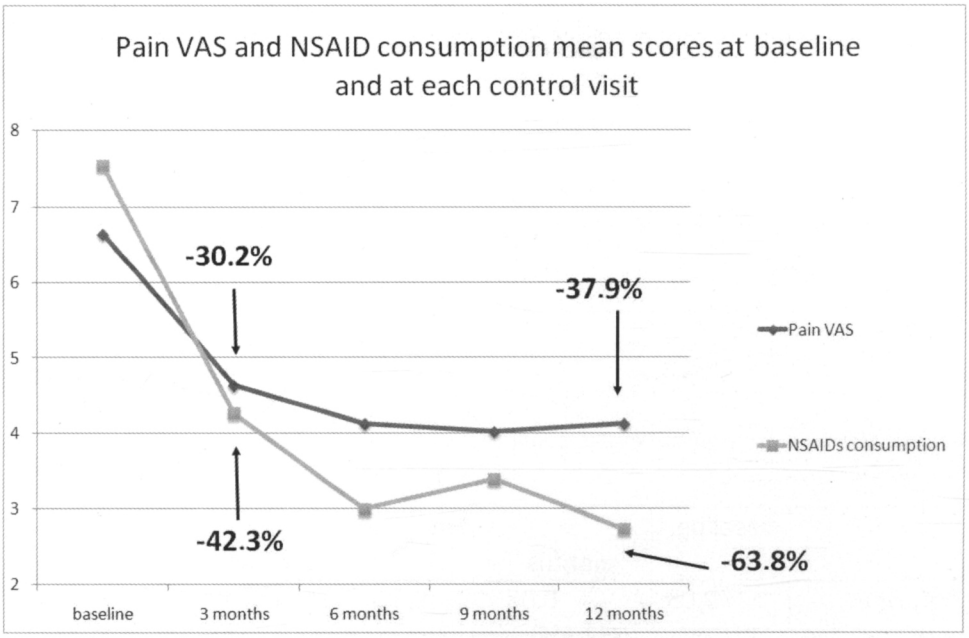

Fig. 2. *Pain VAS and NSAID consumption mean scores obtained at baseline visit and at each control visit. P<0.001 when compared with baseline for each value obtained at control visit for both parameters. Entity of reduction in respect to baseline value in Pain VAS and NSAID consumption are also reported for 3-month control visit and 12-month control visit. Such reduction was persistent for all study duration.*

Table I. *Patients' characteristics.*

Males	n.97
Females	n.83
Smokers	n.53
Mean age ±SD	69±9.2 years
Age range	38-82 years
Mean Height ±SD	170±8.1 cm
Mean BMI ±SD	25.7±3.2
HIP OA, *n* (%)	
Unilateral right	n.97 (53.88%)
Unilateral left	n.65 (36.12%)
Bilateral	n.18 (10%)
DURATION OF OA (years)	
Mean ± SD	3.89±2.93 years
Min. – Max	1 – 20 years
RADIOLOGICAL GRADE*, *n* (%)	
2	n.18 (10%)
3	n.127 (70.56%)
4	n.35 (19.44%)

have demonstrated the safety and efficacy of intra-articular injections of several kinds of hyaluronan in knee OA. Recently, even though little evidence seems to show similar effects of hyaluronans on hip OA, some kinds of HA products are used (12-15, 19-22). In this study 4 ml of another product of HA, a highly purified sodium hyaluronate, 800-1.200 KD, seemed to be effective in the relief of hip OA symptoms. The present study demonstrates the safety and efficacy of Jointex® for the treatment of hip OA injected under ultrasound-controlled procedure (13). The data from this cohort study are similar to our previous studies (12-15), giving additional evidence that viscosupplementation may be useful in treating hip OA.

The patients enrolled in this cohort study showed a clinically significant reduction of Lequesne index and VAS pain scores. Such improvement was achieved at 3 months, afer the first injection, and characterized by an improvement in Lequesne index of 35% which was maintained for 12 months

Table II. *Number of patients enrolled in the study and reaching control visits, number of drop outs, causes of drop out and distribution along the study.*

baseline visit	3 months	6 months	9 months	12 months
180	172	166	154	144
Drop out	8	14	26	36
Deceased	0	0	0	0
Irreperible	8	13	23	33
Surgical joint replacement	0	1	3	3

Table III. *Mean values for primary study endpoint, Lequesne algo-functional index, and secondary endpoints, Pain VAS and NSAIDs consumption.*

	baseline	3 months	6 months	9 months	12 months
Lequesne index	9.05	6.08 **(-32.9%)**	5.59	5.46	5.59 **(-38.3%)**
Pain VAS	6.64	**4.64 (-30.2%)**	4.13	4.03	4.13 **(-37.9%)**
NSAIDs consumption	7.53	4.27 **(-42.3%)**	3	3.4	2.73 **(-63.8%)**

$P<0.001$ when comparing each mean value at each control visit with baseline mean value for all endpoints.

by repeating 1 injection of 4 ml of Jointex® at least every six months. This may suggest that this treatment may reduce inflammatory or painful relapses that are typical in the course of hip OA. On the contrary, a relevant improvement of 70% was achieved at 3 months and maintained at 12 months only in 20% of treated patients. It suggests that hip VS with Jointex® cannot be effective by itself, and it may have to be associated to usual non-pharmacological and pharamcological treatments in the management of hip OA. Nevertheless, this study also shows a significant reduction of NSAID consumption which is an index of achieving clinical benefit, but it may also imply broader considerations about cost/benefit of such treatments. In this study patients who had received VS treatment benefited from a 63% reduction in NSAID intake at 12 months; it is known that side effects are directly correlated to the amount of NSAID intake (26-28). The limitation of the present study is the inability to exclude the placebo effect of this injection as there is no comparative arm involved. It is known from experience with knee OA that the placebo effect of VS tends to be substantial (29). Also in this study we can confirm safety, good local tolerability and the absence of any serious or systemic effect of the use of HA in hip OA. This was also due to the safe and effective technique by ultrasound guidance used for the intra-articular injection. Moreover, the ultrasound guidance of IA injection can make this treatment simple, repeatable and relatively cheap. This contributes to a good adherence - at 12 months more than 50% of patients are still undergoing such therapy.

This study supports the substantial aggregate of clinical literature suggesting that hip viscosupplementation is clinically safe and may be effective for pain relief and function improvement. However, the uncertain burden of placebo effect and lack of RCT with Jointex® may reduce the strength

of this evidence. Taking into consideration the above-mentioned limitations our data need substantiation from larger, prospective, placebo-controlled, double blind trials. Further studies are also warranted to address the definition of a responder population and to establish possible disease-modifying aspects and the long-term effects of IA admnistration of Jointex® in hip OA.

The data from our cohort study seem to demonstrate the long-term efficacy and safety of intra-articular ultrasound guided treatment with Jointex® in symptomatic hip osteoarthritis. They do, however, need to be confirmed by RCT to show how Jointex® could be more effective than placebo or IA steroids. VS could be suitable as a complementary tool in hip OA treatment given the efficacy and the possible reduction of NSAID and their consequences.

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