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INTRA-ARTICULAR ULTRASOUND-GUIDED INJECTION OF SINOVIAL® FORTE 1.6% IN PATIENTS AFFECTED BY SYMPTOMATIC HIP OSTEOARTHRITIS: EFFECTIVENESS AND SAFETY IN A LARGE COHORT OF PATIENTS

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The aim of this prospective observational study is to assess the efficacy and safety profile of intra-articular Sinovial® Forte 1.6% administered under ultrasound-guidance in a large cohort of patients affected by symptomatic hip osteoarthritis (OA). Patients with symptomatic hip OA referred to our clinic in 2008-2010 received one 4 ml (2 vials) intra-articular injection of Sinovial® Forte 1.6% under ultrasound guidance. Patients were followed-up every 3 months for a total of 6 months and were offered an optional, additional injection at the 3-month follow-up visit if clinically justified. At each visit, pain scores [0-10 Visual Analogue Scale (pain VAS)], Lequesne index scores and NSAID intake were recorded. Adverse events (AEs) were recorded throughout the study. An effect size of 30% and 50% reduction in Lequesne index and Pain VAS scores was evaluated for each patient to ascertain the number of patients achieving partial remission of symptoms and functional impairment by the use of intra-articular hyaluronic acid in hip osteoarthritis. One hundred and fourteen patients completed the 6-month follow-up and received a total of 142 injections. A statistically significant reduction in Lequesne index scores, VAS pain scores and NSAID consumption was observed at all time-points ($p < 0.05$). No systemic, severe or even moderate side effects were observed. Only 7 patients reported mild local reaction at the injection site, consisting of mild pain and localized warmth, which resolved spontaneously without any additional medication. This study provides evidence of the efficacy and tolerability of Sinovial® Forte 1.6% in the treatment of patients affected by symptomatic hip OA. Sinovial® Forte may also offer economical benefits, owing to the reduction in NSAID consumption associated with this treatment. The percentage of patients achieving the effect size of 30% and 50% reduction in Lequesne index and pain VAS scores encourages the use of intra-articular hyaluronic acid in patients with hip osteoarthritis.

Osteoarthritis is a chronic degenerative disease characterised by progressive alterations in the molecular and structural composition of the extracellular matrix and cells of cartilage, which lead to mechanical, functional and morphological changes in the cartilage itself and in the subchondral bone. Such structural and molecular changes are evidenced by the onset of a painful and functional symptomatology and by a reduction in articular function (1).

Osteoarthritis (OA) of the hip is common in western countries and is responsible for a high

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percentage of mobility impairment (2). Currently adopted treatments for hip OA range from patient education and rehabilitation to simple analgesics, local therapies such as intra-articular (IA) injections to total hip replacement (3-5).

Viscosupplementation (VS) (6) represents a valid treatment option for reducing the pain associated with knee osteoarthritis (OA) and improving function in the affected joint. Viscosupplementation is a therapeutic tool which exerts its effects by intra-articular (IA) injection of exogenous hyaluronic acid (HA), or its derivatives, into the osteoarthritic joint, with the aim of restoring the synovial fluid's rheological properties (7).

The analgesic effect is thought to be achieved by multiple mechanisms which include reduction of pain-eliciting nerve activity by providing an elastoviscous protective barrier around the nociceptive afferent fibres in the intercellular matrix (8). The long-term effect of the therapy on symptoms (which lasts much longer than the residence time of the product in the joint) may be due to the restoration of normal, endogenous synthesis of high quality HA (9).

Viscosupplementation is included both in the American College of Rheumatology and EULAR guidelines for the management of OA (10, 11).

Many literature data report on the efficacy and safety profiles of HA products in patients with knee OA (12-16). Several meta-analyses and systematic reviews have also been performed on the entire therapy class, which broadly agree that viscosupplementation is effective and safe (17-21).

Sinovial® Forte 1.6% (IBSA Institut Biochimique SA, Lugano, Switzerland) is a medical device made up of a physiological solution of unmodified, non-immunogenic sodium hyaluronate obtained by bio-fermentation, 100% free of animal proteins, characterized by an MW of 800-1200 KDa at a concentration of 32 mg/2 ml for one vial. To date, there are several data available in the scientific literature reporting on the safety and efficacy of Sinovial® for IA use in OA-affected patients (22-25). None of the previously published data have reported on the efficacy and safety profiles of Sinovial® Forte in hip OA.

The disparity between the large amount of published data on the use of VS in knee OA and the relative paucity of those on the subject of VS in hip OA is mainly due, in our opinion, to technical difficulties in reaching the hip joint. It is more challenging to place a needle into the intra-articular space in the hip joint, which is a deep joint, than into the knee, which means that IA injections into the hip require imaging guidance, be it fluoroscopy, computer tomography or ultrasonography (26-28). This makes performing studies on the hip more difficult.

In recent years, we have developed an ultrasound-guided technique, which has proved safe for IA treatment of the hip (29). In several previous studies, we reported on the short and medium-term clinical outcome obtained with different HA preparations when using this technique for treating patients with hip OA (30-31).

The aim of this study is to test the 6-month efficacy and tolerability of ultrasound-guided IA injections of Sinovial® Forte in clinical practice, by enrolling a large number of patients with symptomatic hip OA who regularly attend the rheumatologic Outpatient Clinic at the Ospedale San Pietro in Rome.

MATERIALS AND METHODS

Trial design

This was a prospective, observational, open, post-marketing study performed on patients with hip OA following ACR criteria (32). All patients who received IA injections of Sinovial® Forte 1.6% in the hip from 2008 to 2010 were included. Data were collected from the patients' notes and were analysed by descriptive statistics. Written, informed consent was obtained from each patient before enrolment, and the study was approved by the Ethics Committee of the Ospedale San Pietro.

Patients

Patients were eligible for inclusion if they met the following criteria: aged $\geq$ 40 years; symptomatic hip OA according to the ACR criteria (32); grade II or III hip OA as defined by the Kellgren and Lawrence classification (33), evaluated on a non-weight bearing X-ray taken not more than two months before enrolment and hip OA of at least one year's duration.

Exclusion criteria were as follows: concomitant use of oral anticoagulant; X-ray evidence of no articular space; previous intra-articular steroid or other HA therapy in the hip; significant co-morbidities (rheumatological disease, low back pain, femoral head osteonecrosis); hypersensitivity to HA and chronic systemic steroid

treatment.

Dosing

Patients were injected with a single 4 ml (2 vials) injection of Sinovial® Forte, with optional, additional injections at the 3-month follow-up visit if symptomatically appropriate. Patients were followed up for 6 months with visits at enrolment, first injection (baseline), and then 3 and 6 months after the first injection.

Outcome measures

Outcome measures scored at baseline, 3- and 6-month follow-up were: the Lequesne index (34); patient evaluation of pain in the target hip during the previous week measured on a 0-100 mm visual analogue scale (pain VAS) and NSAID intake, calculated as the number of days in the previous month (0 to 30) in which the patient had taken an NSAID, independently of the drug taken and of the number of administrations per day. Patients who were unable to take NSAIDs (e.g. because of allergy) were excluded from the statistical analysis of NSAID intake. An effect size of 30% and 50% for both VAS pain and Lequesne algofunctional index was evaluated for every patient and the percentage of patients achieving a 30% and 50% improvement in outcome measures was evaluated. This is the first time that an effect size evaluation of this kind has been performed in patients affected by hip OA. Adverse event (AE) reports were collected and recorded throughout the 6-month study period.

Injection technique

Patients were examined supine, with the hip internally rotated by 15-20°. A 3.5 MHz convex transducer (Astro 256, Hitachi-Esaote, Genoa, Italy) had a sterile device for biopsy attached. Ultrasound scans of the hip joint were taken on an anterior parasagittal axis, lateral to the femoral vessels. The probe was aligned along the long axis of the femoral neck to visualise both the acetabulum and the femoral head.

No local anaesthetic was administered to any patient before, during or after the injections of Sinovial® Forte 1.6%. Using an anterosuperior approach, a G20 (9 cm) spinal needle was inserted through the biopsy guide into the joint capsule, until the femoral head was reached. Using real-time imaging software, the needle was inserted until it was visualised in the articular recess, without touching the femoral head. A total of 4 ml of Sinovial® Forte was injected, and its correct intra-articular placement was verified by direct visualisation of hyperechoic flow on the screen.

Statistical analyses

Data were summarised by descriptive statistics. Categorical variables were expressed as frequencies and percentages. Continuous variables were expressed as means and standard deviations (SD), or by medians and inter-quartile ranges (IQR).

The non-parametric Wilcoxon signed rank test was performed for each outcome measure to compare values at baseline with each subsequent time-point. Confidence intervals were set at 95%.

Responders were defined as those achieving an improvement of ≥30% at 6 months in either the Lequesne index or the pain VAS score. A further analysis was performed to identify patients with an improvement in pain VAS and Lequesne index of at least 50% as well.

The level of significance was fixed at 0.05. Statistical analyses were performed using STATA 8.2 (Stata Corp, College Station, Texas, USA).

RESULTS

Patients

Of the 129 patients enrolled in the study 114 completed the 6-month follow-up. Summary demographic data are shown in Table I. Fifteen patients were lost to follow-up and did not complete the 6-month follow-up.

During the study, all completer patients (n = 114) received a first IA injection of 4 ml of Sinovial® Forte 1.6% under ultrasound guidance, 7 patients (6.14%) received a second injection at 3 months if this was clinically necessary to relieve the symptoms that the first injection was unable to improve.

Efficacy outcome measures

For each of the three outcome measures (Lequesne index, target hip pain VAS, NSAID consumption) the scores at each follow-up visit (3 and 6 months) were compared to baseline values (Table II).

A statistically significant improvement was observed at all time-points compared to baseline (Figs. 1 and 2) in all outcome measures ($p < 0.05$). The effect size of a 30% and 50% reduction in Lequesne index and pain VAS scores was obtained in different percentages of patients (Table III).

Safety

No systemic AEs were observed. Only 7 patients reported a local reaction at the injection site, consisting of mild pain and localized warmth, which resolved spontaneously even without additional medication. All 7 local AEs occurred after baseline injection. No patient experienced more than a single

Table I. *Summary of patient demographics for patients achieving the 6-month follow-up visit.*

Parameter	Summary statistic	All patients
Number of patients	N	114
Gender: Male	N	55
Female	N	59
Age	Mean (SD)	61.7 (10.4)
Weight (kg)	Mean (SD)	72.8 (12.8)
Height (cm)	Mean (SD)	166 (8)
Body mass index (kg/ m^2)	Mean (SD)	26.3 (3.9)
OA location: Right hip	%	46.7
Left hip	%	39.9
Bilateral	%	13.4
OA disease severity		
Grade II	n (%)	57 (50)
Grade III	n (%)	57 (50)
Ultrasound pattern		
Regular	%	32.9
Irregular	%	67.1

local AE. Patients' daily activities were unaffected by these events. No septic complications were observed.

DISCUSSION

Osteoarthritis of the hip is very common and is the cause of a significant proportion of mobility dysfunction. Viscosupplementation is largely used for the treatment of knee OA, but it is used less frequently in routine clinical practice as an approach to hip OA, probably because of the need for imaging guidance and the technical complexity of injecting into the hip joint.

The use of VS in hip OA is gathering interest in the scientific community as additional treatment modalities for this disease are necessary in the large cohort of patients suffering for OA which continues

Table II. *Mean study parameter values at each time-point in the study (baseline, 3 months, 6 months).*

Parameter	Baseline	3 months	6 months
Lequesne index	9.33	6.99*	6.76*
Pain VAS	6.42	4.85*	5*
NSAID consumption	8.97	4.42*	4.54*

** $p<0.05$ vs baseline. All parameters observed at 3 and 6 months control visits achieved $p<0.05$ compared to baseline.*

Table III. *Summary of patients achieving 30% or 50% reduction for the study parameters at each time-point.*

Pain VAS reduction 30%			**Pain VAS reduction 50%**		
Time	*N pts*	*%*	*Time*	*N pts*	*%*
3 months	63	**55.27**	3 months	38	**33.30**
6 months	56	**49.12**	6 months	31	**27.19**
Lequesne index reduction 30%			**Lequesne index reduction 50%**		
Time	*N pts*	*%*	*Time*	*N pts*	*%*
3 months	59	**51.75**	3 months	35	**30.70**
6 months	61	**53.50**	6 months	36	**31.58**

to grow in line with the increase in population mean age (35, 36). Data obtained from our and other groups in previous studies support the hypothesis that VS may represent a valid therapeutic tool for the management of hip OA (21). These data seem to confirm that the benefits are similar to those achieved from injecting knee OA (12-20).

This is the first 6-month post-marketing study to assess the safety and effectiveness of Sinovial® Forte 1.6% in a large cohort of patients with symptomatic hip OA. In our study, Sinovial® Forte provided a significant reduction in hip OA pain and a significant increase in mobility as evaluated by the mean of the Lequesne index. These clinical improvements occurred as early as the third month follow-up visit and were maintained up to 6 months. The effect size of a 30% reduction in pain VAS was observed in 55.27% of patients at 3 months and 49.12% of patients at 6 months. This provides convincing evidence of the efficacy of IA therapy with HA, in this case Sinovial Forte 1.6%, in hip OA-affected patients. The effect size of 50% for pain VAS was observed in 33.3% at 3 months and 27.19% at 6 months. These data were confirmed by a Lequesne index effect size of 30% (51.75% at 3 months and 53.5% at 6 months) and of 50% (30.7% at 3 months and 31.58% at 6 months). This result also gives some indication of the kind of results that patients and clinicians may expect from this therapy.

The efficacy of Sinovial® Forte in reducing pain

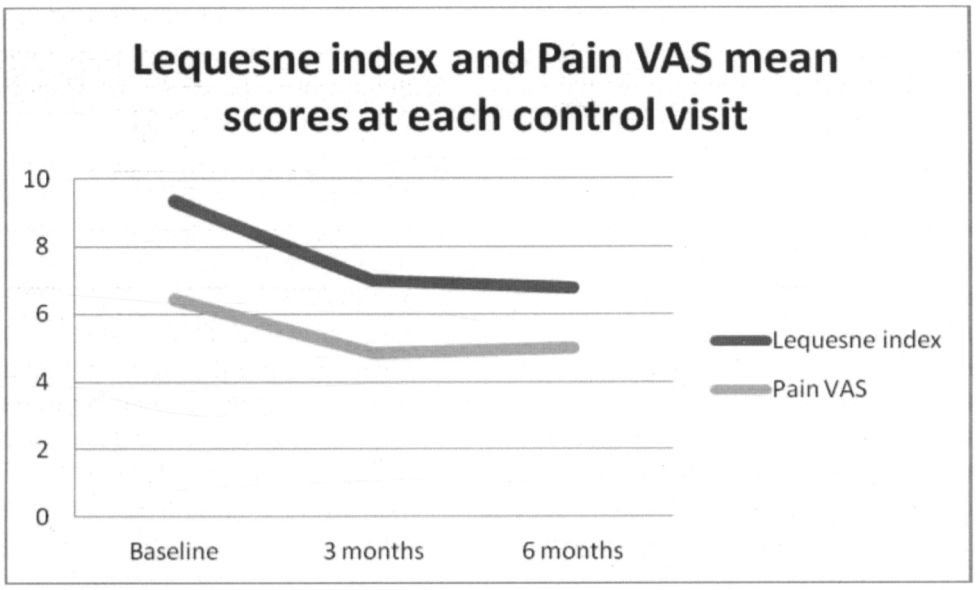


Fig. 1. *Mean Lequesne index scores at each time-point and mean target hip OA pain VAS scores at each time-point.*

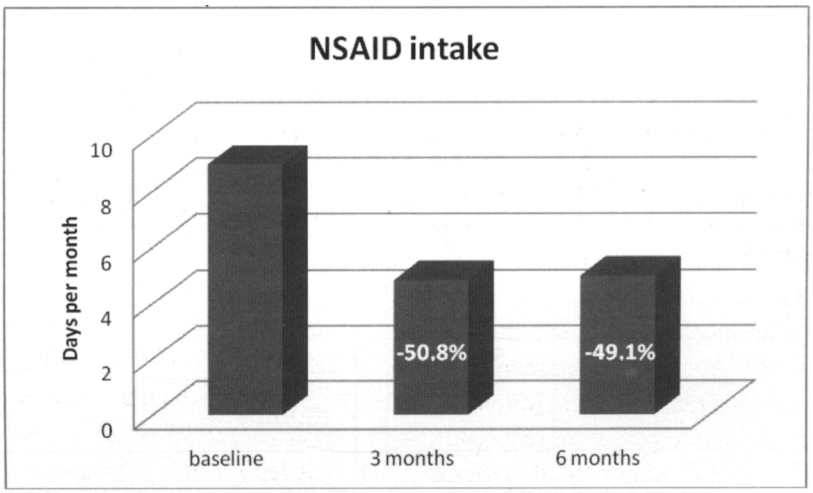


Fig. 2. *Mean NSAID usage at each time-point (days per month).*

was demonstrated by the changes from baseline in the Lequesne Index and hip OA pain VAS scores. Similarly, NSAID consumption reduction was statistically significant at the 3-month follow-up and was maintained at the 6-month follow-up visit.

These data regarding NSAID consumption confirm evidence previously presented in several studies (30). Pain killers, NSAIDs and Cox-2 inhibitors are widely employed in clinical practice in patients affected by OA and are considered as standard and common tools in the management of OA (5, 35, 36). It is also known that these drugs are sometimes associated with severe gastrointestinal, cardiovascular, renal and hepatic side effects that are more frequent in long-term users (38). Although Cox-2 inhibitors have a better gastrointestinal safety profile, their long-term use has recently been associated with cardiovascular side effects (39).

In the light of this results, it is appropriate, in our opinion, to consider viscosupplementation in the management of hip OA, as improvement in function and in the pain experienced by patients

after treatment with Sinovial® Forte 1.6% enabled them to return to work and social activities, thereby creating additional economic savings in addition to those associated with the reduction in NSAID consumption.

In this study, no serious, severe or moderate AEs were reported or observed. The most commonly reported local AE was mild and transient (1-3 days) post-injection pain at the injection site, which either resolved spontaneously or after the use of analgesics. None of patients who received two injections (7 patients) reported any AE.

The use of ultrasound guidance not only ensured the accurate placement of Sinovial® Forte into the hip joint, but also spared both patients and clinicians the X-ray dose associated with fluoroscopic guidance. Additionally, ultrasonography can be repeated as many times as necessary avoiding radiation load for both patient and operator. Another consideration is that, in the case of fluoroscopy, the use of a contrast medium may also compromise results in terms of safety and efficacy.

Correctly performed prospective cohort studies provide useful information which may assist the effective and safe management of "real practice" patients even if the data obtained are not as robust as data from randomised controlled trials. In fact, one of the strong points of the observational cohort studies is the general applicability of their results. In contrast, the application of results obtained from RCTs to actual clinical practice is often limited by the difference between the two types of patients (40). It has been observed that the majority of patients considered candidates for OA therapy by their physicians would not meet the eligibility criteria for inclusion in randomised controlled trials. Since the population within this cohort study consists of subjects with a mixture of health and disease characteristics, the results are more likely to be generally applicable to other "real practice" populations.

The data obtained from this 6-month observational open study carried out on a large cohort of patients with hip OA who received intra-articular US-guided injections of Sinovial® Forte 1.6% confirm the clinical effectiveness of this approach in patients with symptomatic hip OA. The reduction in OA pain and improvement in joint function are similar to those reported in the literature both in knee and hip OA.

The safety of Sinovial® Forte observed in this study makes it particularly suitable for use in patients contraindicated for, or intolerant to, NSAID use and in patients suffering from OA isolated in the hip joint. Furthermore, VS in this cohort proved to be safe and effective in patients with comorbidities and those taking concomitant medications.

This study has its own limitations which must be reported. It is not a prospective or randomized double-blind controlled study. Data from patients who were lost to follow-up are missing.

Future prospective and controlled studies are needed to confirm the data presented here, and to define clearly the role of VS in the therapeutic armamentarium for hip OA.

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