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Viscosupplementation: a suitable option for hip osteoarthritis in young adults

A. MIGLIORE[1], E. BIZZI[1], U. MASSAFRA[1], F. VACCA[1], A. ALIMONTI[1], F. IANNESSI[2], S. TORMENTA[2]

U.O. of Rheumatology[1] and Department of Radiology[2], San Pietro, Fatebenefratelli (FBF) Hospital, Rome (Italy)

Abstract. – *Introduction:* **Young adult hip osteoarthritis (OA) is a noteworthy problem, although rarer than the elderly form of the disease, causing limitations in social and working activities and prospects. Treatment options are scarce and surgical procedures, frequently necessary, imply the major drawback of revising the prostheses periodically, whereas chronic non-steroidal anti-inflammatory drugs (NSAID) consumption may provoke side effects. To explore alternative options to both surgery and long-term NSAID use, especially in the case of young patients, viscosupplementation seems to appear as an appropriate tool to relieve pain, ameliorate the function and delay surgery.**

Aim of the Study: **In this study we tackle the issue of the use of hyaluronic acid (HA) injections in young adults with symptomatic hip OA.**

Results and Conclusions: **These data, collected from 78 young patients, show that viscosupplementation is a safe procedure, and may provide significant relief from pain and functional recovery.**

Larger controlled studies are needed to establish otpimal treatment strategies and clinical factors predictive of treatment response.

Key Words:

Hip, Osteoarthritis, Young, Viscosupplementation, Hyaluronic acid, Ultrasound.

Introduction

Osteoarthritis (OA) is the major source of functional disability and reduced autonomy in elderly adults[1-4]. It involves an estimated 21 million people in the United States[5] and represents an important economic problem[6,7].

If currently the management of severe hip osteoarthritis in patients older than 50 years encompasses total hip arthroplasty (THA), the problem of long term durability and the prospect of multiple revisions make things difficult for adolescent and young adults (16 to 40 years old) suffering from this disease[8]. Treatment should relieve symptoms in the most conservative manner to allow the best surgical treatment in the future. The present mainstay of treatment in osteoarthritis is exercise and non-steroidal anti-inflammatory drugs (NSAIDs) to control pain and stiffness, but neither has the ability to modify the course of the disease.

The revision rates in the long term results of THA have been estimated 33 to 45%[9-11].

Generally young adults suffer from secondary rather than primary osteoarthritis. Several troubles at birth or later during growth may injure the hip joint producing disadvantageous biomechanics, which cause cartilage breakdown[12].

The paradigm is acetabular dysplasia, a congenital disease, estimated to cause over 40% of all cases of young adult hip osteoarthritis[13]. Another condition is osteonecrosis, and patients suffering from hip disease secondary to it seem to have poorer results than those with inflammatory illnesses[14]. History of a joint injury is associated with an increased risk of developing osteoarthritis[15-18] and joint trauma may be a more common cause of osteoarthritis than has been previously recognized[19].

In the case of young adults OA, physicians have three options: (a) delay surgery using physiotherapy and NSAIDs; (b) perform a THA; 3) execute a bone-conserving procedure such as a hip arthrodesis or osteotomy.

In recent years viscosupplementation (VS), the injection of hyaluronan preparations into the joints in order to renovate the properties of normal hyaluronic acid (HA)[20], has been proved to provide long-lasting relief from symptoms in patients with OA of the knee[21,22].

Corresponding Author: Emanuele Bizzi, MD; e-mail: ebizzi@email.it

Although increasingly attempted in recent years, VS is not yet routinely used in hip OA. Because of the anatomic features of hip joint, i.e. deeper location than the knee and proximity of large vessels, hip access is not ideally achieved by blind injections, so imaging techniques have been advocated to assist intra-articular viscosupplementation.

We optimised an efficacious and safe[23,24] viscosupplementation technique consisting of an intra-articular injection of a hyaluronan compound under ultrasound guidance using an anterosagittal approach. This procedure is safe because the operator, with the assistance of realtime ultrasound and Doppler imaging, is sure to avoid vessel injection, and to reach intra-articular space.

Furthermore, ultrasonography allows the recognition of joint features, the evaluation of OA severity and the detection of potential presence of bursitis, effusion and intra-articular free bodies[25,26].

In this paper, we describe a case series of young adults suffering from hip OA and treated with VS.

Methods

This is an open retrospective study, without a control population undergoing to placebo therapy. Among the 1962 outpatients suffering from hip OA who attended the Rheumatology Day Hospital of S. Pietro Hospital, Rome (Italy) for viscosupplementation in the years going from 2004 to 2007, 121 (6.2%) were younger than 40.

In this study we describe data relative to 78 patients who were followed for 12 months. (See Table I for demographical and clinical data).

Each patient signed an informed consent regarding the therapy they were undergoing.

Each patient selected had a recent normal blood examination (cell count, ESR, CRP) and a hip X ray image taken within the last six months before first injection.

All X ray images were scored according to Kellgren-Lawrence criteria by two experienced radiologists (S.T. and F.I.)[27]. All patients satisfied ARA criteria[28] for OA except for age, as patients considered for this study are all under 40 years old.

Exclusion criteria for VS were current anticoagulant treatment or coagulation abnormalities, allergy to avian proteins, dermatitis or mycosis or other local inflammations in the site of injection.

Comorbidities were calculated through validated ICED score[29].

Patients underwent to a physical examination and an interview, to evaluate OA related pain, hip functional status and NSAID intake.

Pain was assessed by the patient with a score on a visual analogue scale (VAS) ranging from zero (no pain) to ten (maximum pain). Functional status was evaluated by Lequesne index questionnaire[30].

NSAIDs intake was assessed through the number of days per month patient took NSAIDs, independent from the type of drug and the number of pills taken per day.

In the following interviews, patients were asked to compare overall symptoms related to the hip treated to the overall symptoms at the time of the first injection (time zero) and to describe them as one of the following: very improved (VI), improved (I), unchanged (U) or worsened (W).

Subjects receiving bilateral treatment were asked to measure pain on the VAS and to fill in Lequesne questionnaire separately for the two hips.

Patients were interviewed after 3 months from the first injection, then injected again at 6 months, interviewed at 9 and 12 months.

The patients who complained unchanged symptoms at the third month visit were injected again shortly after the visit.

Injection Technique

Patients were laid in supine position with the hip in 15-20° internal-rotation and underwent hip injection under ultrasound control as described elsewhere[31].

Hip joint was visualized by a 7.5 MHz linear or 3.5 MHz convex transducer (Star 256, Hitachi-Esaote, Genova, Italy), by an anterior parasagittal approach, lateral to the femoral vessels. The ultrasound transducer equipped with a sterile biopsy guide was aligned with the long axis of the femoral neck, including acetabolum and femoral head.

A 20 gauges (9 cm) spinal needle was inserted 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 was shown to be under the capsule profile, hyaluronan preparation was injected into the hip joint. Intra-articular placement was proven by real-time direct visual-

ization of viscous fluid in the articular space and by Doppler imaging showing intra-articular flow. Doppler vision helps prevents injecting blood vessels.

For each injection we used a single dose of Hylan G-F 20 (Synvisc), 2 ml.

Statistics

T-test was performed versus baseline for all parameters evaluated at three months and six months.

Results

Seventyeight patients less than 40 years old (56 males and 22 females) suffering from hip OA have been followed up for twelve months in our Hospital throughout the year 2004. Among the other 121 patients undergoing to hip joint US-guided injection of HA, only 78 were followed for 12 months as 2 patients dropped out after first injection (both scored as Kellgren-Lawrence grade 4), and 41 patients still didn't reach a long enough follow up time (less than 12 months).

Demographic baseline characteristics of these patients are shown in Table I.

Table I. Demographic characteristics of the patients on an intention to treat basis.

Patients (n)	78
Males	56 (72%)
Females	22 (28%)
Age (years, mean)	36.82 (26-40)
Risk factors	
Congenital hip luxation	20
Dysplasia	17
Heavy work	8
Perthes	4
Professional sport	8
Not assessed	2
BMI (mean)	25.90
25<BMI>29.9	24 pts
BMI>30	11 pts
Smoking habit	4 pts (4F)
Systemic OA	none
Knee OA	none
Hip treatment	
Monolateral	60 pts
Bilateral	18 pts
Comorbidities	
Hypertension	4 pts (4M)
Diabetes	2 pt (2F)
Other	1 pt (1M, multiple sclerosis)
Total number of injections*	202

*The second injection was administered at 3 or 9 months, when needed (see text).

At the first visit, patients were screened for hip OA risk factors. 20 of them had congenital hip luxation, 17 dysplasia and 4 Calve Legg Perthes illness. Moreover, 8 patients had a physically tough job, while 8 played a sport professionally.

Eighteen patients received bilateral treatment, so that in total 96 hips were treated.

Six patients with monolateral hip OA and 2 patients with bilateral hip OA whose partial or total amelioration faded after 3 months (10 hips) were submitted to a second VS session shortly after. Only 1 patient affected by monolateral hip OA required a third infusion at 9 months. A total of 203 injections were performed altogether.

All patients received Synvisc (Hylan G-F 20) preparation.. Data are shown on an intention to treat (ITT) base.

Pain VAS evaluation significantly diminished from a baseline value of 6.0 to 3.72 at three months ($p<0.0005$). It raised again to 4.17 points at 6 months ($p<0.0005$) when compared to baseline values. At 9th and 12th month the values attested on 3,88 and 3,63 respectively ($p<0.0005$ respectively).

Functional Lequesne evaluation, which was 7.84 at baseline, decreased to 4.38 and 5.0 at three and six months respectively, which represents a statistically significant reduction ($p<0.0001$ and $p<0.001$ respectively). At 9th and 12th month Lequesne index mean values were 4,38 and 4,12 respectively (for both $p<0.0001$) (Figure 1, Table II).

NSAID intake decreased from 3.83 days per month to 1.8 at three months ($p>0.04$, non significant change), and to 1.12 at six months ($p>0.04$, non significant change). Similar results were obtained when analyzing data from 9th and 12th month follow up visit, with mean values of 2.01 and 1.19 respectively ($p>0.04$ for both). Still important percentile reductions in NSAID intake were observed for all patients (Figure 2 and Table II).

At the third month visit, 28 patients (35.9% of all patients) described their hip symptoms as very much improved, 39 patients, 50% of all the patients described symptoms as improved and 8 patients, 25% of all the patients (11 hips, 26.3% of all) as unchanged, when compared to baseline.

Significantly, no patient described worsened complaints.

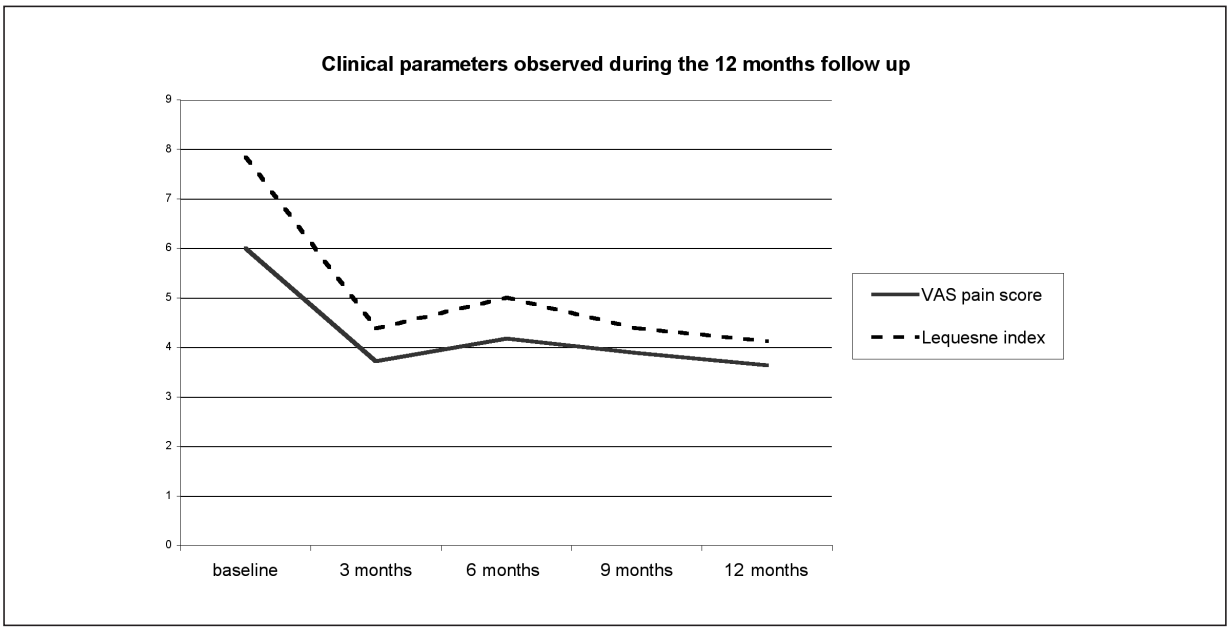

Figure 1. Pain VAS score mean evaluated at baseline, 3 months, 6 months, 9 months and 12 months. * p<0,0005 when values at 3, 6, 9 and 12 months are compared with baseline mean value.

At the six months visit, 28 patients reported very improved symptoms (35.9% of all patients), 41 patients improved symptoms (52.56%), 9 patients unchanged (11.54%) when compared to baseline symptoms.

Again, no worsened complaints were reported compared to baseline conditions.

At ninth month follow up visit, 30 patients (38.46% of all patients) reported very improved symptoms, 41 patients (52.56%) reported improved symptoms, 7 patients (8.98%) reported unchanged symptoms when compared to baseline symptoms. No worsened symptoms were reported.

At 12th month of follow up visit, 30 patients (38,46% of all patients) reported very improved symptoms, 42 patients reported improved symptoms (53.85%), 6 patients (7.69%) reported unchanged symptoms when compared to baseline. Again, no worsened symptoms were reported (Figure 3 and Table IV).

None of the patients referred systemic adverse events after each injection. We didn't find any adverse events such as local or systemic infections, allergic reactions, or other systemic side effects or adverse events. 7 patients (8.97% of patients, 3.44% of injections) referred local transient pain after the injection that lasted for 1-3 days and that completely reverted by the assumption of paracetamol 1 g twice per day.

Discussion

In this study we report data relative to young patients, under 40 years of age. Even though poor in numbers when compared to the much larger population of the elderly, still the group of young patients affected by OA deserves special attentions.

Table II. Values obtained at baseline and follow up visits regarding VAS pain score and Lequesne algo-functional index.

	Baseline	3 months	6 months	9 months	12 months
VAS pain score	6	3.72*	4.17*	3.88*	3.63*
Lequesne index	7.84	4.38*	5*	4.38*	4.12*

*p<0,0005 when compared with baseline value.

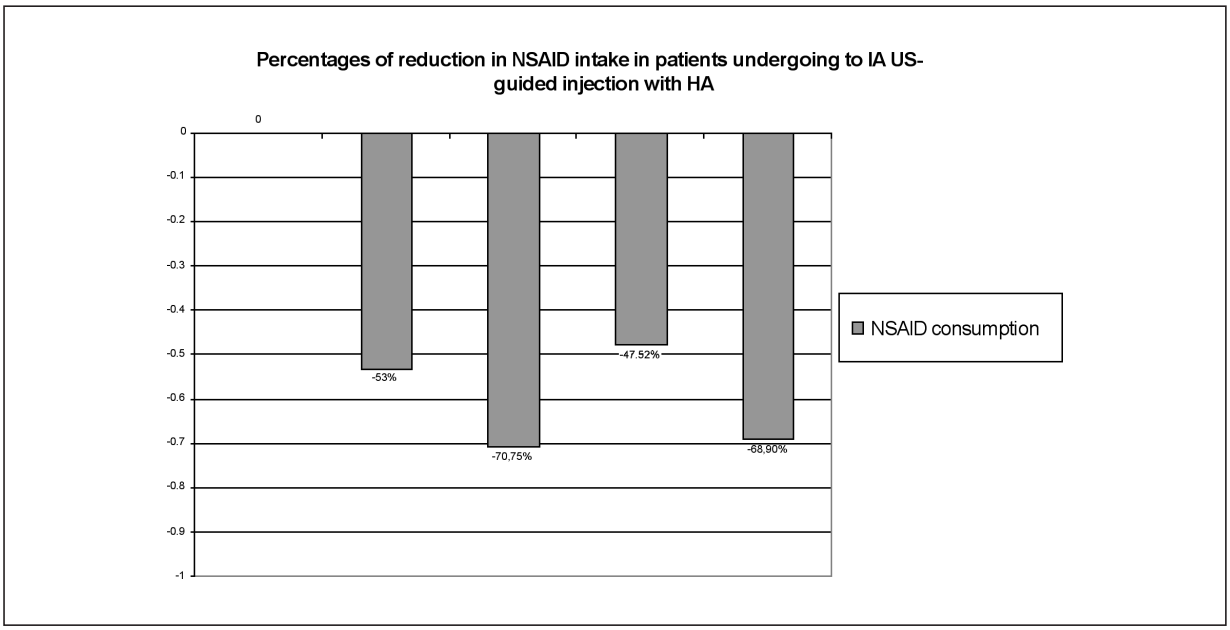

Figure 2. NSAID consumption decrease over time in patients object of the study. No statistically significative difference was observed when comparing values obtained at 3, 6, 9 and 12 months with baseline value (p>0,04), but still important percentile reductions in NSAID consumption were observed.

As described above, hip OA of the young has few treatment options, and very frequently the patient has to be deferred to the surgeon for total hip arthroplasty, one or more times in a lifespan.

The need for optimal articular function is important for patients of every age group, especially for young adults, as limited mobility provoked by OA severely impairs working and recreational activities ultimately decreasing quality of life.

Although less frequent than in the elderly hip OA is not so rare in under 40s. In our series of 1962 subjects 121 (6.2%) people are under 40 years of age. Interestingly in our young patients case series 72% are males (56 males out of 78) differing from the general case series in which males are 52.7%.

Since gender distribution of hip dysplasia is equal or even unbalanced, given that it is apparently more frequent in girls[31], present data may suggest that hard work or professional sport activities, more common in males than in females, may be important cofactors in determining OA onset.

Results of the this study show promising data.

First of all, no patients had worsened symptoms after intra-articular injection. Furthermore, all reported outcomes are statistically significant for both pain relief and hip function at 3, 6, 9 and 12 months.

Of the 78 patients treated, 11 have had no improvement at three months, which represents less than 15%. At 12 months, the number of patients still reporting unchanged symptoms was 6 (7.69%).

All of those with favourable outcome after the first injection maintained the improvement.

The 11 patients reporting no benefit from the first treatment, underwent a second injection shortly after the 3-months visit except. At six

Table III. NSAID intake for patients undergoing to US guided IA injection of hip joint. Values obtained at baseline and follow up visits at 3, 6, 9 and 12 months. No statistically significative differences (° p>0,04) were observed when comparing values from follow up visits with baseline value.

	Baseline	3 months	6 months	9 months	12 months
NSAID consumption	3.83	1.8°	1.12°	2.01°	1.19°

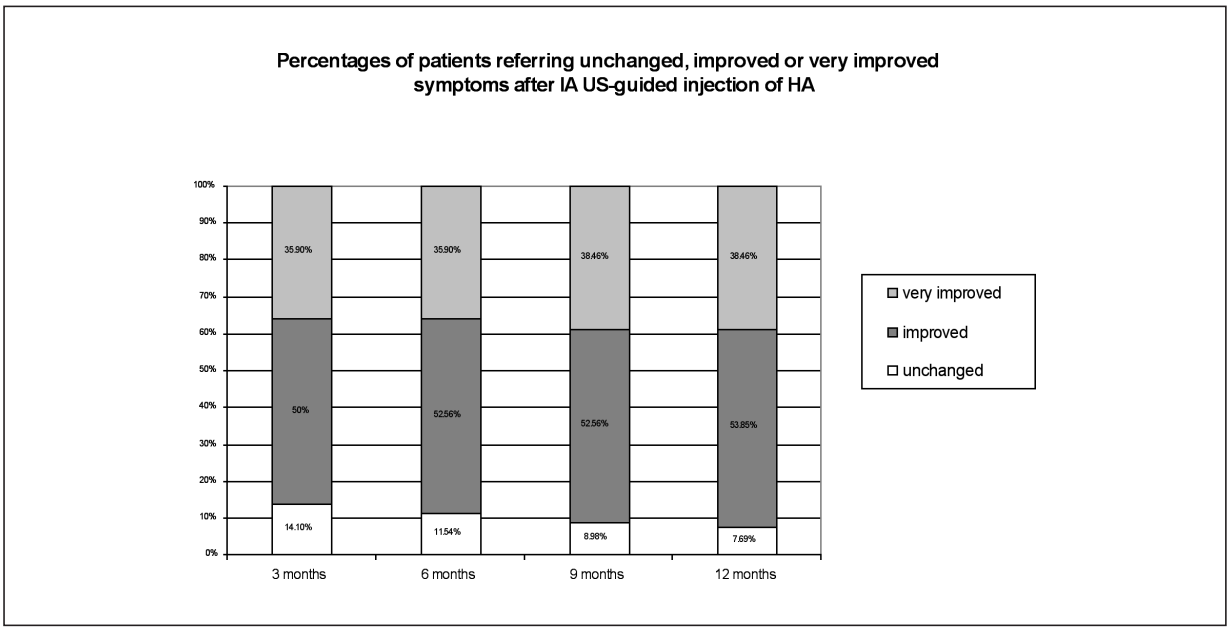

Figure 3. Symptoms description made by patients at month 3 visit, month 6 visit, month 9 visit and month 12 visit. Patients were asked to establish if symptoms regarding Hip OA were Worsened (W), Unchanged (U), Improved (I) or Very Improved (VI). No patients at 3, 6, 9 and 12 months visit reported worsened symptoms.

months two of those patients reported improved symptoms, while the other nine still had no benefit. At 9th month visit, 2 of them reported improved symptoms after third injection and were not injected again until the end of the study. Of the seven patients still reporting unchanged symptoms that were newly injected at 9 months, only 1 reported improved symptoms at 12 months.

These results show the importance of keeping a close follow up on the patients. It helps to state the exact number of injections needed and the best interval among them. Close follow up and careful interviews also help investigate cofactors interfering with the treatment, such as physical overload.

Studies with a longer follow up are needed, and in our case series patients observed for longer time courses show that subsequent treatments maintain and prolong the benefit.

Other than the efficacy, data show very good tolerability of this treatment, both local and systemic, meaning that the procedure is endowed with satisfying safety. Actually ultrasound guidance assures that HA is injected within joint capsule, and that blood vessels are avoided. Moreover, US guide is more economic, versatile and faster in comparison with CT and fluoroscopy guidance, so US guided injections can be repeated often over time, without the drawback of radiation load for the operator nor for the young patients.

In this particular group of patients joint function improvement comes along with the recovery of working and social activity resulting in further saving.

Table IV. Patients referral on hip joint symptoms at every follow up visit. No patients referred worsened symptoms, while percentages of patients referring unchanged symptoms slightly decreased over time.

	3 months	6 months	9 months	12 months
Unchanged	11 (14.1%)	9 (11.54%)	7 (8.98%)	6 (7.69%)
Improved	39 (50%)	41 (52.56%)	41 (52.56%)	42 (53.85%)
Very improved	28 (35.9%)	28 (35.9%)	30 (38.46%)	30 (38.46%)

Even though results about NSAID intake do not reach statistical significance in the out case series, symptoms relief due to viscosupplementation leads to the reduction of NSAIDs consumption. This statement is not only a noteworthy clinical achievement but also a cost saving achievement as NSAIDs have direct costs and imply indirect costs[33,34]. These costs are associated with the management of side effects, mainly of gastrointestinal and cardiovascular nature, whose occurrence rate is directly related to NSAIDs daily dose[35]. Conversely, HA injections are well tolerated and have no systemic adverse effects even in the long term.

From bench research studies it appears that exogenous HA implementation might normalize synovial fluid viscoelastic properties in a long term, and affect chondrocyte and synoviocyte homeostasis so to restore the physiological production of matrix macromolecules such as proteoglycans and HA[35]. Recent literature papers[36] report how HA may affect OA progression and truly represents a disease-modifying drug.

US epidemiological studies have pointed out that hip replacement accounts for 2.5% of annual medical expense budget, without taking into account all collateral expenses related to possible post-surgical complications and functional rehabilitation.

If future evidences will prove HA to be a disease modifying drug, capable of changing OA natural history, viscosupplementation will represent a first line option in delaying surgical intervention. The delay and reduction of hip replacements would decrease the costs of OA treatment and the mortality rate correlated to surgery.

Conclusions

US-guided inrta-articular VS is a feasible and safe procedure, providing significant relief from pain and functional recovery in young patients suffering from hip OA. Surgical replacement carries major drawbacks such as the need to replace the prostheses in the patient's later life. It is important to have a feasable alternative to surgery to improve patients' self-sufficiency in their social and working activity, especially for young patients, where multiple surgical interventions are needed in their longer expected life lenght.

For all these reasons we believe VS is an appropriate alternative to immediate surgery especially for young patients.

Further studies are still needed to confirm the role of HA in the treatment of young adults hip OA and for the production of meaningful guidelines for future management.

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