



Viscosupplementation in symptomatic severe hip osteoarthritis : A review of the literature and report on 60 patients

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Osteoarthritis of the hip is a frequent joint disorder in adults aged 50 years and older. The management focuses on pain reduction, by means of non-steroidal anti-inflammatory drugs and analgesics, physical therapy and weight reduction. When these treatments fail, total hip replacement can be considered. Viscosupplementation is a local therapeutic approach with the objective to decrease pain and to improve joint mobility. The treatment consists of injecting hyaluronic acid or hyaluronate derivatives intra-articularly. Although this approach is frequently used in young sportive adults to avoid knee surgery, its use in the severe osteoarthritic hip is less well documented. Moreover the injection of the hip joint is more difficult than injection of the knee joint, and on another hand the general condition of the patients is often already compromised. In this article we present a literature review on the subject and report the results in 60 patients who received intra-articular viscosupplementation of the hip with the objective to delay total hip replacement surgery.

Keywords : hyaluronic acid ; viscosupplementation ; hip osteoarthritis ; non-operative treatment.

INTRODUCTION

Osteoarthritis is the most prevalent joint disorder in adults aged 50 years and older, and is a major source of pain and disability (27). The increasing life expectancy of the general population will lead to an increased incidence of this condition ; its management is a burden on the health care budget.

It is characterised by loss of articular cartilage, subchondral sclerosis, joint deterioration and osteophyte formation (1). The conservative treatment focuses mainly on reduction of pain and inflammation, thus leading to an improvement of the mobility. Non-steroidal anti-inflammatory drugs are most frequently used but they may cause serious adverse events. There are many other treatment modalities available for the management of osteoarthritis including education, counselling, analgesics, glucosaminoglycans, intra-articular corticosteroid injections, weight reduction, physical therapy, occupational therapy, ambulatory aids, orthotics, arthroscopic joint debridement, joint

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lavage and/or total joint replacement (21). Viscosupplementation is a local therapeutic approach with the objective to improve joint mobility and to decrease pain by injecting intra-articular visco-elastic solutions of hyaluronic acid – also known as hyaluronan – and glycosaminoglycan or hyaluronate derivatives (4, 5).

In the normal joint, hyaluronic acid (HA) provides the elastic and viscous function of the synovial fluid. In osteoarthritis (OA) its concentration and molecular weight are diminished due to dilution effects, aberrant hyaluronan synthesis and free radical degradation (6). Consequently, the biologic and mechanical properties normally provided to synovial fluid by hyaluronan are compromised in the osteoarthritic synovial fluid.

Literature search

We searched the Medline® and Embase® electronic databases since 1966 until June 2005. Reference lists of relevant articles were controlled for additional references. We used the search terms viscosupplementation, hyaluronic acid and hip osteoarthritis. We only included original articles written in arabic script. Articles that were not written in English were considered after translation. We limited our search to viscosupplementation for hip osteoarthritis in humans. From the title and abstract we reviewed the literature searches to identify potentially relevant articles for our review.

Results of the literature search

Our search yielded 10 articles published between 1984 and 2005 ; the details of those studies are illustrated in table I. Patients treated with viscosupplementation in these studies showed clinically significant reduction in different outcome measurements during the follow-up period which varied from 3 months to 5 years (11-15, 31-33, 39, 40). The following outcome measurements were used : Pain visual analogue scale (VAS) (PAS), joint mobility, Lequesne scale, NSAID and analgesics use, WOMAC™ osteoarthritis index (pain, stiffness and physical function scores, patient's and physician's global assessment), AAOS (American

Association of Orthopedic Surgeons) Lower Limb Core Scale score, 15 meter walking time and patients' satisfaction.

Injections of HA were well tolerated and safe ; some authors report patients who experienced a mild increase in pain after the viscosupplementation injection (11-13, 15, 31, 39).

Bragatini *et al* (12) showed that the improvement observed at the end of the treatment period (30th day) was significant, compared with baseline, for pain and joint motion.

Tikiz *et al* (39) showed no significant difference in outcomes after 6 months between higher and lower molecular weight hyaluronan (Hylan G-F 20 and Ostenil) in the treatment of hip osteoarthritis. It appears from the published information that viscosupplementation may be considered in patients with severe osteoarthritis of the hip prior to surgical THA. The duration of the beneficial effects and the optimal number of injections needs further research in large studies. Observational contemporary cohort studies may be useful to confirm the efficacy of this technique compared to the natural evolution of the disease (15, 32).

Molecular structure and physiology of hyaluronic acid

Hyaluronic acid is a long, unbranched polysaccharide chain that is formed by approximately 2,500 repeating disaccharide units consisting of D-glucuronic acid and N-acetyl-D-glucosamine (C₁₄H₂₀N₁O₁₁) linked by alternating beta 1.4 and beta 1.3 glycosidic bonds. Hyaluronic acid belongs to the family of glycosaminoglycans, which also includes chondroitin sulphate, dermatin sulphate and heparin sulphate. However, unlike these compounds, hyaluronic acid does not bind covalently with proteins. In neutral aqueous media, hydroxyl bonds form between water molecules and the carboxyl and acetyl groups. The capacity of hyaluronic acid for binding in water is directly proportional to its molecular weight and can occur in the presence of up to 6 gram/litre of hyaluronic acid.

Hyaluronic acid is found in virtually all higher mammals and in humans, with the highest concentrations occurring in the vitreous body of the eye

Table I. — Overview of the publications on viscosupplementation of the hip

| | | | | | | | | | | |
|---------------|--------------------------|--|--|--|---|--|---|-------------------------------|-------------------------------|--|
| Study | Bragatini (12) | Brocq (13) | Vad (40) | Conrozier (15) | Migliore (31) | Berg (11) | Cagliar-Yagci (14) | Migliore (33) | Migliore (32) | Tikiz (39) |
| Year | 1984 | 2002 | 2003 | 2003 | 2003 | 2004 | 2004 | 2005 | 2005 | 2005 |
| Country | Italy | France | U.S. | France | Italy | Sweden | Turkey | Italy | Italy | Turkey |
| Patients | 44 (50 hips) | 22 | 22,(25 hips) | 57 | 28 | 31 | 14 | 26 | 12 (14 hips) | 43 (56 hips) |
| Mean age | 57 ± 13 | 54.7 ± 10.0 | 56.4 (39-72) | 59.8 ± 9.5 | 66 (55-78) | 60.0 ± 10,1 | 65.4 ± 5.9 | 70.5 (55-89) | 68.4 ± 11.9 | Group 1 58.8 ± 9.8 and group 2 60.4 ± 9.6 |
| Product | Hyaluronic acid | Hylan G-F 20 | Hylan G-F 20 | Hylan G-F 20 | Hyaluronic acid | NASHA | Hylan G-F 20 | Hylan G-F 20 | Hylan G-F 20 | Hylan G-F 20, Ostenil |
| Infiltrations | 3 to 5 | 1 or 2 | 3 | 1 or 2 | 1 to 3; 78 infiltrations in 28 patients | 1 | 3 | 46 infiltrations in 26 | 1 | 3 |
| Interval | 1 week | 30 days | 1 week | 30 days | 15 days | | 1 week | 2 months | | 1 week |
| Outcome | Pain VAS, joint mobility | Lequesne, Pain VAS, NSAID and analgesics use | Pain VAS, AAOs Lower Limb Core Scale score | Pain VAS, Womac, patient's and physician's global assessment | Lequesne, Pain VAS, NSAID use. | Womac pain, stiffness and physical function scores | Lequesne, Pain VAS, 15 meter walking time, patients satisfaction, analgesic use | Lequesne, Pain VAS, NSAID use | Lequesne, Pain VAS, NSAID use | VAS, Womac, Lequesne |

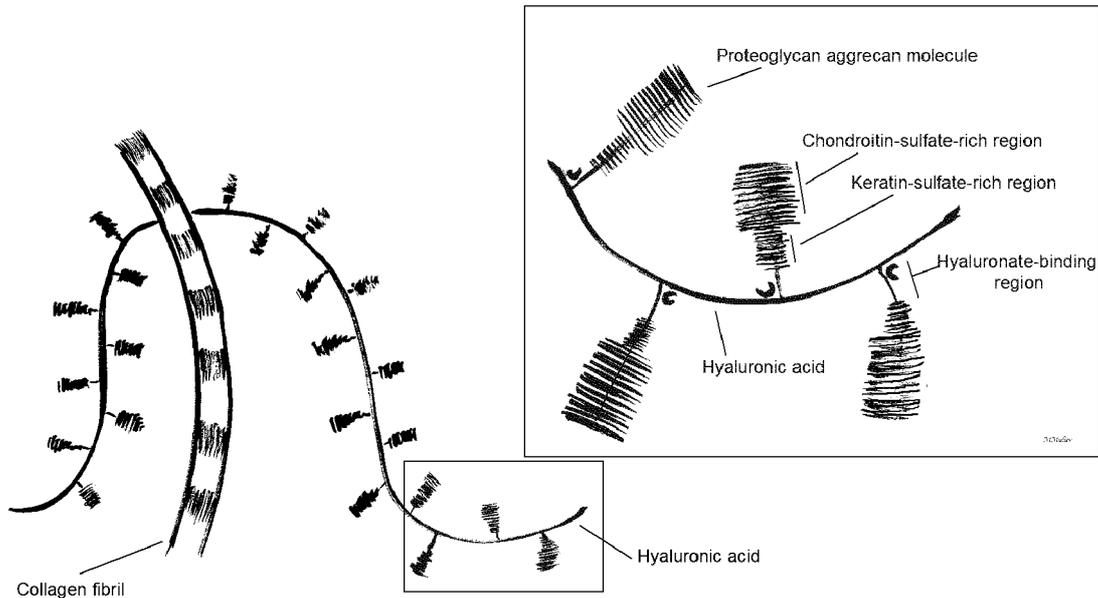


Fig. 1. — Schematic representation of the molecular structure of hyaluronic acid

and in the synovial fluid of the articular joints (34).

Hyaluronic acid is continuously synthesised and released into the synovial fluid by specialised synoviocytes. In healthy adult synovial fluid, its molecular weight is 4-5 million and its concentration ranges from 2.5-4 mg/mL (6-8, 35).

Even at relatively low concentrations, the molecule's large size and highly coiled configuration cause it to form an entangled network (26). The structure of hyaluronic acid is illustrated in figure 1. This network confers to synovial fluid its rheologic properties, thus the elasticity and viscosity responsible for shock absorption under conditions of high compression or shear, and lubrication in low load states.

The hydrated hyaluronic acid network also conveys anti-inflammatory and anti-nociceptive properties to synovial fluid by a molecular exclusion effect (4, 8, 16).

Rationale for and mechanisms underlying hyaluronic acid based viscosupplementation

Viscosupplements are hyaluronic acid -based preparations that have been developed to improve

the altered biology and the mechanical properties of synovial fluid in osteoarthritis.

Since hyaluronate is completely metabolised when administered orally, the product is injected into the joint cavity. Hyaluronan preparations have a half-life of 17 hours ; therefore the long-term effects of the viscosupplementation cannot solely be attributed to the substitution of the molecule itself (25).

There are at least four mechanisms whereby intra-articular injection of hyaluronate- derivatives may provide therapeutic benefit in symptomatic osteoarthritic joints (29) :

- 1) Restoration of elastic and viscous properties of the synovial fluid ;
- 2) Anti-inflammatory effects ;
- 3) Anti-nociceptive effects ;
- 4) Normalisation of hyaluronan synthesis by synoviocytes.

Viscosupplements have demonstrated molecular weight dependent decreases in inflammatory cell migration and reduced concentrations of prostaglandin E2 and bradykinin (3, 17, 19).

The analgesic effects of high molecular weight hyaluronate have been linked to decreases in the firing rate of the articular nociceptors (10, 36).

Importantly, injection of hyaluronate derivatives promotes restoration of endogenous hyaluronic acid synthesis by synoviocytes toward normal levels (37).

This molecular weight dependent effect is a particularly interesting mechanism that may account for the extended duration of the clinical benefit (beyond the time of effect of viscosupplementation in the joint) that is often seen in clinical human and animal practice (2, 9, 37, 41, 43).

Several anti-catabolic effects have also been identified in animals (9, 22, 42).

In experimental rabbit osteoarthritis, hyaluronic acid inhibited matrix metalloproteinase (MMP)-3 production but did not affect MMP-1 production (20). Synovial expression of interleukin 1 beta and MMP-3 decreased following hyaluronic acid treatment in a rabbit model of mild osteoarthritis (38). Hyaluronic acid reduced interleukin 1 beta mediated suppression of transcriptional activity for type VI collagen in cultured rabbit chondrocytes (18).

In human cartilage, fibronectin fragments induce catabolic cytokines that suppress proteoglycan synthesis and induce matrix metalloproteinase. Hyaluronic acid completely blocked fibronectin-fragment mediated decreases in proteoglycan content and delayed MMP-3 synthesis in human cartilage explants (23).

Synthesis of hyaluronic acid

1) Extraction from chicken combs. In this complex process, high molecular weight hyaluronic acid is extracted from the aforementioned biological matrix (30). Hyaluronic acid obtained in this fashion sometimes contains low concentrations of avian proteins, which can provoke sensitisation problems.

2) Bacterial fermentation. Hyaluronic acid occurs in Gram positive bacteria (*Streptococcus Zoepidermicus*) in the form of a mucoid capsule that envelops the bacterium (24). This hyaluronic acid "covering" infiltrates the host body without inducing an immune response. The mean molecular weight of the hyaluronic acid obtained through

fermentation is 1 to 4 Million Dalton (MDa). However the molecular weight can be manipulated over a wide range by simply changing fermentation parameters such as temperature and glucose concentrations.

Balazs and Denlinger (5) outlined four characteristics that a material should have to be an acceptable material for viscosupplementation :

- 1) Tissue and blood compatibility (not immunogenic) ;
- 2) Permeability to metabolites and macromolecules (to allow diffusion of blood proteins and smaller molecules through the molecular network) ;
- 3) Appropriate rheological properties (viscoelastic properties similar to those of human synovial fluid) ;
- 4) Slow elimination rate (to maintain extended protection).

Hyaluronate derivatives fulfil these requirements better than hyaluronic acid alone.

Clinical experience

Patients judged eligible for total hip arthroplasty (THA), presenting with continuous hip pain (also at night), requiring daily intake of NSAID's or analgesics, a disabling gait and need of walking aid, and regardless of potential complications, most likely to have a significant improvement with surgery, were offered a viscosupplementation treatment.

We present here the initial results of patients treated with viscosupplementation.

PATIENTS AND METHODS

Sixty patients, 32 males and 28 females, responding to the eligibility criteria listed below, received viscosupplementation with one of the following preparations : Orthovisc (molecular weight : 1.0-2.9 million Daltons and extracted from rooster combs) (n = 20), Synvisc (Hylan GF 20 with an average molecular weight of 6.0 million Daltons) (n = 20) and Fermatron (synthetic hyaluronic acid analogue) (n = 20).

Eligibility criteria

Patients aged between 30 years and 70 years, suffering from idiopathic osteoarthritis and reporting a VAS score for pain greater than 30 (on a 100-point scale ; 0 no pain and 100 "the worst pain imaginable") are eligible when they have persistent pain for longer than 1 month despite use of analgesics or NSAID's. They should be candidate for surgical treatment with a THA and be able to understand the information relative to viscosupplementation and give informed consent.

Exclusion criteria

Pregnancy,
 Contraindications to intra-articular hyaluronic-acid preparations,
 Major hip dysplasia or congenital abnormality of the hip,
 Patients with systemic corticosteroids or intra-articular corticosteroid injections,
 Contra-lateral THA or hip arthroscopy in the last 6 months,
 Oral or parenteral anticoagulant therapy,
 Previous hyaluronic acid hip infiltrations,
 Skin diseases or infections,
 Signs of haemarthrosis,

Treatment

Each patient could receive maximum three infiltrations with one of the three viscosupplementation products with an interval of two weeks. Injection of the viscosupplementation was performed under sterile conditions by the same orthopaedic surgeon (MM) in all patients. After skin cleaning a lumbar puncture needle was inserted from a lateral approach. Layer by layer local anaesthesia was performed using lidocaine 1%. Iodinated contrast agent was injected and fluoroscopy was used to check the needle positioning into the joint cavity. Any present effusion was carefully evacuated prior to injection.

After resting for two hours the patient was allowed to walk and to return home. The patient was advised to rest at home until the next morning.

In case of bilateral hip OA, one hip per patient was included in the study.

Continuing oral medication for osteoarthritis was authorised if taken at a regular dose for more than 3 months prior to inclusion in the study.

Evaluation

Six weeks after the last infiltration all patients provided information on their pain intensity, measured with a 100-point VAS, and on the daily use of analgesics and NSAID's. Six months after the last injection patients were contacted to evaluate the success of the treatment and the need for surgery.

All side effects and complications of viscosupplementation were noted.

RESULTS

Overall the mean VAS score decreased from 66.3 to 49.3 six weeks after the last infiltration in the 60 patients included in this study. Prior to viscosupplementation 39 of the 60 patients needed daily analgesics and/or NSAID's. Six weeks after the last infiltration this number decreased to 16 patients, which represents a 59% decrease in the patients' need for daily analgesics.

Patients were only considered for THA when pain increased in intensity and could no longer be controlled by means of pharmacological treatment.

Six months after the third infiltration, 27 of the 60 patients (45%) were not operated.

In the three groups of 20 patients each, we noticed no differences in efficacy, but given the small size of the groups, no statistical analysis was done.

The treatment was generally well tolerated, although some patients reported stiffness and pain the first days after the injection. No external symptom was noted. Side effects of inflammatory origin were noted in 5 patients (8.3%) : two had a Synvisc infiltration (10%) and the other three had an infiltration with Orthovisc (15%). No infections of the hip joint were seen.

DISCUSSION

Injection of osteoarthritic joints and especially knee joints is frequently reported for the management of young sportive adults as a therapy that might prevent knee surgery (28). Our patient population consists of candidates for THA, with severe symptomatic osteoarthritis of the hip, and the use

of viscosupplementation in this population has as its main objective to delay surgical intervention. Six months after the last infiltration, still 45 % of our patients had not undergone THA.

These findings in patients with severe osteoarthritis of the hip are promising. When they can be confirmed in larger studies over an extended follow-up period, the minimal invasive character of the intra-articular injection compared to the invasive surgery of total hip replacement may offer an alternative for patients whose general condition may form an obstacle for prolonged general anaesthesia and long immobilisation.

The main objective of this study was to substantiate the impression in a small group of patients that different preparations of hyaluronic acid or its derivatives succeeded in postponing THA. The data are retrospectively retrieved from the patient's charts. The short follow-up period of 6 months only allows indication of a trend.

CONCLUSION

Viscosupplementation aims to restore intra-articular joint homeostasis that is disrupted by the degenerative joint changes. This technique has been in use for more than 25 years in the treatment of osteoarthritis of several joints and appears to be effective. Viscosupplementation is reasonably well tolerated and safe. Adverse events are possible (8.3%) but usually resolve quickly. In our series we could delay surgical intervention for at least 6 months in 45% of the patients. The efficacy and the potential financial advantages of this technique need to be confirmed in larger preferably prospective and randomised and blinded studies over a longer period.

ABBREVIATIONS

| | |
|---------|---|
| AAOS : | American Association Orthopaedic Surgeons |
| AE : | Adverse Event |
| HA : | Hyaluronic Acid |
| IA : | Intra Articular |
| LMW : | Low Molecular Weight |
| MDa : | Million Dalton |
| MMP : | Matrix Metalloproteinase |
| NASHA : | Non Animal Stabilised Hyaluronic Acid |

| | |
|---------|--|
| NSAID : | Non Steroidal Anti-Inflammatory Drug |
| OA : | Osteoarthritis |
| PAS : | Pain Analogue Scale |
| THA : | Total Hip Arthroplasty |
| VAS : | Visual Analogue Scale |
| VS : | Viscosupplementation |
| WOMAC : | Western Ontario and McMaster Universities Osteoarthritis Index |

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