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ABSTRACT

With the aging of the world's population, the prevalence of age-related diseases is continually increasing, especially osteoarthritis, the most common form of joint disease. In addition to its high prevalence, osteoarthritis has been correlated with high medical and social costs. Among the treatment methods, viscosupplementation (intra-articular injection of hyaluronic acid derivatives) has been gaining more prominence. The substances used are high molecular weight polysaccharides that, in addition to mechanical functions of weight distribution and joint lubrication, have anti-inflammatory properties and physical-chemical action on a variety of joint

characteristics. These effects are directly proportional to the molecular weight and concentration of the drug used and any cross-links that may be present in the drug. Viscosupplementation is a simple procedure and can be performed in outpatient clinics. It provides benefits regarding pain and function, and also favorably alters the course of the disease, through quantitatively and qualitatively improving the joint cartilage. It has a good safety profile and favorable cost-effectiveness relationship, and is indicated both for osteoarthritis cases and after an arthroscopic procedure.

Keywords – Hyaluronic Acid/administration & dosage; Hyaluronic Acid/therapeutic use; Osteoarthritis

INTRODUCTION

Osteoarthritis, the commonest form of joint disease, is a condition of multifactorial origin that leads to joint cartilage degeneration and affects all components of the joint. It is a slow, progressive and debilitating process, with high prevalence in the adult population. Around 40% of individuals over the age of 65 years in the United Kingdom suffer from symptoms associated with osteoarthritis of the knees or hips⁽¹⁾.

There are more than 50 types of treatment for gonarthrosis⁽²⁾. The main non-surgical treatment options include pharmacological management using analgesics, non-steroidal anti-inflammatory drugs (NSAIDs)^(2,3), oral corticosteroids and disease-modifying drugs for osteoarthritis (DMDOA)⁽⁴⁾, especially glucosamine, chondroitin, avocado and soybean unsaponifiable extracts and diacerhein; orthoses^(5,6), acupuncture, physiotherapy, body and mind therapies^(2,7), intra-articular corticosteroid injections⁽⁸⁾ and intra-articular hyaluronic acid injection (viscosupplementation)^(9,10).

VISCOSUPPLEMENTATION

Properties

Viscosupplementation consists of injection of exogenous hyaluronic acid into diarthrodial joints, with the aim of restoring the rheological properties of the synovial fluid, thereby producing mechanical, analgesic, anti-inflammatory and chondroprotective effects. Hyaluronic acid is a high-viscosity polysaccharide that is produced naturally by the B cells of the synovial membrane. From a biochemical point of view, it is classified in the glycosaminoglycan (GAG) group⁽¹¹⁾. Under physiological conditions, it behaves like a salt and is therefore named sodium hyaluronate or hyaluronan⁽¹²⁾. Its physicochemical properties are determined by its molecular weight and spatial shape. High molecular weight molecules of hyaluronic acid interlink to form a high-viscosity solution that serve both as a lubricant and as a shock absorber⁽¹³⁾.

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Mechanism of action

Osteoarthritic joints present high activation of synoviocytes, which produce a variety of cytokines and enzymes related to this disease, such as interleukin (IL)- β 1, IL-6, IL-8, TNF- α , metalloproteinases, aggrecanases and nitric oxide (NO)⁽¹⁴⁾. Hyaluronic acid is an important modulator, especially through interaction with CD44 receptors that are present in fibroblast-like synoviocytes⁽¹⁵⁾. Therefore, in addition to the mechanical effects of promoting better force distribution, diminishing the pressure due to weight⁽¹⁶⁾ and recovering the rheological properties of the synovial fluid⁽¹⁷⁾, hyaluronic acid also acts biochemically. It diminishes the gene expression of the cytokines and enzymes that are associated with osteoarthritis⁽¹⁴⁾, and diminishes prostaglandin production⁽¹⁸⁾ and the intra-articular metalloproteinase concentration⁽¹⁹⁾. Its presence stimulates greater production of hyaluronic acid by the synoviocytes⁽²⁰⁾; it has an analgesic effect, thereby diminishing nerve impulses and the sensitivity of nociceptive nerve ends^(21,22); stabilizes the cartilaginous matrix⁽²³⁾; stimulates chondrocyte proliferation; it increases type 2 collagen and aggrecan production by chondrocytes⁽²⁴⁾; and diminishes the degradation of type 2 collagen⁽²⁵⁾.

Structural benefit

The structural benefit of viscosupplementation has been seen through second-look arthroscopy, performed one year after treatment started, in which the joint surface was seen to have a better visual appearance, compared with a placebo group⁽²⁶⁾. Increased cartilage volume was observed by means of imaging examinations; and biopsies performed before and after viscosupplementation showed that, six months later, the surface layer had been reconstituted, with better matrix quality, higher chondrocyte density and greater numbers of organelles inside⁽²⁷⁾. Diminished loss of joint space was observed one year after the procedure, also in comparison with the placebo group⁽²⁸⁾. From an economic point of view, there are increasing numbers of studies demonstrating that if viscosupplementation is incorporated into treatments for knee osteoarthritis, it may present a good cost-effectiveness relationship, including the capacity to delay a total knee arthroplasty⁽²⁹⁻³¹⁾.

Synthesis

Exogenous hyaluronic acid is produced from two sources:

- Avian origin: from poultry material (cock crest). This presents allergenic potential due to avian antigens. The following avian products are on the Brazilian market: Polireumin[®] (=Hyalgan[®]) and Synvisc[®]/Synvisc[®] One[™]; or
- Non-avian origin: Bio-fermentation products using bacteria (*Streptococcus zooepidermicus*). These have lower allergenic potential. The following non-avian products are on the Brazilian market: Suprahyal[®] (=Adant[®]), Suplasyn[®], Orthovisc[®], Osteonil[®] (=Ostenil[®]), Durolane[®] and Viscoseal[®].

In addition, in relation to hyaluronic acid synthesis, these substances can be classified into two types:

- hyaluronans: Long-chain molecules of avian or bio-fermentation origin, with a molecular weight of between 0.5 and 1.8 x 10⁶ Da (Polireumin[®], Suplasyn[®], Fermathron[®], Orthovisc[®], Osteonil[®] and Viscoseal[®]);
- hylan: hyaluronan molecule chemically modified by means of cross-links, with a liquid phase of higher molecular weight (around 6x10⁶ Da), through cross-linking connections between long chains of hyaluronan, and a solid portion (of infinite molecular weight) formed by even greater presence of links (Synvisc[®]).

Molecular weight

In relation to molecular weight, although all the hyaluronic acids used in orthopedics can be considered to have high molecular weight, the current products can be classified as:

- “Low molecular weight”, i.e. between 0.5 and 1 x 10⁶ Da, including: Suplasyn[®], Polireumin[®] (=Hyalgan[®]), Fermathron[®], and Suprahyal[®] (=Adant[®]);
- “Intermediate molecular weight”, i.e. between 1 and 1.8 x 10⁶ Da, including: Osteonil[®] (Ostenil[®]), Orthovisc[®], Durolane[®] and Viscoseal[®]; or
- “High molecular weight”, i.e. 6 x 10⁶ Da: Synvisc[®] and Synvisc[®] One[™].

The molecular weight, concentration and presence of cross-links on the viscosupplementation⁽³²⁾ results. However, this topic continues to be a matter of controversy. In relation to the protective physicochemical functions of hyaluronic acid, most of the abovementioned studies indicate that the effect is directly proportional to the molecular weight. However, a large proportion of these studies were in vitro experiences, and some

authors believe that the *in vivo* effects will not be the same, given that precisely the excessive molecular size (between 1 and 6×10^6 Da) would prevent hyaluronic acid from moving from the intra-articular environment to the intercellular environment, such that it would not have the capacity to act on synoviocytes and chondrocytes⁽³³⁾. According to these authors, products with molecular weight between 0.5 and 1×10^6 Da would have the best *in vivo* effects. However, because of the great heterogeneity between studies, the principal reviews and guidelines have not shown any advantage for any product over any other^(2,9,10). In relation to pain, it can be affirmed with greater certainty that both the *in vitro* results and the *in vivo* results indicate that there is a direct relationship between molecular weight and analgesia.

Indications

Viscosupplementation is indicated for treating osteoarthritis, in order to recover the rheological properties of the synovial fluid, achieve analgesia, improve function and regenerate the joint cartilage articular. It is also indicated after arthroscopy.

Practically any osteoarthritic joint can be infiltrated. The great majority of studies have been on knees, but intra-articular injection of hyaluronic acid has also presented good results in hips, shoulders, ankles, elbows, hand and feet^(34,35). Viscosupplementation is done as an outpatient procedure, and the application method has only been well established for knees. It is still a matter for discussion in relation to other joints, for which the quantity to be applied and the frequency of applications will depend on the characteristics of the product and the experience of the professional.

In knees, hylan G-F 20 is the only drug that enables a single application of 6 ml (three injections of Synvisc® Classic or one injection of Synvisc® One™)⁽³⁶⁾. On the other hand, with hyaluronans, one injection per week should be applied, for three to five weeks^(9,37). Sodium hyaluronate has an intra-articular half-life of 13 hours, while the half-life of hylan G-F 20 is 1.5 days (liquid phase) and 8.8 days (solid phase), probably because of the presence of cross-links. This may explain why good results were obtained with only one application⁽³⁸⁾. One study reported application of three doses of a hyaluronate of 1.3×10^6 Da (15 mg/ml; 2 ml per injection; Orthovisc®) immediately after arthroscopy, and showed that there was an improvement in the results from arthroscopy through intra-articular

injection of hyaluronic acid⁽³⁹⁾. However, other than hylan G-F 20, no other presentation available in Brazil has been used to study the effect of injecting multiple doses, as one, two or three injections per week, in order to really prove that the agent can be injected in a single dose with equal or superior results.

On the other hand, intra-articular injection of hyaluronic acid of two million Daltons diluted in 10 ml (Viscoseal®) immediately after arthroscopy showed that the functional and analgesic results obtained through arthroscopy were maintained up to two years after the arthroscopy, and much more so in the injected group than in the group that only underwent the operation⁽⁴⁰⁾. Arthroscopy washes away the layer of hyaluronic acid that covers the cartilage and synovial membrane and protects the underlying tissues from damage due to free radicals and other destructive elements. A few days are needed for the synovium to start producing this hyaluronic acid again. Viscosupplementation after arthroscopy has the function of replacing this film, as well as the analgesic and anti-inflammatory properties already cited, thereby diminishing the inflammatory pain caused by surgical aggression. The main care to be taken here is to close the arthroscopic portals well, because this anti-inflammatory property of hyaluronic acid injected after arthroscopy will inhibit the inflammatory healing response and may give rise to a synovial fistula through the arthroscopic portal.

RESULTS

The clinical results from viscosupplementation are important and its benefit has now been well established. Meta-analyses and systematic reviews have proven its efficacy, with statistical significance shown in comparison with placebo. The best results from viscosupplementation occur between the fifth and thirteenth weeks. Viscosupplementation has also been shown to be more effective than intra-articular injection of corticosteroids, particularly from the fifth week onwards. Over the first four weeks, it is not superior, probably because of the fast and potent action of corticosteroids, which act to directly paralyze the inflammatory action of the joint, while hyaluronic acid has a role that is considered to be more “modulatory”. However, the benefits from infiltration with corticosteroids disappear after two to four weeks and, from the fifth week onwards, there is already a statistically significant difference favoring viscosupple-

mentation. The benefit from this may last from six months to two years. It is known that using drug associations, i.e. infiltration of corticosteroids together with hyaluronic acid, improves the initial results from viscosupplementation⁽⁴¹⁾. It is also known that this alleviates pain better than using acetaminophen and that it has a treatment effect similar to use of COX2 inhibitors (from the point of view of analgesia)^(42,43).

It is known that the patients who would benefit most from this treatment are those whose disease is at an initial stage (low degrees of osteoarthritis) and who use their joints more actively. Prior joint washing improves the results⁽⁴⁴⁾, as does correctly respecting the application regime, according to the type of hyaluronic acid used. The intra-articular positioning of the needle at the moment of the infiltration is fundamental, and injection of medication outside of the interior of the joint has been put forward as the main cause of poor results. Adverse effects may occur in around 4.2% of the patients, and these present as effusions, arthralgia, heat and joint erythema⁽⁴⁵⁾. In such cases, as in any acute arthritis crisis, the treatment should consist of ice, rest, limb elevation and use of anti-inflammatory medication, if not contraindicated. If necessary, the joint can be punctured. Analysis on the synovial fluid will confirm that these are not cases of infection. After controlling the allergic or inflammatory reaction, the effect of viscosupplementation remains. Pseudo-sepsis, i.e. prominent aseptic synovitis with heat and large-scale joint effusion (which may occur after infiltration), seems to occur more frequently with hylan infiltration and with infiltration of hyaluronan of avian origin. It is not known whether

this is due to cross-links of the hylan, or an allergic reaction to avian's proteins. Nonetheless, there is no doubt that the other complications are more related to infiltration of hyaluronic acid that does not take place into the joint space.

FINAL REMARKS

It is fundamental to bear in mind that the Osteoarthritis treatment is multimodal. The causes of osteoarthritis need to be identified, along with its severity. Mechanical deviations should be corrected. Medications do not compensate for deviation from the axis. Patients need to be educated about their disease and stimulated to take active measures regarding their treatment. The disease does not have a cure, but it can be controlled through the diet, physical exercise, use of orthoses and administration of medications. The usual treatment for osteoarthritis is improved through addition of viscosupplementation, which is cost effective. We do not know whether there is any better product, but we know that there are products with different characteristics. We believe that it is important for physicians to know about the hyaluronic acid that they intend to use and thus to respect its characteristics. Physicians need to bear in mind what their objectives are (analgesia, chondroprotection, practicality or safety), in order to optimize the viscosupplementation as much as possible. In 2012, it is expected that a Brazilian study showing that viscosupplementation is also cost effective in this country will be presented.

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