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Review article

Viscosupplementation: Techniques, indications, results

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ABSTRACT

Viscosupplementation by hyaluronic acid (HA) injections is frequently used for local treatment of osteoarthritis (OA), due to ease of use and good tolerance. A profusion of linear or reticulated HA derivates are marketed, with varied characters and levels of evidence. Viscosupplementation has demonstrated moderate but significant efficacy (20%) versus placebo in terms of pain and function, with a high rate of responders (60–70%) in knee osteoarthritis. It allows reduced administration of opioid analgesics and NSAIDs, with improved risk/benefit ratio, and may delay joint replacement. Cartilage protection remains to be proven. Clinical efficacy shows 1–4 weeks' later onset than corticosteroids, but is maintained for 6 or even 12 months. Systematic association of corticosteroid and HA injection is not justified, and an interval has to be left before undertaking arthroplasty. Intra-articular injection of HA requires a skilled specialist, and may be difficult in a non-swollen joint; some tips and tricks may be helpful. In other joints than the knee, radiologic or ultrasound guidance is recommended. The efficacy of viscosupplementation is a matter of ongoing debate, after discordant findings in some meta-analyses. Some poor results may be due to inappropriate use of HA injections, poorly adapted to the patient's OA phenotype. Viscosupplementation is a treatment for chronic moderate symptomatic OA, and not for flares with joint swelling. Application in sport-related chondropathy has yet to be properly assessed. The optimal response profile remains to be determined. The ideal indication in the knee seems to be moderate femorotibial OA without swelling. Results have been generally disappointing in hip osteoarthritis but promising in OA of the ankle and shoulder (with and without rotator cuff tear). Further studies are needed to determine response profile and optimal treatment schedule, according to the joint.

1. Introduction

Viscosupplementation, consisting in intra-articular injection of hyaluronic acid (HA) derivatives, is the main local treatment in osteoarthritis (OA) along with corticosteroid injection. It has been used in humans for more than 30 years, mainly in OA of the knee but increasingly in other joints.

A very large number of clinical trials have been performed; in knee OA, several meta-analyses gave discordant results, sparking controversy around the efficacy of the technique.

The present update aims to determine good practice and indications for viscosupplementation as local treatment for symptomatic OA, so as to optimize efficacy.

1.1. Action of intra-articular HA injection [1]

HA, the main constituent of cartilage and synovial fluid, is a long polysaccharide (glycosaminoglycan) chain, with a hydrophilicity that gives it the viscoelastic properties underlying the mechanical properties of cartilage (shock absorption) and synovial fluid (joint lubrication, cartilage protection).

OA involves qualitative and quantitative HA deficiency: mean molecular weight (MW), corresponding to chain length, is 4–5 mD in the healthy joint and 2–4 mD in OA, with concentration halved.

Injecting exogenous HA into the joint is intended not only to restore the mechanical properties of the cartilage and synovial fluid, but also to achieve certain biological effects. The HA is taken up by specific joint receptors, providing numerous beneficial effects: moderate anti-inflammatory action, reduced cytokine-induced enzyme production, anti-oxidant action, anabolizing effect on cartilage, and direct analgesia by masking the joint nociceptors.

Its visco-inductive properties (synoviocyte-mediated stimulation of endogenous HA production) could account for the prolonged

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Table 1
Hyaluronic acid forms available in France in 2014.

Hyaluronic acid	Forms
Linear HA	Sodium hyaluronate: (MW 0.5–3 mD) Multi-injection: Adant®, Arthrum®, Euflexxa®, Go-on®, Hyalgan®, Orthovisc®, Ostenil®, Sinovial®, Structovial®, Synocrom® Single-injection: Arthrum monodose®, Coxarthrum®, Synochrom forte®
Reticulated HA	(MW > 3 mD) Hylan GF-20: Synvisc®, Synvisc one® Sodium hyaluronate: Monovisc®, Synocrom forte one® happycross NASHA: Durolane®
Combined HA	Single-injection Mannitol: Ostenil plus® Happyvisc®, Happycross® Chondroitine sulfate: Arthrum HCS®, Synovium surgical®

NASHA: non-animal stabilized hyaluronic acid.

efficacy of injected exogenous HA despite its short joint residence time, as it is rapidly degraded after injection.

1.2. What forms of HA are available in France?

In France, more than 12 HA derivatives are on the market, classified as "devices", except in the case of Hyalgan®, which counts as a drug with market authorization in knee OA.

Two groups can be distinguished (Table 1): low-MW linear HA; and reticulated HA (3-dimensional structure of linked HA chains), with higher MW and probably slower degradation and longer joint residence, often administered as a single-injection.

Low-dose (1 ml) preparations are available for small joints.

Preparations with associated adjuvants (mannitol, sorbitol, chondroitin sulfate), reticulated or not, have come onto the market more recently, with the aim of prolonging joint residence, although this has not been demonstrated.

HA derivatives differ not only in reticulation and MW (chain length) but also in origin (avian: cockscomb; synthetic: bacterial fermentation), sterilization process (heat or ultra-filtration), conditioning (2–6 ml syringes) and validation on high-quality therapeutic trials.

The reference forms, which have been the focus of most studies, are Hyalgan® for linear HA and Synvisc® for reticulated HA. The clinical impact of the various characteristics of HA remains unclear, and no product can be clearly recommended over another.

2. Technique

Injection technique is of prime importance for both efficacy and tolerance. Injection must be strictly intra-articular, which is not easy to ensure in non-swollen joints, which are the main indication for viscosupplementation.

In the knee, 10–30% of injections performed by senior physicians are known to be defective [2]. A lateral lateropatellar approach has been shown to be clearly preferable; anterior approaches show high rates of failure and poor tolerance. Local reaction rates of up to 30% have been found for anteromedial injection [3].

In the hip, shoulder and thumb joints, success is even less sure, and radiologic guidance is recommended.

2.1. General rules for injection

The classic technique for HA knee injection is presented in Fig. 1.

The general procedure is as follows:

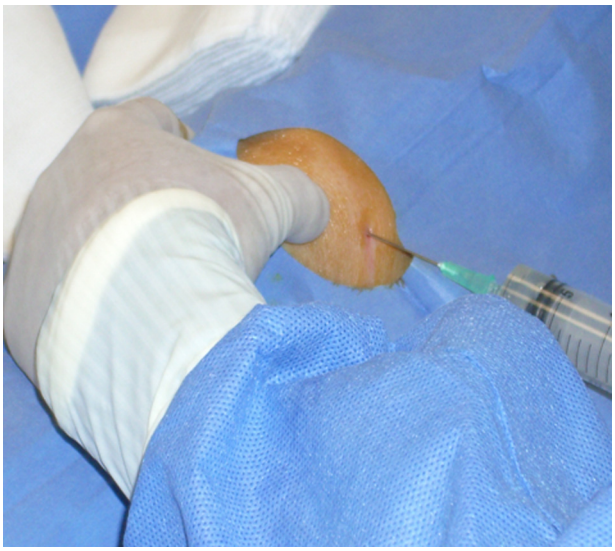

Fig. 1. Usual HA injection technique in non-swollen knee. Introduction of 21-gauge needle by lateral lateropatellar approach (1–2 cm below and down from the superolateral edge of the patella, knee in extension or slight flexion, quadriceps relaxed). Prior lateral subluxation of the patella, imposed by the other hand, facilitates the sensation of capsule passage. Attempted synovial fluid aspiration. Then injection of 2–6 ml HA without resistance or pain. Withdrawal of needle and mobilization of knee in flexion-extension.

- relevant personalized prior information to patient;
- asepsis as in joint corticosteroid infiltration. Certain HA derivatives, like ready-to-use corticosteroid syringes, do not have sterile exterior conditioning (outer surface of syringe) and this is to be borne in mind;
- choice of appropriate approach according to joint;
- appropriate needle caliber (21-gauge for reticulated derivatives);
- aspiration of any synovial fluid;
- injection without resistance or pain;
- joint mobilization after injection;
- record of HA batch number;
- 24 hours' relative rest (no sports, no effort with the limb).

2.2. Tricks and tips

Some tricks and tips may be useful in difficult cases: obesity, postoperative fibrosis, severe femoropatellar OA, etc.:

- the back-flow technique (Fig. 2), which we developed and validated for the knee, provides very precise injection, with the needle positioned intra-articularly in 100% of cases when back-flow is clearly obtained [4]. The method can be applied in other joints, notably the ankle, although not yet validated;
- the "squishing sound" confirms that injection has been successful. It can be heard in passive flexion-extension of the knee after injection of an HA derivative with air-bubble once the needle has been withdrawn. This frequently employed test has been validated [5], but is just a retrospective check, as it requires the substance to have been actually injected;
- in some less easily accessible joints (hip, shoulder, thumb), radioscopic guidance with a small injection of contrast medium (Fig. 3) or ultrasound guidance is recommended. Ultrasound has advantages: with no radiation and no risk of allergic reaction, it detects deep effusion; however, it requires a trained operator and special asepsis.