Review

Hyaluronic acid in ankle osteoarthritis: why evidence of efficacy is still lacking?

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ABSTRACT

Intra-articular injections of hyaluronic acid (HA) are useful in the treatment of osteoarthritis (OA), as shown by studies on knee, hip, and trapezio-metacarpal joints. The positive results can be explained by several factors: the restoration of elastic and viscous properties of intra-articular fluid, the anti-inflammatory and the anti-nociceptive activity, and the normalisation of hyaluronan synthesis and inhibition of hyaluronic acid degradation.

However, evidence of efficacy of hyaluronic acid in ankle osteoarthritis is still lacking: several studies have been performed without a control group, or have shown similar results to those obtained with different therapeutic procedures.

The aim of this paper is to analyse the reasons which can explain the discrepancy between the sound biological background and the inconclusive clinical results.

First, it must be considered that the ankle joint, from a biomechanical point of view, is more complex than other joints, and that greater stress is sustained by the articular surfaces. Second, the limited benefit can be related to the use of hyaluronic acid mostly in cases of post-traumatic osteoarthritis, where the treatment must be addressed to solve the biomechanical problems, and then to restore the rheological properties of the ankle joint. A third important explanation of the failure may be the improper technique of administration, that has been performed in all studies, but one, without imaging guidance. Indeed, it is well known that hyaluronic acid, if not delivered directly into the intra-articular space, is unlikely to be effective.

Introduction

Osteoarthritis (OA) is a chronic disease, characterised by loss of articular cartilage, subchondral sclerosis, joint deterioration, and biochemical and biomechanical alterations of extracellular matrix (1).

Pain, muscle weakness, limited range of motion and increasing disability are usually complained by patients.

None of the therapeutic options available, such as analgesics, non-steroidal anti-inflammatory drugs (NSAIDs) and COX-2 inhibitors, has been shown to delay the progression of OA or reverse joint damage in humans (2). Moreover, some NSAIDs, in pre-clinical studies, have shown a deleterious effect on cartilage metabolism (3) because of their catabolic effects (4).

Viscosupplementation (VS) by intra-articular injections of hyaluronic acid (HA) is useful in the treatment of OA in different joints, as confirmed by several studies on knee, hip, and trapezio-metacarpal joints (5-7).

However, the trials performed in ankle OA have shown inconclusive results (8).

The aim of this article is to analyse the reasons which can explain these results, and to suggest lines of future research.

Physiological background

In physiological conditions, the synovial fluid has different functions, which limit the axial forces on the articular surface, and decrease the friction between joint surfaces (9).

These actions include: shock absorption, traumatic energy dissipation and storage, lubrication and protective coating of the articular cartilage, and of the inner lining of the synovial membrane.

In both synovial fluid and articular tissues, HA acts as viscous fluid or elastic solid, being a lubricant at low shear, and a shock absorber at high shear (10).

Besides its rheologic properties, HA influences a number of other factors critical to the articular environment (11).

When the balance between mechanical stress and protective factors is impaired, the OA process takes place.

In OA, the concentration of HA in the synovial fluid is decreased, due to dilution effect; its molecular weight is also reduced, as well as the interaction between hyaluronic molecules, related to fragmentation, and free radical degradation (12).

The loss of lubrication and the increased stress forces can disrupt the collagen network surrounding the joints (13), increasing the vulnerability of articular cartilage to damage (14).

The VS rationale is based on the removal of pathologic synovial fluid, and replacement with products that restore the concentration of hyaluronan towards normal levels (15).

Besides fluid replacement, HA also plays a major role in biologic activation, or biosupplementation, that may decrease the symptoms and the disease progression (16).

The mechanisms, whereby intra-articular injection of hyaluronan derivatives provides therapeutic benefit, can be summarised as follows (Table I):

1. restoration of elastic and viscous properties
2. anti-inflammatory effects
3. anti-nociceptive activity
4. normalisation of hyaluronan synthesis and inhibition of HA degradation (17).

When HA is injected into the articular space, it behaves as shock absorber, due to its viscoelastic properties (18): under low shear stress, it enables the joint to dissipate the mechanical damage and heat production; under high shear forces, it is responsible for elasticity.

The decreased migration of inflammatory cells and the lower levels of specific mediators explain the anti-inflammatory action of HA (19, 20). In particular, in joints treated with HA, the formation and release of prostaglandin E2 and bradykinin are reduced (14), and the activity of macrophages and leukocytes is inhibited (15).

The pain threshold decreases, due to the direct analgesia through inhibition of pain receptors (21). The analgesic effect is also provided by a direct action on synovial nerve endings and stimulation of synovial lining cells (22).

Table I. Beneficial effect of hyaluronic acid (modified from Carpenter (34)).

Action	Target	Result
Inhibition	Lymphocyte transformation	Slow down the progression
	Phagocytic activity of macrophages and leukocytes	of joint damage
Promotion	Release of prostaglandins	Anti-inflammatory activity
	Normalisation of native hyaluronan synthesis	
	Production of tissue inhibitor of MMP-1	Anti-nociceptive effects
	Scavenging of free radicals	
	Proteoglycans synthesis by chondrocytes	Modified structural organisation towards
Protective	Effects on chondrocytes or cartilage explants from degradation by enzymes, IL-1, and oxygen-derived free radicals	normal appearance

Finally, injection of HA derivatives appears to stimulate synoviocytes to produce normal HA, that can favour an easier flow of water, which in turn allows for cartilage cells to be nourished (23).

The above-mentioned properties have been demonstrated in experimental studies. In a partial meniscectomy rabbit model of OA (24) and in equine cultured chondrocytes (25), the total proteoglycan synthesis is significantly higher in the hyaluronan group compared with the control group. Moreover, HA blocks the catabolic action of fibronectin fragments, as well as decreases the synovial expression of Interleukin (IL)-ß, and of the metalloproteinase (MMP)-3, in canine, bovine and rabbit cartilage models (26-28).

Finally, in a bovine model, HA, marked with a fluorescent probe, penetrates by up to 300 micron from the surface in a 48-hour period, specifically targeting the chondrocytes, as shown by its recognition in the lacunae surrounding these cells (29).

All these effects have been also confirmed by studies in human cartilage explants, cultured *in vitro* (30).

Clinical studies

Only few studies have been performed in ankle OA and, among these, four were randomised controlled trials (RCTs) (level of evidence 1) (18, 31-34), while seven studies (29, 35-40) were case series (level of evidence 4).

In all these studies, patients suffering from post-traumatic Kellgren-Lawrence (K-L) grade II–IV ankle OA were enrolled. Different HA preparations (Low and High molecular weight HA [LMW and HMW]) were used, and patients received 1 up to 5 injections. Only in one study, the injections were performed by means of image guidance (fluoroscopy) (32). Clinical benefit was evaluated by means of different scales (VAS, AOS, AOFAS, SF-12, SF-36, WOMAC), and the follow-up period varied from 6 to 18 months.

In studies performed without control group (29, 35-40) (Table II), an improvement in all the outcome measures was reported, with the effect lasting for 18 months (37). However, it is not clear from reports whether the pain reduction was clinically significant, and / or could be ascribed only to a placebo

Table II. Case series.

Authors	Patients	Age	Imaging	HA	Dose	Follow-up	Results
Mei Dan (29)	15	43	No	LMW	1 x 5 weeks	7 months	Positive
Sun (35)	75	50.2	No	LMW	1 x 5 weeks	6 months	Positive
Luciani (37)	21	45	No	HMW	1 x 3 weeks	3 months	Positive
Witteveen (38)	55	41	No	HMW	1 or 2*	6-9 months	Positive
Witteveen (39)	26	43	No	HMW	1 or 2 or 3**	6 months	Positive

*The second injection was offered after 3 months. **The interval between injections was 1 week. Valiveti (36) and Hanson (40) are not reported due to the small number of cases reported (2 and 5, respectively).

Table III. Randomised controlled trials.

Authors	Patients	Age	Imaging	HA	Dose	Control	Follow up	Results	HA *vs*. Controls
Salk (18, 31)*	17	58.8	No	LMW	1 x 5 weeks	Saline	6 months	Positive	No difference
Cohen (32)	30	49.8	Fluoroscopy	LMW	1 x 5 weeks	Saline	6 months	Positive	No difference
Karatosun (33)	30	55.1	No	LMW	1 x 3 weeks	Exercise	12 months	Positive	No difference
Carpenter (34)	26	55.1	No	HMW**	1 x 3 weeks	Arthroscopy	13 months	Positive	> HA (moderate)

**These authors presented their results in two different journals. **After arthroscopic lavage of ankle OA.

effect. In addition, the lack of controls does not allow definitive conclusions on the efficacy of HA.

The level 1 evidence studies are more qualified to assess the therapeutic efficacy, but also these trials show several limitations (no clear patients randomisation, imbalance of baseline characteristics between intervention and control groups, statistical weakness), and therefore have to be considered as low quality studies.

In these trials (18, 31-34) (Table III), patients treated with HA showed a significant decrease in pain and disability at 6 months (18, 31, 32), with the effects lasting 12-13 months (33, 34). Besides the reduction of these parameters, an improvement in ankle sagittal ROMs, and gait quality was observed (33).

The authors in any study found difference between the HA and the controls groups. In particular, in the studies performed by Salk (18, 31) and Cohen (32), the patients, treated with a 1–2 ml phosphate-buffered saline solution injection, reported a similar improvement in all parameters evaluated. Analogously, positive results were observed in patients, who followed a 6-week exercise therapy (muscle strengthening and ankle ROM exercises) (33), and after arthroscopic lavage of OA ankle joint (34).

On the basis of these observations, no clear evidence on the efficacy of HA in reducing pain, and improving function, in ankle OA, is provided.

Hypotheses about the limited efficacy

As shown in previous paragraphs, there are sound biological reasons which can explain the positive effects of HA in OA, and its superiority in comparison to conventional therapies in the treatment of hip and knee OA (8).

Indeed, VS is included in the guidelines for the treatment of the disease of these joints (35, 41).

Why the results in ankle OA are inconclusive without significant differences among HA therapy and other therapeutic options?

Several factors can explain these discrepancies:

a. the anatomic and functional specificity of ankle joint;

b. the characteristics of OA patients enrolled;

c. the improper technique of administration of HA without imaging guidance.

a. The ankle joint, anatomically and functionally, is more complex than other joints, which are usually treated with positive results with HA (hip, knee) (8). First of all, it must be considered more than a simple uniaxial hinge, from a biomechanical point of view, because its axis is oblique (42). The movements are therefore triplanar, and many stresses are sustained by the articular surfaces.

On this joint, during stance, the reaction forces applied are 4 times the body weight, and, for that reasons, the structure, metabolism, physical properties are different from other joints (43).

Indeed, in the comparison with knee cartilage, ankle chondrocytes synthesise proteoglycans at an higher rate, confirmed by the abundant content of water, and show a decreased response to catabolic factors (IL-1 and fibronectin fragments) (44). All of these factors are responsible for the increased stiffness and reduced permeability of ankle cartilage.

On the basis of these observations, it can be suggested that ankle cartilage is more resistant to damage (43), and has a greater capacity for repair (45).

However, when a certain threshold is overcome, this healing potential is no more adequate, and OA can take place.

From a clinical point of view, pain is the alarm bell of an important articular damage; in fact, pain does not arise from the cartilage lesion itself, but is most probably caused by the stimulation of the highly innervated subchondral bone underneath the cartilage defect, induced by repetitive high fluid pressure during walking (46).

b. Another possible reason for the limited benefit of HA in the treatment of ankle OA can be related to its use mostly in post-traumatic OA (47); indeed, significant differences exist among idiopathic and secondary OA.

In primary OA, the articular injury depends exclusively from a cartilage degeneration, induced by several factors (age, sex, overweight, metabolic diseases, drugs, etc.) (48), while in post-traumatic OA, besides these factors, the cartilage damage is the result of bones fractures, and/or repeated soft tissue injuries, such as capsule, ligaments and tendons traumas (49).

In these conditions, after the recovery from damage, the optimal biomechanical function and alignment may be not restored, an instability can be generated, and ankle joint can be further stressed.

The observation that VS does not appear to benefit patients with post-traumatic (50) ankle OA can be possibly explained by the fact that, in this case, the treatment must be firstly addressed to solve the biomechanical problems, guilty of the OA process (33), and then to restore the rheological properties of ankle joint.

Finally, it must be considered that, being ankle traumas often sports-related, patients suffering from OA are, on average, relatively young (51). These subjects wish to be physically active without any discomfort, and therefore are less satisfied after treatment, when they still complain of a little pain.

The partial pain relief, sometimes reported in the studies, can explain the declared limited efficacy, the high dropout percentage and the low satisfaction.

c. In all studies (18, 29, 31, 33-40), but one (32), the injections have been performed blindly, without imaging guidance. This can be a valid explanation of several unsatisfactory results, because there is evidence that about one third of intra-articular injections are not delivered into the intra-articular cavity, when performed without a visual aid (52).

Indeed, it is well known that hyaluronan products, if are not delivered directly into the intra-articular space, are unlikely to be effective.

In this regard, ankle joint presents many technical difficulties of injecting intra-articularly, due to its complex anatomy, still further complicated from the OA joint changes. Moreover, in a recent study, Woo *et al*. (53), evaluating the most common portals used in arthroscopic procedures, reported an high number of variations in the neurovascular structures, that can be injured during injections.

The use of appropriate imaging guidance has important advantages: first, it allows the needle placement into the articular space, without harming nerves and vessels; second, it permits the removal of all accessible OA synovial fluid, that could dilute the drug; third, it reduces the adverse reactions (pain, swelling, infection), consequent to failed injections.

Ultrasound has to be preferred to fluoroscopy, because is simple, fast (7–10 minutes), economic and safe; it does not require the use of contrast media, allowing the infiltration in patients intolerant to iodised contrasts. Moreover, it can be repeated without any limits, it is able to reveal the position of the needle, and, by means of continuous colour Doppler monitoring, to evaluate its distance from vessels (6).

Conclusions

It is our opinion that, at present, it is impossible to draw any conclusion about the efficacy of viscosupplementation by intra-articular injections of HA in the treatment of ankle OA.

In addition to topics previously taken into account (primary or post-traumatic OA; imaging guidance), further questions are still open:

1. What K-L grade mostly benefits from HA injections?
2. Which patients (young or older) are eligible for VS treatment, and can better respond to the therapy?
3. Which is the best dose regimen (type of HA preparation (54), number of injection, injection per week)?
4. Which outcomes measures are the best to demonstrate the effects of therapy?

Therefore, further high quality studies, with appropriate criteria, are needed, before abandoning this new option, which, on a theoretical level, seems to be very useful in the therapy of this very common and disabling condition.

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