I.S.Mu.L.T. Hyaluronic acid injections in musculoskeletal disorders guidelines

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Summary

Intra-articular and peri-articular hyaluronic acid (HA) injections are widely used to treat several musculoskeletal pathologies. Although clinical
outcomes are often positive for different conditions, an holistic consensus on this topic is still lacking. Our work is divided in two main sessions: in the first section we analyzed the preclinical bases for HA treatment in musculoskeletal pathologies, while in the second part we discussed the evidence on the use of HA injections in each district of musculoskeletal system. The aim of this work is to provide to the physician a feasible guideline rapidly to consult in the clinical practice.

Level of evidence: Ia.

**Approach to guidelines**

These recommendations developed through a process of systematic review of the literature and expert opinion, to be used to improve the quality of care and rationalize the use of resources. Clinical decisions on individual patients require the application of the recommendations, based on the best scientific evidence and clinical experience of the physician.

**Methodology**

The Authors were divided into four groups:
- a coordinator conceived and organized the work and the groups, and selected the most important questions on the topic at hand;
- a overseeing group controlled the development of the work and discussed the recommendations;
- the group of the experts individually received a question and developed the answers according to the rules of EBM, when it was possible;
- the group of preparation and evaluation of literature drew up the text and assisted the group of experts in evaluating the literature.

**Methods and criteria of study selection**

For the research were consulted the following databases:
- PubMed
- Embase
- Google Scholar
- Cochrane Library.

Randomized controlled trials (RCTs); systematic reviews; to follow if missing the first two, the other levels of evidence. The literature is updated at December, 2016.

**Level of evidence**

<table>
<thead>
<tr>
<th>Level of evidence</th>
<th>Criteria for analysis and inclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Meta-analyses and systematic reviews of randomized controlled trials (RCTs) of high quality, or RCTs with minimum or low risk of bias. Systematic reviews of high quality relative to cohort studies or case-control.</td>
</tr>
<tr>
<td>II</td>
<td>Cohort studies or randomized case-control high quality, with minimal risk of confounding or bias and with high or discrete probability of causation.</td>
</tr>
<tr>
<td>III</td>
<td>Case-control studies and retrospective comparison of well-conducted with reasonable probability of causation.</td>
</tr>
<tr>
<td>IV</td>
<td>Non-analytic studies as case series or individual cases.</td>
</tr>
</tbody>
</table>

**Hyaluronic acid**

Hyaluronic acid (HA) is a non-sulfated glycosaminoglycan (GAG), formed by repetitive units of glucuronic acid and N-acetyl glucosamine, widely express in the extracellular matrix (ECM) to confer protection, shape and mechanical support to cells and tissues. HA for its composition and expression is a key-component of cartilage and tendon structures, where it contributes to viscoelastic properties1-5. Stiff segments, linked by flexible domains to confer a super-helix, form the 50-70% of the molecule6. Therefore, viscoelastic properties of HA solutions can therefore be explained by the development of a dynamic three-dimensional network formed by transient associations between stiff segments7-9.

However, the importance of this molecule depends in part by its structure and hygroscopic properties, in part by the interaction with a large number of surface and intracellular receptors: CD44 glycoproteins, ICAM-1 and RHAMM, HARE, and intracellular proteins binding the hyaluronic acid CDC37, RHAMM/IHABP, P-32 and IHABP410-12.

**Injection techniques and good clinical practice**

Intra-articular and peri-articular procedures should be accomplished in adequate clinical settings following evidence based medical recommendations and a point-to-point procedure13-15:
- collect history and clinical examination;
- obtain oral/written informed consent;
- prepare the equipment;
- prepare the patient;
- disinfect the skin before and after the injection;
- program follow-up evaluation.

The equipment required is:
- gloves/sterile gloves;
- sterile swabs and sterile drapes;
- prepacked sterile needles and syringes;
• disinfectant (iodopovidone/chlorhexidine);
• synovial fluid collection bottles;
• sterile ultrasound kit (only for US-guided injection);
• emergency kit\(^\text{16,17}\).

The choice of the right needle is mandatory, considering the characteristics of the target joint. A needle of 21 gauge should be preferred in large joints as the shoulder or the knee, while 23-25 gauge needles are indicated in small joints\(^\text{13}\). Deep joints as the hip required the adoption of spinal needles (length of 3,5 inches; 8-9 centimeters)\(^\text{18}\).

Clinicians should identify any possible contraindications to the procedure. Absolute contraindications are: systemic infections and bacteremia, articular infections, skin lesions in the area, osteomyelitis, septic arthritis, unstable coagulopathy and severe thrombocytopenia, allergy (hypersensitivity) to any of the components and pregnancy. Injections procedures should be carefully performed in patients that use anticoagulants or other medications that alter INR. Injections should be avoided in patients with prolonged bleeding time or platelet count < 100 000/μl\(^\text{18}\). Generally, adverse effects are local and well-tolerated. Common local side effects are redness and pain in the site of injection (<72 hours after injection). Septic arthritis is rare (1:1000), while some cases of calcium pyrophosphate dihydrate crystal deposition disease (CPPD) are documented to be exacerbated by hyaluronic acid injections. Cross-linked products were shown to have better side effects and longer lasting effects\(^\text{14}\).

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**Key points**

- The injection should always be performed respecting sterile standardized procedures. It is mandatory to carefully disinfect the area preferring chlorhexidine preparations, mixtures of chlorhexidine gluconate and ethyl alcohol, iodopovidone solutions and analogs.
- The choice of the needle should consider the type of injection, the characteristics of the target joint and patient.
- Injection could be precede by arthrocentesis, which is helpful to the diagnosis of underlying pathological process in selected patients.
- Patients should observe a waiting period of 20-30 minutes in an outpatient facility after the injection.

**KEY WORDS:** musculoskeletal injection, guidelines, hyaluronic acid, principles, accuracy, disinfection.

### Hyaluronic acid properties in joint disorders and osteoarthritis

It was demonstrated that HA should protect articular environment through several mechanisms of action: anti-inflammatory effect, chondroprotection, analgesic effect, subchondral bone protection and increased production of endogenous HA.

#### Anti-inflammatory effect

Several *in vitro* and *in vivo* studies suggest that anti-inflammatory action is determined by the reduction of the principal mediators of inflammation as IL-1\(^\text{21}\), TNF-α\(^\text{22}\), IL-6, IL-8\(^\text{23}\) and prostaglandin E2 \(\text{PGE}_2\)\(^\text{24,25}\). Interaction with CD44 leads to decrease in IL-1β and metalloproteinases (MMPs) in cartilage and synovial fluid\(^\text{21,26}\), decrease in PGE2 expression in synovial fluid\(^\text{27}\), increase of TIMP-1 production and inhibition of anti-inflammatory response\(^\text{28}\).

New products as HYADD-4 (Hyomvis®, Fidia Farmaceutici SpA, Abano Terme, Italy) and H/L-HA (Sinovial HL®, IBSA SA, Switzerland) may determine a better anti-inflammatory response\(^\text{29,30}\).

#### Chondroprotection

Chondroprotection is determined by the reduction of chondrocyte apoptosis and by the increase in chondrocyte proliferation and viability, with the consequent increase in the production of ECM components (GAGs and PGs)\(^\text{31-34}\). Increased viability and proliferation is due in part to the down-regulation of proteolytic enzymes as MMPs and aggrecanases (ADAMTS)\(^\text{35-38}\). Anti-apoptotic effects is linked to different mechanisms as Fas/Fas-ligand and mithocondrial function\(^\text{39-44}\).

#### Analgesic effect

HA seems to exert analgesic effects through different mechanisms. In part, this action should be explained by the modulation of nociception due to down-regulation of main inflammatory mediators, as PGE2 and bradykinin\(^\text{45-49}\). Furthermore, viscoelastic properties of HA should reduce mechanical forces transmitted to nociceptive endings\(^\text{50-52}\). Recent findings evidenced that HA can induce activation of k-opioid receptor (KOP), suggesting other possible pathways of analgesic activity\(^\text{53}\).

#### Subchondral bone protection

HA can directly reduce osteoblast expression of MMP-13 and IL-1β induced expression of MMP-3, ADAMTS-4 and ADAMTS-5\(^\text{54,55}\). HA should also act on osteoclasts enhancing expression of osteoprotegerin (OPG) and inhibiting RANK-ligand\(^\text{56,57}\).

#### Production of endogenous HA

HA injections determine a concentration dependent increase of endogenous HA production\(^\text{57}\). Endogenous HA concentration was found to be increased also at 3 and 6 months post-injection\(^\text{58-61}\).

**Key points**

- HA intra-articular injections could determine disease-modifying effects through several mechanisms of action: anti-inflammatory effect, chondroprotection, analgesic effect, subchondral bone protection and increased production of endogenous HA.
- Currently it is not clear whether any formulation is...
superior as disease-modifying molecule.
- New formulations (HYADD-4, H/L-HA) may determine a greater anti-inflammatory effect.

**Level of recommendation: A.**

**KEY WORDS:** hyaluronic acid, chondroprotection, cartilage, subchondral bone, anti-inflammatory, intra-articular, osteoarthritis, chondrocyte, osteoblast.

### Hyaluronic acid properties in soft tissues: tendons, ligaments and bursas

**Tendons**

HA should enhance tenocyte viability and proliferation and reduce collagen III production, while it is not well established if HA may determine increase in collagen I production.

**Keypoints**

- In Achilles tendinopathy, HA injections stimulate healing process, reducing adhesion formation and regulating the expression of vascular endothelial growth factor (VEGF) and type IV collagen.
- In rotator cuff diseases, HA injections exert mechanical (anti-adhesion) and biological effects (reduction of PGE2, C4S, IL-1 and modulation of leukocytes migration).
- In patellar tendinopathy, HA injections associated to rest should increase anabolic metabolism of tenocytes.

**Level of recommendation: B.**

**Ligaments**

Actually, there are no evidences that support the use of HA injections in ligament pathologies or a direct action of HA on ligament structure. Some trials suggest the possible role of early HA injection after ACL surgery

**Level of recommendation: D.**

**Bursas**

Some studies have recently investigated the possible role of US-guided injections importance in different bursas, including the subacromial bursa; however, it is not univocally known whether HA could improve the composition of the synovial fluid of bursa pathologies.

**Level of recommendation: D.**

### Hyaluronic acid in shoulder disorders

**Glenohumeral injections**

Intra-articular injections in glenohumeral joint are widely used in clinical practice and several studies promote the efficacy in short and medium term (Tab. I). Intra-articular injections in glenohumeral joint are proposed for different pathologies, as osteoarthritis and rotator cuff pathology and frozen shoulder.

**Level of recommendation: A.**

**Adhesive capsulitis**

Several Authors evaluated the role of HA injections in adhesive capsulitis, but in many studies patients affected by AC represent a subgroup. Injection therapy should be considered in a multimodal approach that includes capsular stretching and exercise therapy.

**Level of recommendation: B.**

**Subacromial injections**

Five studies were selected (Tab. II). Subacromial injections are proposed in rotator cuff pathology or subacromial space syndrome. This procedure should be ultrasound-guided to permit sufficient accuracy.

**Level of recommendation: A.**

**Key points**

- Intra-articular injections in glenohumeral joint should determine a great efficacy in osteoarthritis in short and medium term, while the procedure is not superior to other therapies in ROM improvement in adhesive capsulitis.
- Ultrasound-guided subacromial injections improve pain and function in rotator cuff pathology.
- There is lack of evidence about the possible role of HA in acromion-claviclar disorders.

**KEY WORDS:** hyaluronic acid, tendon, tendinopathy, ligaments, extra-articular.

### Hyaluronic acid in elbow disorders

**Lateral epicondylitis**

Lateral elbow pain could be reported in several pathologies as chondromatosis, chondral lesions, intra-articular loose bodies, elbow instability or posterior interosseus nerve syndrome. Thus, correct differential diagnosis is mandatory to achieve good clinical outcomes.

Several conservative modalities were described to treat lateral tennis elbow syndrome, while surgery is indicated only in refractory cases.

Only one RCT and few level IV trials investigated the possible role of HA in epicondylitis (Tab. III). These studies are heterogeneous for methodologies and outcome measures.

**Level of recommendation: B.**

**Elbow osteoarthritis**

Elbow is not a common site of osteoarthritis, characterized by cartilage loss, osteophytes formation and intra-articular loose bodies. The low prevalence should partially explain that the
role of HA is not well established and limited in secondary osteoarthritis. Only two case series investigated HA in elbow osteoarthritis (Tab. IV)\textsuperscript{96,97.}

**Keypoints**

- Low grade evidences support HA injections in elbow tendinopathies.
There are not sufficient evidences to recommend or avoid HA in primary and secondary elbow osteoarthritis.

No adverse effects were observed with HA injections in patients affected by elbow pathologies.

KEY WORDS: hyaluronic acid, lateral epicondylitis, elbow osteoarthritis, elbow stiffness, elbow injection of hyaluronic acid, medial epicondylitis, hyaluronan elbow, sodium hyaluronate elbow.

Hyaluronic acid in hip disorders

Only few randomized controlled trials investigated the use of intra-articular injections of HA in hip osteoarthritis and they are very heterogeneous for methodologies and type of HA used (Tab. V).

In a recent systematic review and meta-analysis, Piccirilli et al. concluded that HA represents a valid conservative therapeutic option for hip pathology, although there is lack of uniformity regarding choice of HA type, timing and number of injections.

Level of recommendation: B.

Keypoints

- Viscosupplementation is the best conservative treatment for osteoarthritis and it acts on pain reduction.
- Actually there is no uniformity regarding number or timing of infiltrative procedures.
- Ultrasound-guided infiltrative procedure is the best approach in terms of safety.
- In absence of comparative RCTs, no significant outcome differences seem to occur with different molecular weight HA formulations.
- Effectiveness on symptoms is only demonstrated in mild to moderate osteoarthritis, while infiltrative therapy is not indicated for severe forms of pathology.

Table II. Selected studies of subacromial space injections

<table>
<thead>
<tr>
<th>Author and year</th>
<th>Study design</th>
<th>Protocol/pathology</th>
<th>Follow-up (weeks)</th>
<th>Outcome measures</th>
<th>Results</th>
<th>Level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meloni et al. 2008</td>
<td>RCT</td>
<td>5 injections of Hyalgan® (28 patients) 5 injections of placebo (28 patients)</td>
<td>48</td>
<td>VAS pain scale</td>
<td>Significant improvement in pain and function for treated group compared to controls at all endpoints (p&lt;0.001)</td>
<td>I</td>
</tr>
<tr>
<td>Chou et al. 2010</td>
<td>RCT</td>
<td>5 injections of Artz® (25 patients) 5 injections of placebo (26 patients)</td>
<td>2 years</td>
<td>VAS, Constant-Murley</td>
<td>Significant improvement in pain and function for treated group compared to controls at all endpoints (p&lt;0.001)</td>
<td>I</td>
</tr>
<tr>
<td>Tagliafico et al. 2011</td>
<td>Perspective, open-label</td>
<td>2 injections of high molecular weight HA ND (33 patients) Group that refused infiltrative therapy (60 patients)</td>
<td>24</td>
<td>VAS, Constant-Murley</td>
<td>Significant improvement in pain and function for treated group at 1, 2, 3 and 4 months follow-up, without statistical differences compared to controls at 6 months</td>
<td>III</td>
</tr>
<tr>
<td>Moghtaderi et al. 2013</td>
<td>RCT</td>
<td>3 injections of Fermatron® (20 patients) 3 injections of placebo (20 patients)</td>
<td>12</td>
<td>VAS, Constant-Murley</td>
<td>Significant improvement in pain and function for treated group compared to controls (p&lt;0.001)</td>
<td>I</td>
</tr>
<tr>
<td>Merolla et al. 2013</td>
<td>Perspective randomized</td>
<td>2 injections of SportVis® (25 patients) Standard rehabilitative treatment (23 patients) Supraspinatus tendinopathy</td>
<td>12</td>
<td>Oxford Shoulder Score, Constant-Murley Score</td>
<td>Significant improvement in pain and function for treated group from 2 to 12 weeks and in CS at 4 and 12 weeks compared to controls</td>
<td>II</td>
</tr>
</tbody>
</table>
Table III. Selected studies on epicondylitis.

<table>
<thead>
<tr>
<th>Author and year</th>
<th>Study design</th>
<th>Protocol/pathology</th>
<th>Follow-up (weeks)</th>
<th>Outcome measures</th>
<th>Results</th>
<th>Level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Petrella et al. 2010</td>
<td>RCT</td>
<td>2 injections of HA ND (165 patients) 2 injections of placebo (166 patients)</td>
<td>48</td>
<td>VAS pain scale, gripping force with dynamometer, return to sport</td>
<td>Significant improvement in pain and function for treated group compared to controls at all endpoints (p&lt;0.001)</td>
<td>I</td>
</tr>
<tr>
<td>Kumai et al. 2014</td>
<td>Perspective, non randomized</td>
<td>1 injection of Suvenyl® (16 patients)</td>
<td>1</td>
<td>VAS</td>
<td>Improvement ≥2 cm in VAS scale in 10 patients (62.5%)</td>
<td>IV</td>
</tr>
<tr>
<td>Tosun et al. 2015</td>
<td>RCT</td>
<td>1 injection of Ialural® (25 patients) 1 injection of triamcinolone acetonide (32 patients)</td>
<td>12</td>
<td>VAS, PRTEE</td>
<td>Significant improvement in pain and function for HA+CS group at 3 months and in pain at 6 months compared to CS group</td>
<td>II</td>
</tr>
</tbody>
</table>

Table IV. Selected studies on elbow osteoarthritis.

<table>
<thead>
<tr>
<th>Author and year</th>
<th>Study design</th>
<th>Protocol/pathology</th>
<th>Follow-up (weeks)</th>
<th>Outcome measures</th>
<th>Results</th>
<th>Level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Van Brakel &amp; Eygendaal 2006</td>
<td>Case series</td>
<td>3 injections of Fermathron® (18 patients -19 joints) Post-traumatic osteoarthrtis</td>
<td>24</td>
<td>VAS, EFA score, Broberg-Morrey Functional Rating Index</td>
<td>Slight non-significant improvement in pain and rigidity at 3 months</td>
<td>IV</td>
</tr>
<tr>
<td>Pederzini et al. 2013</td>
<td>Case series</td>
<td>1 injection of Hyaloglide®+arthrolysis (17 patients) Arthroscopic arthrolysis (19 patients) Post-traumatic osteoarthrtis</td>
<td>10</td>
<td>VAS, ROM, Liverpool elbow score (LES)</td>
<td>Higher percentage of patients with pain reduction in HA group (p=0.0419), significant reduction in pain intensity in both groups (p&lt;0.0001)</td>
<td>IV</td>
</tr>
</tbody>
</table>

KEY WORDS: hyaluronic acid, hip injections, hip osteoarthritis, hip diseases.

Hyaluronic acid in knee disorders
Knee is the most studied application of HA injections and a common site of pathology, representing over 45% of total cases of symptomatic osteoarthritis. Several high-quality meta-analyses and review of RCTs were performed (Tab. VI).

Effects on symptoms
Intra-articular injections of HA lead to symptom relief comparable or superior to traditional treatments, such as intra-articular corticosteroids, NSAIDs, analgesics, lifestyle changes and physical exercise.

Level of recommendation: A.

Structural effects
Different studies have shown that the use of HA in knee osteoarthritis leads to structural improvements, including reduction of grade and extension of cartilage lesions, accompanied by decrease in synovial fluid inflammation, improvement in quantity and density of chondrocytes, increase in synovial repair processes.

Level of recommendation: A.

Effects on delay of prosthetic replacement surgery
Even if only few studies have been conducted on this topic, those carried out agree that repeated treat-
ments with HA infiltrations are effective in delaying total knee replacement surgery.\textsuperscript{117-120}

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### Table V. Selected studies on hip osteoarthritis.

<table>
<thead>
<tr>
<th>Author and year</th>
<th>Study design</th>
<th>Protocol/pathology</th>
<th>Follow-up (weeks)</th>
<th>Outcome measures</th>
<th>Results</th>
<th>Level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tikiz et al. 2005\textsuperscript{38}</td>
<td>RCT</td>
<td>3 injections of Synvisc\textsuperscript{®} (25 patients, 32 hips) 3 injections of Ostenil\textsuperscript{®} (18 patients, 24 hips)</td>
<td>24</td>
<td>VAS, WOMAC, Lequesne</td>
<td>Both treatments are effective without statistical differences</td>
<td>I</td>
</tr>
<tr>
<td>Qvistgaard et al. 2006\textsuperscript{99}</td>
<td>RCT</td>
<td>3 injections of Hyalgan\textsuperscript{®} (33 patients) 3 injections of placebo (36 patients) 1 injection of Depo-Medrol\textsuperscript{®}+ 2 sham injections (32 patients)</td>
<td>12</td>
<td>VAS scale during walk</td>
<td>Significant pain reduction in CS group compared to placebo and HA at 14 and 28 days</td>
<td>I</td>
</tr>
<tr>
<td>Van den Bekerom et al. 2008\textsuperscript{100}</td>
<td>Perspective, non randomized</td>
<td>1 injection of Adant\textsuperscript{®} (91 patients) 1 injection of Synocrom\textsuperscript{®} (20 patients) 1 injection of Synvisc\textsuperscript{®} (15 patients)</td>
<td>6</td>
<td>VAS, Harris Hip Score</td>
<td>Significant improvement in pain and function for Adant Synocrom groups</td>
<td>III</td>
</tr>
<tr>
<td>Richette et al. 2009\textsuperscript{101}</td>
<td>RCT</td>
<td>1 injection of Adant\textsuperscript{®} (42 patients) 1 injection of placebo (43 patients)</td>
<td>12</td>
<td>VAS</td>
<td>No significant differences between groups</td>
<td>I</td>
</tr>
<tr>
<td>Migliore et al. 2009\textsuperscript{102}</td>
<td>RCT</td>
<td>2 injections of Hyalubrix\textsuperscript{®} (22 patients) 2 injections of mepivacaine (20 patients)</td>
<td>12</td>
<td>VAS, Lequesne</td>
<td>Significant improvement in pain (p&lt;0.05) and Lequesne (p&lt;0.001) for HA group at all follow-up</td>
<td>I</td>
</tr>
<tr>
<td>Spitzer et al. 2010\textsuperscript{103}</td>
<td>RCT</td>
<td>3 injections of Synvisc\textsuperscript{®} (150 patients) 2 injections of methylprednisolone (155 patients)</td>
<td>26</td>
<td>WOMAC</td>
<td>HA is better than CS in advanced stages of pathology, same effectiveness in less advanced stages</td>
<td>I</td>
</tr>
<tr>
<td>Atchia et al. 2011\textsuperscript{104}</td>
<td>Perspective, randomized</td>
<td>1 injection of Durolane\textsuperscript{®} (19 patients) 1 injection of placebo (19 patients) 1 injection of corticosteroid (20 patients) 1 injection of corticosteroid (155 patients) Standard care (20 patients)</td>
<td>8</td>
<td>NRS, WOMAC</td>
<td>Significant improvement in pain and function for CS group</td>
<td>II</td>
</tr>
<tr>
<td>Battaglia et al. 2013\textsuperscript{105}</td>
<td>RCT</td>
<td>3 injections of PRP (50 patients) 3 injections of Hyalubrix\textsuperscript{®} (50 patients)</td>
<td>52</td>
<td>VAS, Harris Hip Score</td>
<td>Significant improvement in both groups (p&lt;0.005) without differences at all follow-up</td>
<td>I</td>
</tr>
</tbody>
</table>

Level of recommendation: B.
### Hyaluronic acid in knee disorders

- Knee infiltration with HA is strongly recommended for pain relief and potential disease-modifying effects.
- Evidence is greater for patients with mild to moderate osteoarthritis (K/L II-III).
- HA injections may delay the need for prosthetic knee replacement.

**KEY WORDS:** hyaluronic acid, molecular weight, knee, osteoarthritis, intra-articular injection, viscosupplementation, pain, tolerability, safety, meta-analysis, adverse events, total knee replacement.

### Hyaluronic acid in ankle disorders

Hyaluronic acid is frequently used to reduce symptoms in early stages of ankle osteoarthritis. Many methods of treatment have been proposed, but actually no precise algorithm has been defined. HA is typically used when first-level analgesics have not determined adequate benefit and it could represent an option to postpone surgery. 121-122.

In selected studies (7 studies; 5 RCTs) response to treatment was moderate even a large share of the samples respond to the treatment (Tab. VII). 123-129. It remains unclear which patients (age, degree of ankle osteoarthritis) may have greater improvement from HA injections and the number of injections to perform per patient.

**Level of recommendation:** B.

**Keypoints**
- HA is safe in ankle joint, although improvements in clinical scores appear to be slightly significant in higher quality trials.
- HA can be recommended in patients who respond inadequately to common analgesics.
- It remains unclear which patients may have greater improvement from HA injections and the number of injections to perform per patient.

**Key words:** viscosupplementation, hyaluronic acid, ankle, arthritis.

### Hyaluronic acid in small joints

The role of HA in small joints is not well established yet. Few studies investigated HA injections trape-
ziometacarpal (TMC) and first metatarsophalangeal joint (MTPJ) OA, while other small joints were not studied.

Trapeziometacarpal joint osteoarthritis

Studies selected have heterogeneous protocols and only two RCTs were found (Tab. VIII)\textsuperscript{130-139}. Although some studies demonstrate a significant decrease in pain at a medium-term follow-up, no significant superiority compared to corticosteroid or placebo is emerged. A volume of 0.3 cm\textsuperscript{3} injected for each injection seems to be ideal in order to reduce volume effect and post-injection pain\textsuperscript{15}.

Level of recommendation: B.

First metatarsophalangeal joint osteoarthritis

Only few studies were conducted, while a high quality RCT showed that an intra-articular injection of hylan G-F 20 is no more effective than placebo in reducing symptoms in people with symptomatic first MTPJ OA (Tab. IX)\textsuperscript{140-142}.

Level of recommendation: C.

Keypoints

- In TMC OA a significant superiority compared to corticosteroids or placebo is not emerged, while HA seems to lead to higher improvements in long-term follow-up.
- In first metatarsophalangeal joint, no high-quality study demonstrate the superiority of HA in comparison to corticosteroids or placebo.

KEY WORDS: carpometacarpal joint, trapeziometacarpal, thumb, hallux rigidus, rhizarthrosis, metatarsophalangeal joint, golfer’s toe and or viscosupplementation, hyaluronic acid, intra-articular injection.

Hyaluronic acid in tendon and bursa

HA after flexor tendon repair surgery

HA has been widely used for topical application and injections after surgical repair of flexor tendons of the hand with the aim of promoting tendon sliding and preventing post-surgical adhesions. Many Authors have showed a lower granulation tissue formation with reduction of post-surgical adhesions, in part for reduced peritendinous inflammation. Four high-quality RCTs were found (Tab. X)\textsuperscript{143-146}. HA products with higher molecular weight and longer half-life favor a greater permanence of HA into intrasynovial peritendinous space compared to native HA and low molecular weight formulations, ensuring greater clinical efficacy.

Level of recommendation: A.

---

Table VII. Selected studies on ankle pathologies

<table>
<thead>
<tr>
<th>Author and year</th>
<th>Study design</th>
<th>Protocol</th>
<th>Follow-up (weeks)</th>
<th>Outcome measures</th>
<th>Results</th>
<th>Level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salk et al. 2006\textsuperscript{123}</td>
<td>RCT</td>
<td>5 injections of Hyalgan\textsuperscript{®} (10 patients) 5 injections of placebo (10 patients)</td>
<td>24</td>
<td>AOS</td>
<td>Significant improvement in both groups (p&lt;0,001)</td>
<td>I</td>
</tr>
<tr>
<td>Cohen et al. 2008\textsuperscript{124}</td>
<td>RCT</td>
<td>5 injections of Hyalgan\textsuperscript{®} (15 patients) 5 injections of placebo (15 patients)</td>
<td>12</td>
<td>AOS</td>
<td>Significant improvement in HA group compared to control group</td>
<td>I</td>
</tr>
<tr>
<td>Karatosun et al. 2008\textsuperscript{125}</td>
<td>Perspective, randomized</td>
<td>3 injections of Adant\textsuperscript{®} (15 patients) Exercise (15 patients)</td>
<td>52</td>
<td>AOFAS score, VAS pain</td>
<td>Significant improvement in both groups (p&lt;0,001)</td>
<td>II</td>
</tr>
<tr>
<td>Carpenter et al. 2008\textsuperscript{126}</td>
<td>Perspective, non randomized</td>
<td>Ankle arthroscopy + 3 injections of Synvisc\textsuperscript{®} (14 patients) Ankle arthroscopy (12 patients)</td>
<td>48</td>
<td>10 points pain score scale</td>
<td>Significant pain reduction in comparison to controls</td>
<td>IV</td>
</tr>
<tr>
<td>Mei-Dan et al. 2012\textsuperscript{127}</td>
<td>RCT</td>
<td>3 injections of Euflexxa\textsuperscript{®} (15 patients) 3 injections of PRP (14 patients)</td>
<td>28</td>
<td>AOFAS</td>
<td>Significant improvement in both groups (p&lt;0,001), higher for PRP group (p&lt;0,05)</td>
<td>II</td>
</tr>
<tr>
<td>DeGroot et al. 2012\textsuperscript{128}</td>
<td>RCT</td>
<td>1 injection of Supartz\textsuperscript{®} (32 patients) 1 injection of placebo (32 patients)</td>
<td>12</td>
<td>AOFAS</td>
<td>Significant improvement in both groups (p&lt;0,001)</td>
<td>I</td>
</tr>
<tr>
<td>Sun et al. 2014\textsuperscript{129}</td>
<td>RCT</td>
<td>1 injection of Hyalgan\textsuperscript{®} + exercise (37 patients) 1 injection of botulinum toxin (38 patients)</td>
<td>24</td>
<td>AOS</td>
<td>Significant improvement in both groups (p&lt;0,001)</td>
<td>II</td>
</tr>
</tbody>
</table>
In two recent randomized clinical trials, ultrasound-guided infiltration of medium molecular weight HA has been proposed for the treatment of stenosing tenosynovitis of finger flexor tendons, with encouraging results.\textsuperscript{147-148}

Evidence on clinical efficacy for HA in human insertional tendon disorders is limited at four studies, although results are promising.\textsuperscript{68,94,149,150} (Tab. XI).

HA injections have also been proposed for the treatment of bursitis. Actually only two prospective studies without a control group are available, respectively on Table VIII. Selected studies on injections in trapeziometacarpal joint.

<table>
<thead>
<tr>
<th>Author and year</th>
<th>Study design</th>
<th>Protocol</th>
<th>Follow-up (weeks)</th>
<th>Outcome measures</th>
<th>Results</th>
<th>Level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Figen Ayhan et al. 2009\textsuperscript{130}</td>
<td>RCT</td>
<td>1 injection of Hylan G-F 20 (33 patients) 1 injection of saline solution (33 patients)</td>
<td>24</td>
<td>VAS, gripping force, Dreiser</td>
<td>Significant improvement in function (p=0.001), VAS pain (p=0.002), gripping force (p=0.004) for HA group</td>
<td>I</td>
</tr>
<tr>
<td>Salini et al. 2009\textsuperscript{131}</td>
<td>Perspective non randomized</td>
<td>1 injection of HA 800-1200 kDa (18 patients)</td>
<td>4</td>
<td>VAS, FANS consumption, Dreiser, gripping force</td>
<td>Significant improvement in pain (p&lt;0.001), function (p&lt;0.004), force (p&lt;0.001)</td>
<td>II</td>
</tr>
<tr>
<td>Di Sante et al. 2011\textsuperscript{132}</td>
<td>Perspective non randomized</td>
<td>3 weekly injections of HA ND (31 patients)</td>
<td>24</td>
<td>VAS, Duruöz Hand Index</td>
<td>Significant improvement only in pain at 1 and 3 months, but no improvement at 6 months nor in function</td>
<td>III</td>
</tr>
<tr>
<td>Frizziero et al. 2014\textsuperscript{133}</td>
<td>Retrospective non randomized</td>
<td>3 weekly injections of Hyalgan\textsuperscript{®} (58 patients)</td>
<td>24</td>
<td>VAS, FANS consumption, gripping force</td>
<td>Significant improvement in pain (p&lt;0.001) and reduced FANS consumption (p&lt;0.017)</td>
<td>IV</td>
</tr>
<tr>
<td>Roux et al. 2007\textsuperscript{134}</td>
<td>Perspective randomized</td>
<td>Sinovial\textsuperscript{®} 1 injection (14 patients) 2 injections (14 patients) 3 injections (14 patients)</td>
<td>12</td>
<td>VAS, Dreiser</td>
<td>Significant improvement in pain and function, without significant differences between groups</td>
<td>II</td>
</tr>
<tr>
<td>Heyworth et al. 2007\textsuperscript{135}</td>
<td>RCT</td>
<td>2 injections Synvisc\textsuperscript{®} (20) 1 injection of placebo + 1 injection of betamethasone acetate (22 patients) 2 injections of placebo (18)</td>
<td>26</td>
<td>VAS, gripping force, DASH</td>
<td>No significant differences between groups, even if there is a positive trend for HA group after 4 weeks</td>
<td>I</td>
</tr>
<tr>
<td>Fuchs et al. 2005\textsuperscript{136}</td>
<td>Perspective randomized</td>
<td>3 injections of Ostenil Mini\textsuperscript{®} (28 patients) 3 injections of triamcinolone acetonide (28 patients)</td>
<td>26</td>
<td>VAS, gripping force</td>
<td>Pain resolution, improvement in articular movement more lasting for HA group</td>
<td>II</td>
</tr>
<tr>
<td>Ingenoli et al. 2010\textsuperscript{137}</td>
<td>Case series</td>
<td>3 injections of Hyalubrix\textsuperscript{®} (32 patients)</td>
<td>24</td>
<td>VAS, Dreiser, gripping force</td>
<td>Significant improvement in pain and local inflammation at short and medium term</td>
<td>IV</td>
</tr>
<tr>
<td>Bahadir et al. 2009\textsuperscript{138}</td>
<td>Perspective randomized</td>
<td>3 injections of Ostenil\textsuperscript{®} (20 patients) 1 injection of triamcinolone acetonide (20 patients)</td>
<td>48</td>
<td>VAS, Duruöz Hand Index, gripping force</td>
<td>No significant differences between groups at all follow-up</td>
<td>II</td>
</tr>
<tr>
<td>Stahl et al. 2005\textsuperscript{139}</td>
<td>Perspective randomized</td>
<td>3 injections of Ostenil Mini\textsuperscript{®} (26 patients) 3 injections of methylprednisolone (26 patients)</td>
<td>24</td>
<td>Pain, gripper, gripping force, Purdue Pegboard Test</td>
<td>Both treatment are effective, HA group shows higher improvement in gripping force and PPT</td>
<td>II</td>
</tr>
</tbody>
</table>
### Table IX. Selected studies on first metatarsophalangeal joint injections.

<table>
<thead>
<tr>
<th>Author and year</th>
<th>Study design</th>
<th>Protocol</th>
<th>Follow-up (weeks)</th>
<th>Outcome measures</th>
<th>Results</th>
<th>Level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Munteanu et al. 2011&lt;sup&gt;140&lt;/sup&gt;</td>
<td>RCT</td>
<td>1 injection of Hylan G-F 20 (75 patients) 1 injection of placebo (76 patients)</td>
<td>24</td>
<td>Foot Health Status Questionaire</td>
<td>No significant differences between groups at all follow-up</td>
<td>I</td>
</tr>
<tr>
<td>Pons et al. 2007&lt;sup&gt;141&lt;/sup&gt;</td>
<td>Perspective randomized</td>
<td>1 injection of Ostenil Mini® (20 joints) 1 injection of triamcinolone acetonide (20 joints)</td>
<td>11</td>
<td>VAS, AOFAS score</td>
<td>Significant difference in pain during movement and AOFAS score for HA group (p&lt;0,05)</td>
<td>II</td>
</tr>
<tr>
<td>Petrella &amp; Cogliano 2004&lt;sup&gt;142&lt;/sup&gt;</td>
<td>Perspective non randomized</td>
<td>8 injections of HA ND (47 patients)</td>
<td>16</td>
<td>VAS, tiptoe walking pain, ROM, global patient satisfaction</td>
<td>Significant improvement in all outcome measures</td>
<td>III</td>
</tr>
</tbody>
</table>

### Table X. Selected studies on flexor tendons tendon pathology.

<table>
<thead>
<tr>
<th>Author and year</th>
<th>Study design</th>
<th>Experimental groups</th>
<th>Protocol/pathology</th>
<th>Follow-up</th>
<th>Outcome measures</th>
<th>Results</th>
<th>Level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wiig et al. 2014&lt;sup&gt;143&lt;/sup&gt;</td>
<td>RCT</td>
<td>PXL01 in (46 patients) (1,5-8,1 MDa, 15 mg/ml) Placebo (49 patients)</td>
<td>Injection between tendon and sheath and around sheath during surgery Surgical repair of hand areas I-II flexor tendons: adhesion prevention</td>
<td>Until 12 months</td>
<td>TAM, tip-bend distance, sensitivity, degree of tenolysis, gripping force</td>
<td>HA improves post-surgical recovery, with more pronounced difference 6 months after surgery</td>
<td>I</td>
</tr>
<tr>
<td>Özgenel &amp; Etöz 2012&lt;sup&gt;144&lt;/sup&gt;</td>
<td>RCT</td>
<td>High molecular weight HA (11 patients) (1,0-2,9 MDa, 15 mg/ml) Placebo (11 patients)</td>
<td>1 injection during surgery, 2 injections at weekly intervals</td>
<td>Hand area II flexor tendon injury: adhesion prevention</td>
<td>TAM, TPM, functional outcome with Strickland grading system</td>
<td>No differences at 3 weeks, improvement in HA group at 3 months and long-term</td>
<td>I</td>
</tr>
<tr>
<td>Riccio et al. 2010&lt;sup&gt;145&lt;/sup&gt;</td>
<td>RCT</td>
<td>Hyaloglide® (26 patients) Standard surgical release (19 patients)</td>
<td>Application of Hyaloglide® along the exposed tendon surface and in digital canal</td>
<td>Adhesions recurrence after tenolysis of flexor tendons in hand zone II</td>
<td>TAM, QuickDASH, working days lost after surgery</td>
<td>Better recovery of TAM and faster return to work and daily life activities in HA group</td>
<td>I</td>
</tr>
<tr>
<td>Hagberg et al. 1992&lt;sup&gt;146&lt;/sup&gt;</td>
<td>RCT</td>
<td>High molecular weight HA (4.0 Mda) Placebo (120 cases stratified in 6 classes)</td>
<td>Injection in tendon sheath after tenorrhaphia or tendon graft</td>
<td>4 months</td>
<td>TAM, extension deficit, DIPAM (active motion)</td>
<td>No significant effects of HA on recovery of TAM</td>
<td>I</td>
</tr>
</tbody>
</table>
Table XI. Selected studies on tendon and bursal pathologies.

<table>
<thead>
<tr>
<th>Author and year</th>
<th>Study design</th>
<th>Experimental groups</th>
<th>Protocol/pathology</th>
<th>Follow-up</th>
<th>Outcome measures</th>
<th>Results</th>
<th>Level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liu et al. 2015&lt;sup&gt;147&lt;/sup&gt;</td>
<td>RCT</td>
<td>Medium molecular weight HA (18 cases) (0.8-1.17 Mda) cortisone (19 cases)</td>
<td>1 US-guided injection of HA 1 US-guided injection of cortisone</td>
<td>3 weeks, 3 months</td>
<td>Quinnell scale Michigan scale (MHQ), VAS, TAM, gripping force</td>
<td>Better outcomes for both groups, different trend for MHQ (progressive increase for HA; increase at 3 weeks, decrease at 3 months for steroid)</td>
<td>I</td>
</tr>
<tr>
<td>Callegari et al. 2011&lt;sup&gt;148&lt;/sup&gt;</td>
<td>RCT</td>
<td>Cortisone/lidocaine + medium molecular weight HA (0.8-1.2 MDa) (15 patients) Open surgical release (15 patients)</td>
<td>US-guided injection of cortisone/lidocaine and after 10 days of HA</td>
<td>3 weeks, 3-6-12 months</td>
<td>DASH, Satisfaction Visual Analog Scale (SVAS), VAS</td>
<td>Similar results between groups</td>
<td>I</td>
</tr>
<tr>
<td>Tosun et al. 2015&lt;sup&gt;149&lt;/sup&gt;</td>
<td>RCT</td>
<td>HA + chondroitin sulphate + prilocaine (25 patients) Triamcinolone + prilocaine (32 patients)</td>
<td>Single injection of 1.6 mL in an area of about 2 cm² immediately anterior and distal to the lateral epicondyle</td>
<td>3-6 months after injection</td>
<td>Pain and function with Patient Rated Tennis Elbow Evaluation (PRTEE)</td>
<td>Pain and function significantly improved at 3 and 6 months in both groups, but better results for HA+CS group</td>
<td>II</td>
</tr>
<tr>
<td>Kumai et al. 2014&lt;sup&gt;68&lt;/sup&gt;</td>
<td>Pilot study</td>
<td>High molecular weight HA (2.7 Mda) (61 patients)</td>
<td>Single injection of HMW-HA near affected tendon/insertion Entheopathy (epicondylitis, patellar tendinopathy, insertional Achilles tendinopathy, plantar fasciitis)</td>
<td>1 week after injection</td>
<td>Spontaneous pain (VAS), 5 categories of local symptoms, caused pain</td>
<td>VAS reduction for all infiltrated sites and improvement of local caused pain</td>
<td>IV</td>
</tr>
<tr>
<td>Muneta et al. 2012&lt;sup&gt;150&lt;/sup&gt;</td>
<td>Cohort study</td>
<td>Low molecular weight HA+ lidocaine (50 patients)(9.0 Mda)</td>
<td>Injection between posterior tendon surface and infrapatellar fat (patellar tendinopathy) or more painful point around tendon; repeated from 1 to 11 times spaced at least 1 week</td>
<td>6-88 months</td>
<td>Roles and Maudsley modified score (pain and practice of sport)</td>
<td>Slight increase in pain 1-2 days after injection, then improvement compared to previous condition. Most effective in patellar tendinopathy compared to other types of anterior knee pain</td>
<td>II</td>
</tr>
</tbody>
</table>

To be continued
scapulo-thoracic bursitis\textsuperscript{151} and on suprapatellar bursitis\textsuperscript{152}; both studies reported significant improvements and Authors seem to encourage the use of HA in such conditions.

\textit{Level of recommendation: C.}

\textbf{Keypoints}

- HMW-HA into intrasynovial peritendinous space should be proposed after surgical repair of flexor tendons of the hand with the aim of preventing adhesions and optimize recovery of motility and function.
- Currently, the use of HA in insertional tendon disease, trigger finger and bursitis is not strongly support by evidences, even reporting encouraging results without major side effects.

\textbf{KEY WORDS:} tendon, periarticular, tendinopathy and or hyaluronic acid, injection.

\textbf{Combination therapy with HA}

\textit{Association with corticosteroids}

Several studies investigated combined therapy with corticosteroids in various pathologies, as knee osteoarthritis, stenosing tenosynovitis of fingers flexor tendons, internal derangement of temporomandibular joint, adhesive capsulitis and lateral epicondyritis (Tab. XII)\textsuperscript{89,148,153-157}. Despite the different indications and protocols, all these studies suggested the superiority of the therapeutic association in terms of efficacy (pain reduction) compared to the use of each treatment alone.

\textit{Level of recommendation: B.}

\textit{Association with local anesthetics}

In the selected studies HA and local anesthetics have been used in association to other drugs, so it is difficult to establish the clinical efficacy of this combined therapy, whether the outcome was favorable for combined treatment groups\textsuperscript{148,149,157}. 

\textit{Level of recommendation: C.}

\textbf{Association with NSAIDs}

Only two RCTs analyzed the association between HA and NSAIDs. Both demonstrated a superiority in terms of pain reduction for combined intra-articular therapy compared to HA alone in subjects suffering of knee OA\textsuperscript{158,159}.

\textit{Level of recommendation: C.}

\textbf{Association with PRP}

A retrospective non-randomized clinical trial on patients affected by Kellgren-Lawrence grade III-IV knee OA showed better outcome for the group treated with association between HA and PRP compared to HA alone\textsuperscript{160}.

\textit{Level of recommendation: C.}

\textbf{Association with MSCs}

A recent RCT showed an increased quality of articular cartilage tissue after associative treatment with HA and peripheral blood stem cells compared to HA alone in patients with chondral lesions of the knee\textsuperscript{161}.

\textit{Level of recommendation: C.}

\begin{table}[h]
\centering
\begin{tabular}{|l|l|l|l|l|l|l|l|}
\hline
Study & Type & Treatment & No. of Patients & No of injections & Injection site & Outcome & Level of recommendation \\
\hline
Petrella et al. 2010\textsuperscript{94} & RCT & - HA (165 patients) (molecular weight not specified) - saline solution (166 patients) & 2 weekly injections in subcutaneous and muscular tissue 1 cm from lateral epicondyle & 7-14-30-90-365 days & VAS, gripping force, global satisfaction, return to ADL and sport & Better results in HA group & I \\
\hline
Chen et al. 2014\textsuperscript{152} & Cohort study & High molecular weight HA(6000 kDa) (10 patients) Low molecular weight HA (500-730 kDa) (10 patients) & 3 intrabursal injections after aspiration with lateral access, on a weekly basis & 1-2-3-4 weeks after first injection & Difference in protein concentration in synovial fluid before and after injection & Similar results in both groups & II \\
\hline
Chang et al. 2009\textsuperscript{151} & Pilot study & Cortisone + medium molecular weight HA (22 patients)(940-1020 kDa) No control group & 3 non-guided weekly injections with access at vertebral margin of the scapula between serratus anterior muscle and lateral thoracic wall & 1-2-3 weeks and 3 months after first injection & VAS, Rubin scale Pain reduction, no significant adverse events & & IV \\
\hline
\end{tabular}
\end{table}
Table XII. Selected studies on combination therapies.

<table>
<thead>
<tr>
<th>Author and year</th>
<th>Study design</th>
<th>Population</th>
<th>Treatments</th>
<th>Type of HA</th>
<th>Type of cotherapy</th>
<th>Follow-up period</th>
<th>Level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Callegari et al. 2011148</td>
<td>RCT</td>
<td>30 patients with stenosing tenosynovitis of fingers flexor tendons</td>
<td>2 groups: - corticosteroids + HA (group A) - open surgery (group B)</td>
<td>1 ml 0.8% of HA (Sinoval Mini)</td>
<td>Methylprednisolone acetate 40 mg/1 ml (Depo-medrol)</td>
<td>6 weeks, 3, 6, 12 months</td>
<td>II</td>
</tr>
<tr>
<td>De Campos et al. 2013153</td>
<td>RCT</td>
<td>104 patients with gonarthrosis</td>
<td>2 groups: - 1 injection of HA (VS group); - 1 injection of HA + triamcinolone (VS+T group).</td>
<td>6 ml of Hylan GF-20</td>
<td>1 ml/20 mg of triamcinolone hexacetonide</td>
<td>1, 4, 12, 24 weeks</td>
<td>I</td>
</tr>
<tr>
<td>Giombini et al. 2016162</td>
<td>RCT</td>
<td>70 subjects with gonarthrosis</td>
<td>3 groups (1 injection/week for 5 weeks): - HA only (n = 23); - only O2O3 (n = 23); - HA+O2O3 (n = 24)</td>
<td>20 mg/2 ml of HA (Hyalgan®)</td>
<td>mixture of O2O3 (15 mg/ml with [O3] of 15 μg/ml, obtained through an ozone generator)</td>
<td>2 months from end of treatment</td>
<td>II</td>
</tr>
<tr>
<td>Giraddi et al. 2015154</td>
<td>RCT</td>
<td>14 patients with internal derangement of temporomandibular joint</td>
<td>2 groups (arthrocentesis + injection): - betamethasone + HA - only betamethasone</td>
<td>0.5 ml of HA</td>
<td>- group I: 0.5 ml of betamethasone - group II: 1 ml of betamethasone</td>
<td>2 days, 1, 2, 6 months</td>
<td>II</td>
</tr>
<tr>
<td>Lee et al. 2011158</td>
<td>RCT</td>
<td>43 subjects with gonarthrosis</td>
<td>2 groups: - HA+30 mg of ketorolac (3 weeks), followed by HA alone (2 weeks) - only HA for 5 weeks</td>
<td>2.5 ml (1%) of Hyal (940-1020 kDa)</td>
<td>30 mg of ketorolac</td>
<td>1, 3, 5, 16 weeks after beginning of therapy</td>
<td>II</td>
</tr>
<tr>
<td>Ozturk et al. 2006155</td>
<td>RCT</td>
<td>40 patients with gonarthrosis</td>
<td>2 groups (3 weekly injections for 3 weeks + 3 injections at 6th month): - HA (n = 24, group A) - HA + triamcinolone at I and IV injection</td>
<td>2 ml of HA (Orthovisc): 15 mg sodium hyaluronate +9 mg sodium chloride/1 ml</td>
<td>1 ml triamcinolone acetone (Kenacort-A)</td>
<td>1-3, 6, 7, 9, 12 months</td>
<td>II</td>
</tr>
<tr>
<td>Palmieri et al. 2013159</td>
<td>RCT</td>
<td>62 patients with bilateral gonarthrosis</td>
<td>3 groups: - 66 mg of HA - 49.5 mg of HA + 5 mg of diclofenac - 49.5 mg of HA + 5 mg of sodium clodronate</td>
<td>- 66 mg/2 ml of HA (Variofill®) - 49.5 mg/1.5 ml of HA (Variofill®)</td>
<td>- 5 mg/0.5 ml of sodium diclofenac - 5 mg/0.5 ml of sodium clodronate</td>
<td>3 and 6 months</td>
<td>II</td>
</tr>
<tr>
<td>Petrella et al. 2015156</td>
<td>RCT</td>
<td>98 subjects with gonarthrosis</td>
<td>3 groups: - HA (Hydros) - HA + 10 mg of triamcinolone acetone (Hydros TA) - HA (Synvisc-One)</td>
<td>-Hydros -Hydros TA (HA + 10 mg triamcinolone acetone) -Synvisc-One® (hylan G-F 20)</td>
<td>10 mg of triamcinolone acetone</td>
<td>2, 6, 13, 26 weeks</td>
<td>II</td>
</tr>
<tr>
<td>Rovetta &amp; Monteforte 1998869</td>
<td>RCT</td>
<td>30 subjects with adhesive capsulitis</td>
<td>2 groups (injections every 15 days in first month, then monthly for 6 months): - injection of HA + steroids + physiotherapy - injection of steroids + physiotherapy</td>
<td>20 mg of sodium hyaluronate</td>
<td>20 mg of triamcinolone acetone (both groups)</td>
<td>6 months</td>
<td>II</td>
</tr>
</tbody>
</table>

To be continued
Association with other drugs/medical devices

Three different studies reported significant clinical benefits with the use of HA in association to oxygen-ozone therapy, mannitol and chondroitin sulfate, respectively, in patients with knee osteoarthritis. Level of recommendation: C.

Keypoints
- The association of HA with other drugs or devices could have advantages in comparison to HA alone.
- Dosage and frequency of association with HA in osteoarticular and myotendinous diseases are not defined.
- Future high quality RCTs are needed in order to improve the knowledge about mechanism of action and efficacy of combined therapies.

KEY WORDS: hyaluronic acid, musculoskeletal, injection, intra-articular, sodium hyaluronate, anesthet-

ic, corticosteroid, NSAIDS, PRP, mesenchymal stem cells, ozon.

Ultrasound guidance for HA injection in musculoskeletal disorders

The advantages of ultrasound (US) imaging (real-time execution, absence of ionizing radiation, low cost and availability of device) are responsible of the large diffusion of US-guidance.

US-guidance in shoulder pathologies

Three studies were selected. Two studies investigated the outcome in patients with adhesive capsulitis, while one study in subacromial pain syndrome (Tab. XIII). All studies reported good clinical results after US-guided injections of HA, at least in the short term.

US-guidance in hand pathologies

Four different studies shave reported that US-guided injections of HA appear to be a safe and suitable tool
for the treatment of trigger finger, de Quervain’s disease and rhizarthrosis.\(^{147,148,167,168}\)

**US-guidance in hip**

US-guided injections of HA have shown good results in three studies on patients with hip osteoarthritis.\(^{99,104,105}\) Authors suggested that US could be useful not only as a guide, but also as a biomarker of response to therapy.

**US-guidance in knee**

One level II study reported that the precision of injection is better for US-guided procedure in comparison to anatomical landmark injections in suprapatellar bursitis.\(^{169}\).

**Level of recommendation for US-guided injection in hip joint:** A.

**Level of recommendation for US-guided injection in trigger finger:** B.

**Level of recommendation for US-guided injection in rhizarthrosis, glenohumeral joint and subacromial space:** C.

**Level of recommendation for US-guided injection in other anatomical sites:** D.

---

**Table XIII. Selected studies for on US-guided injections.**

<table>
<thead>
<tr>
<th>Author and year</th>
<th>Population Type of HA</th>
<th>Injection frequency</th>
<th>Follow-up period</th>
<th>Level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atchia et al. 2011(^{104})</td>
<td>77 patients with unilateral coxarthrosis waiting for surgical total hip replacement</td>
<td>3 ml/60 mg of Durolane</td>
<td>Not specified</td>
<td>1, 4, 8 weeks</td>
</tr>
<tr>
<td>Battaglia et al. 2013(^{105})</td>
<td>100 patients with unilateral coxarthrosis</td>
<td>High molecular weight HA (1500 Kd, Hyalubrix)</td>
<td>3 consecutive injections (every 2 weeks)</td>
<td>1, 3, 6, 12 months</td>
</tr>
<tr>
<td>Bum Park et al. 2012(^{169})</td>
<td>99 subjects with gonarthrosis</td>
<td>2 ml 1% high molecular weight HA (940-1020kDa)</td>
<td>3 weekly intra-articular injections</td>
<td>-</td>
</tr>
<tr>
<td>Callegari et al. 2011(^{148})</td>
<td>30 subjects with stenosing tenosynovitis of finger flexors</td>
<td>1 ml 0.8% HA (Sinovial Mini) + methylprednisolone acetate 40 mg/1 ml (Depo-medrol)</td>
<td>2 injections (10 days between them)</td>
<td>6 weeks, 3, 6, 12 months</td>
</tr>
<tr>
<td>Kim et al. 2012(^{166})</td>
<td>80 patients with subacromial conflict syndrome</td>
<td>2 ml/20 mg of Hyruan plus (average molecular weight 300,000,000 Da)</td>
<td>3 weekly injections (AI group); 1 injection (corticosteroid group)</td>
<td>3, 6, 12 weeks</td>
</tr>
<tr>
<td>Lee et al. 2009(^{166})</td>
<td>43 patients with shoulder adhesive capsulitis</td>
<td>2.5 ml/25 mg of low molecular weight HA</td>
<td>I week: 0.5 ml/20 mg of triamcinolone with 1.5 ml of 2% lidocaine and 3 ml of saline solution; II-VI week: HA</td>
<td>Weekly follow-up</td>
</tr>
<tr>
<td>Liu et al. 2015(^{147})</td>
<td>36 subjects (39 fingers) with clinical diagnosis of trigger finger</td>
<td>1 ml medium molecular weight HA (1000-1200 kDa, Artz)</td>
<td>1 injection</td>
<td>3 weeks, 3 months</td>
</tr>
<tr>
<td>Monfort et al. 2015(^{168})</td>
<td>88 patients with rhizarthrosis</td>
<td>0.5 cm3/5 mg of 500-1000kDa HA produced by bacterial fermentation (Suplasyn®)</td>
<td>3 weekly injections</td>
<td>7,14,30,90, 180 days</td>
</tr>
<tr>
<td>Orlandi et al. 2015(^{167})</td>
<td>75 patients with unilateral de Quervain’s disease</td>
<td>16 mg/2 ml of low molecular weight HA (0.8%, Sinovial)</td>
<td>2 injections (15 days between them): I injection: steroid; II injection: HA</td>
<td>1, 3, 6 months</td>
</tr>
<tr>
<td>Park et al. 2013(^{84})</td>
<td>90 patients with shoulder adhesive capsulitis</td>
<td>18 ml of lidocaine 0.5% for capsular distention + 2 ml high MW HA (10 mg/ml)</td>
<td>3 biweekly injections</td>
<td>2 and 6 weeks</td>
</tr>
<tr>
<td>Qvistgaard et al. 2006(^{99})</td>
<td>101 patients with coxarthrosis</td>
<td>2 ml of HA (Hyalgan®)</td>
<td>3 injections every 14 days</td>
<td>14, 28, 90 days</td>
</tr>
</tbody>
</table>
Key points

• Ultrasound imaging is an effective tool for intra-articular injections guidance in several musculoskeletal disorders, in absence of contraindications and severe side effects.
• While US offers various advantages (cost/benefit ratio, availability, real time acquisition), there is still lack of strong evidence regarding the impact of HA injections with ultrasound guidance in terms of accuracy and benefits in comparison to blinded procedures.

KEY WORDS: hyaluronic acid guided injection as mesh term.

Hyaluronic acid and exercise therapy

Four RCTs\textsuperscript{125,170-172} and one review\textsuperscript{174} compared the effectiveness of intra-articular injections of HA to a specific rehabilitative protocol in the treatment of patients with knee and ankle osteoarthritis; only one RCT investigated the combination to each treatment in alone (Tab. XIV). The results lead Authors to conclude that both treatments improve pain and function, although combined treatment seems to guarantee greater efficacy, at least in the short term.

Level of recommendation: B.

Key points

• Both HA injections and exercise therapy alone and in combination should improve pain and function in patients affected by OA.
• A single RCT suggested a possible greater efficacy of combined treatment in the short term.
• More studies are needed to strongly support this recommendation.

KEY WORDS: hyaluronic acid injection, physical exercises, exercise therapy, viscosupplementation, rehabilitation protocol and/or randomized controlled trial, systematic review.

Hyaluronic acid and physical therapies

In clinical practice the association between HA injection and physical therapies is common. Indeed, the effects of these therapies seem to be complementary and synergistic: in particular, physical therapies show beneficial actions in the acute phase reducing pain and inflammation through thermal, biochemical, mechanical and electrical effects, while HA acts mainly by facilitating and maintaining functional recovery over time.

However, the real effectiveness of physical therapies in musculoskeletal pathologies is controversial and only few scientific studies are aimed at validating the association between them and HA.

Osteoarthritis

Three studies\textsuperscript{6,23,25} show better results with the association of HA and physical therapies compared to physical therapies alone in patients with shoulder and knee osteoarthritis\textsuperscript{174-176} (Tab. XV). One pilot study did not show any significant difference, even both short-term (3 weeks) and long-term (3 months) evaluations, index of severity for osteoarthritis of the knee scores were reduced in all three groups\textsuperscript{177}.

Adhesive capsulitis

Two studies\textsuperscript{26,27} agree that the addition of HA to conventional treatments (including physical therapies) does not add significant benefits in patient suffering from adhesive capsulitis.

Level of recommendation: C.

Key points

• HA and physical therapies are commonly used for the treatment of musculoskeletal pathologies.
• Evidence on the effectiveness of physical therapies in joint and tendon disorders is controversial, mainly because of the lack of high quality RCTs.
• Only few studies demonstrated the effectiveness of association between physical therapies and HA, especially in knee and shoulder osteoarthritis, while there is no evidence on shoulder adhesive capsulitis.

KEY WORDS: hyaluronic acid injection, physical therapy, lasertherapy, viscosupplementation, rehabilitation protocol, shockwaves, ultrasound, electrotherapy and/or randomized controlled trial, systematic review.

Hyaluronic acid in post-surgical management

The promising results obtained in the conservative treatment of various musculoskeletal diseases have led many surgeons to propose HA also in post-surgical management, especially after shoulder, knee and ankle arthroscopy (Tab. XVI).

HA after knee arthroscopy

Early viscosupplementation in arthroscopic partial meniscectomy was found to have conflicting results and a possible improvement in short-term pain is not showed in all level I studies\textsuperscript{178-180}.

Different studies on viscosupplementation after ACL reconstruction evidenced inflammation, swelling and pain reduction only in the immediate post-operative period, without any difference in the long-term\textsuperscript{69,181,182}.

Conversely, three RCTs showed significant pain and clinical scores improvement for HMW HA after knee arthroscopy in knee OA\textsuperscript{183-185}.

HA after shoulder arthroscopy

Postoperative capsular stiffness is the main complication after shoulder arthroscopy and may determine prolonged rehabilitation period. HA could be used in post-surgery with the aim of decreasing adhesions and thus facilitating rehabilitation.

However, a recent RCT has not showed significant difference in pain VAS, internal rotation, external rotation and functional scores between two groups at each follow-up period\textsuperscript{186}.
### Table XIV. Selected studies on HA and exercise.

<table>
<thead>
<tr>
<th>Author and year</th>
<th>Study design</th>
<th>Protocol/pathology</th>
<th>Follow-up (weeks)</th>
<th>Outcome measures</th>
<th>Results</th>
<th>Level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Karatosun et al. 2006170</td>
<td>Randomized perspective</td>
<td>3 injections of Hylan G-F 20 (52 patients) Exercise (53 patients)</td>
<td>12,24,48,72</td>
<td>Hospital for Special Surgery (HSS) Knee Score</td>
<td>No differences between groups</td>
<td>II</td>
</tr>
<tr>
<td>Karatosun et al. 2008125</td>
<td>Randomized perspective</td>
<td>3 injections of Hylan G-F 20 (19 patients) Exercise (24 patients)</td>
<td>8,12,24,48</td>
<td>American Orthopedic Foot and Ankle Society (AOFAS) score, VAS score</td>
<td>No differences between groups</td>
<td>II</td>
</tr>
<tr>
<td>Kawasaki et al. 2009171</td>
<td>Randomized perspective</td>
<td>1 injection of ND device + Exercise (45 patients)</td>
<td>24</td>
<td>VAS, Japanese Knee Osteoarthritis Measure (JKOM)</td>
<td>No differences between groups</td>
<td>II</td>
</tr>
<tr>
<td>Saccomanno et al. 2016172</td>
<td>Randomized perspective</td>
<td>3 injections of Orthovisc (55 patients) Exercise (55 patients) 3 injections of Orthovisc + Exercise (55 patients)</td>
<td>4,12,24</td>
<td>Western Ontario and McMaster Universities (WOMAC) Index, Active Range of Movement (AROM)</td>
<td>Significant improvement in pain at 1 month in HA + exercise group</td>
<td>I</td>
</tr>
</tbody>
</table>

### Table XV. Selected studies on combined HA and physical therapies.

<table>
<thead>
<tr>
<th>Author and year</th>
<th>Study design</th>
<th>Protocol/pathology</th>
<th>Follow-up (weeks)</th>
<th>Outcome measures</th>
<th>Results</th>
<th>Level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Di Giacomo &amp; De Gasperis 2015174</td>
<td>Randomized perspective</td>
<td>5 injections of Hyalgan 20 + exercise (31 patients) Physical therapies (30 patients)</td>
<td>16, 24</td>
<td>Constant scale</td>
<td>First group (HA+PT) had statistically better results on disability and pain compared to second group (PT)</td>
<td>II</td>
</tr>
<tr>
<td>Huang et al., 2005175</td>
<td>Randomized</td>
<td>Injection of ND device + exercises + US (32) Exercises (26) Exercises + US (29) Control (31) Gonarthrosis</td>
<td>8, 1 year</td>
<td>Lequesne scale, VAS, ROM, walking speed, peak of strength</td>
<td>Combined treatment with HA, isokinetic exercises and US gave better results on disability and pain compared to exercises alone or exercises + US at 1 year</td>
<td>II</td>
</tr>
<tr>
<td>Bayramoğlu et al., 2003177</td>
<td>Randomized</td>
<td>3 injections of Synvisc® + exercise (12 patients) 3 injections of Orthovisc® + exercise (16 patients) Exercise (9 patients) Gonarthrosis</td>
<td>3,12</td>
<td>Lequesne scale, isokinetic strength</td>
<td>No significant differences in function at 3 weeks and 3 months between treatment with HA+PT (TENS + diathermy) and PT alone</td>
<td>II</td>
</tr>
<tr>
<td>Ip &amp; Fu 2015176</td>
<td>Randomized perspective</td>
<td>Exercise + fake irradiation + 5 years injections of saline solution (70 patients) Exercise + 5 injections of Hyalgan® + LLLT (70 patients) Gonarthrosis</td>
<td>7 years</td>
<td>WOMAC scale, use of prosthesis</td>
<td>Group B treated with LLLT + low molecular weight HA had greater reduction of pain and minor recourse to prosthetic surgery compared to group A treated with traditional physical therapies like US, ET and diathermy</td>
<td>II</td>
</tr>
</tbody>
</table>
Table XVI. Selected studies on post-surgical management.

<table>
<thead>
<tr>
<th>Author and year</th>
<th>Study design</th>
<th>Protocol/pathology</th>
<th>Follow-up (weeks)</th>
<th>Outcome measures</th>
<th>Results</th>
<th>Level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mathies 2006</td>
<td>RCT</td>
<td>25 patients: treatment 25 patients: control</td>
<td>4</td>
<td>VAS, circumference</td>
<td>Less pain and swelling in the first 30 days</td>
<td>I</td>
</tr>
<tr>
<td>Thein et al. 2010</td>
<td>RCT</td>
<td>28 patients: treatment 28 patients: control</td>
<td>12</td>
<td>VAS, circumference</td>
<td>Less pain, less swelling, equal functional scores</td>
<td>I</td>
</tr>
<tr>
<td>Filardo et al. 2016</td>
<td>RCT</td>
<td>45 patients: treatment 45 patients: control</td>
<td>24</td>
<td>IKDC, KOOS, VAS, Tegner scores</td>
<td>No difference</td>
<td>I</td>
</tr>
<tr>
<td>Heybeli et al. 2008</td>
<td>RCT</td>
<td>33 patients: treatment 34 patients: control</td>
<td>24</td>
<td>WOMAC, VAS</td>
<td>Better clinical scores at 6 weeks No difference at 24 weeks</td>
<td>I</td>
</tr>
<tr>
<td>Hempfling 2007</td>
<td>RCT</td>
<td>40 patients: treatment 40 patients: control</td>
<td>2 years</td>
<td>VAS, walking ability, functional results</td>
<td>Better results in treatment group</td>
<td>I</td>
</tr>
<tr>
<td>Huang et al. 2007</td>
<td>RCT</td>
<td>90 patients: treatment 30 patients: control</td>
<td>16</td>
<td>Lysholm scale, ROM, walking speed</td>
<td>Better results in treatment group</td>
<td>I</td>
</tr>
<tr>
<td>Chau et al. 2012</td>
<td>RCT</td>
<td>16 patients: treatment 16 patients: control</td>
<td>12</td>
<td>KOOS, ROM, circumference, use of analgesics</td>
<td>Improvement in pain and swelling at 2 days</td>
<td>I</td>
</tr>
<tr>
<td>Di Martino et al. 2016</td>
<td>RCT</td>
<td>30 patients: treatment 30 patients: control</td>
<td>1 year</td>
<td>ROM, VAS, circumference, SF-36, IKDC, Tegner score</td>
<td>Improvement in ROM and swelling at 30 and 60 days</td>
<td>I</td>
</tr>
<tr>
<td>Oh et al. 2011</td>
<td>RCT</td>
<td>40 patients: treatment 40 patients: control</td>
<td>1 year</td>
<td>VAS, ROM, CONSTANT, ASES</td>
<td>No difference</td>
<td>I</td>
</tr>
<tr>
<td>Doral et al. 2012</td>
<td>RCT</td>
<td>41 patients: treatment 16 patients: control</td>
<td>2 years</td>
<td>Freiburg, AOFAS score</td>
<td>Better results for treatment group</td>
<td>I</td>
</tr>
<tr>
<td>Görmeli et al. 2015</td>
<td>RCT</td>
<td>13 patients: PRP 14 patients: HA 13 patients: control</td>
<td>60</td>
<td>AOFAS score, VAS</td>
<td>Better results in PRP and HA groups compared to controls</td>
<td>I</td>
</tr>
</tbody>
</table>
HA after foot and ankle surgery

Two different level I RCTs showed that HA in addition to microfractures could offer better clinical results in osteochondral lesions of the talus\textsuperscript{187,188}.

Level of recommendation: A after knee arthroscopy in knee OA patients.

Level of recommendation: D after knee arthroscopic meniscectomy and ACL surgery.

Level of recommendation: A in post-surgical pain management.

Level of recommendation: C after shoulder arthroscopy and foot and ankle surgery.

Keypoints

- HA may determine improve in pain in the early post-operative period after knee arthroscopy.
- HA does not appear to offer any long-term clinical benefit after arthroscopic meniscectomy and LCA surgery.
- Further studies are needed to recommend the use of HA after shoulder and ankle surgery.

KEY WORDS: hyaluronic acid, viscosupplementation, sodium hyaluronate, knee arthroscopy, knee surgery, shoulder arthroscopy, shoulder surgery, ankle arthroscopy, ankle surgery, ligaments and tendons, tendon surgery.

Contraindications and adverse effects

Fifty-seven studies (40 RCTs and 17 systematic reviews) were selected\textsuperscript{65,78,98,99,101,102,104,107,108, 114,136,139, 140,148,156,158,159,189-227}.

Absolute contraindications are represented by hypersensitivity to products, suspect or presence of infections at injection skin site or selected joint, joint inflammatory states.

As intra-articular injection represents an invasive procedure, should be carefully considered in patients suffering from hematological disorders.

Hepatic pathologies and venous and/or lymphatic stasis could affect HA metabolism.

Considering the lack of scientific evidence regarding HA safety in pregnancy, breast-feeding and in the pediatric population, viscosupplementation is contraindicated in these conditions (Tab. XVII).

Adverse effects are of minor entity, as usually not limit daily life activities and disappear in a few hours or days (Tab. XVIII).

Minor adverse effects include local superficial or articular pain and/or swelling, myalgia, upper respiratory tract disorders, headache, paresthesia, lipothymia, gastrointestinal minor disorders, general fatigue, skin rash, local pruritus, urticaria, allergic manifestations, phlebitis and other minor events.

Only few studies reported more serious adverse events that however concerned a negligible percentage of included subjects and were considered improbable and unrelated to the treatment.

Level of recommendation: A for safety and tolerability of HA products.

Keypoints

- HA injections are well tolerated.
- Adverse effects due to HA injections are not frequent, minor and transient; serious adverse events recorded were not related to treatment.

KEY WORDS: hyaluronic acid injection, side effects, contraindication.

Authors contributions


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Overseeing group

Anna C Berardi, Francesco Ceccarelli, Cosimo Costantino, Cesare Faldini, Calogero Foti, Nicola Maffulli, Giuseppe Porcellini, Maria Chiara Vulpiani.

Group of preparation and evaluation of the literature

Table XVII. Contraindications reported on leaflets of each HA formulation considered.

<table>
<thead>
<tr>
<th>Trade name</th>
<th>Hypersensitivity to HA</th>
<th>Skin infections</th>
<th>Joint infections</th>
<th>Joint phlogosis</th>
<th>Pregnancy lactation</th>
<th>Lymphatic/venous stasis</th>
<th>Liver pathologies</th>
<th>Pediatric age</th>
<th>Blood disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arthrum</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Arthrum 2.5%</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Artrosulfur HA</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<td>0</td>
</tr>
<tr>
<td>Arz/Supartz</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Condrovis</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Coxarthrum</td>
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<td>0</td>
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<td>Durolane (AF)</td>
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<td>Euflexxa</td>
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<td>1</td>
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<td>0</td>
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<td>Fermathron (AF)</td>
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<tr>
<td>Go-on</td>
<td>1</td>
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<td>Go-on Mini</td>
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<td>Go-on matrix</td>
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Notes: * also Hyalone; AF: all formulations of the same brand.
Table XVIII. Adverse events reported in selected studies after HA injection.

<table>
<thead>
<tr>
<th>Author and year</th>
<th>Study design</th>
<th>Population</th>
<th>Treatments</th>
<th>Type of HA</th>
<th>Adverse events</th>
<th>Level of evidence</th>
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<tr>
<td>Abate et al. 2008</td>
<td>Systematic review</td>
<td>17 clinical trials (coxarthrosis)</td>
<td>No difference between HA formulations (data not shown)</td>
<td>- pain at injection site - heaviness at injection site</td>
<td>I</td>
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<tr>
<td>Altman et al. 1998</td>
<td>RCT multicenter</td>
<td>495 patients with idiopathic gonarthrosis</td>
<td>3 treatment groups: 2 ml/20 mg Hyalgan - HA - placebo - naproxen</td>
<td>- pain at injection site - gastrointestinal disorders - swelling/effusion - death (pre-existing cardiovascular disorders)</td>
<td>I</td>
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<tr>
<td>Altman et al. 2009</td>
<td>RCT</td>
<td>588 subjects with gonarthrosis</td>
<td>2 groups: - Phosphate Buffered Saline (PBS) - BioHA</td>
<td>20 mg/2 ml of EUFLEXXA® (1% bio-engineered sodium hyaluronate)</td>
<td>- pain at injection site - arthralgia - pneumonia - TIA</td>
<td>I</td>
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<tr>
<td>Altman et al. 2011</td>
<td>RCT</td>
<td>433 subjects with gonarthrosis</td>
<td>2 groups: - PBS - BioHA</td>
<td>20 mg/2 ml of EUFLEXXA® (1% bio-engineered sodium hyaluronate)</td>
<td>- pain at injection site - arthralgia - rhinopharyngitis - other upper airways infections - soft tissue edema adjacent to injection site - joint swelling - peripheral edema</td>
<td>I</td>
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<tr>
<td>Arden et al. 2014</td>
<td>RCT</td>
<td>208 patients with gonarthrosis</td>
<td>2 groups: - 3 ml of NASHA (Not Animal Stabilized HA) - 3 ml of saline solution buffered at pH 7</td>
<td>60 mg/3 ml of Durolane (NASHA with unique cross-linked molecular structure)</td>
<td>pain at injection site</td>
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<tr>
<td>Arrich et al. 2005</td>
<td>Systematic review</td>
<td>22 studies (gonarthrosis)</td>
<td>Hyalgan 500-730 kDa Orthovisc 1000-2900kDa HA nms 600-1200 kDa Artz 600-1200 kDa Artzal ~ 1000 kDa Synvisc ~ 7000 kDa Suplasyn 500-730 kDa BioHy 2400-3600 kDa</td>
<td>pain at injection site</td>
<td>I</td>
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<tr>
<td>Atchia et al. 2011</td>
<td>RCT</td>
<td>77 patients with unilateral coxarthrosis waiting for total hip arthroplasty</td>
<td>4 groups: - standard treatment (without infiltrations) - saline solution buffered at pH 7 - NASHA - methylprednisolone acetate (Depomedrol)</td>
<td>3 ml/60 mg of Durolane</td>
<td>post-arthroplasty infection</td>
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<tr>
<td>Bannuru et al. 2014</td>
<td>Systematic review</td>
<td>5 studies (gonarthrosis)</td>
<td>Synvisc, Hyalgan, Suplasyn, Suvenyl</td>
<td>- pain at injection site - TIA - myocardial infarction</td>
<td>I</td>
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### Hyaluronic acid injections in musculoskeletal disorders guidelines

**Continue from Table XVIII.**

<table>
<thead>
<tr>
<th>Study</th>
<th>Type</th>
<th>Subjects/Cases</th>
<th>Groups/Interventions</th>
<th>Injections Details</th>
<th>Side Effects</th>
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<tr>
<td>Blaine et al. 2006&lt;sup&gt;65&lt;/sup&gt;</td>
<td>RCT</td>
<td>660 subjects with shoulder pain</td>
<td>3 groups: - 5 infiltrations of HA - 3 infiltrations of HA + 2 of saline solution - 5 infiltrations of saline solution</td>
<td>2 ml Hyalgan (10 mg/ml) - pain at injection site - arthralgia - rhinopharyngitis - headache - vertebral pain</td>
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<tr>
<td>Brandt et al. 2001&lt;sup&gt;200&lt;/sup&gt;</td>
<td>RCT</td>
<td>226 patients with gonarthrosis</td>
<td>2 groups: - HA - saline solution</td>
<td>2 ml (15 mg/ml) of ORTHOVISC, high MW hyaluronic acid, extract from cock’s crests - pain at injection site - arthralgia - local inflammation - bruising - generalized fatigue - gastrointestinal diseases</td>
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<tr>
<td>Brzusek et al. 2008&lt;sup&gt;201&lt;/sup&gt;</td>
<td>Systematic review</td>
<td>16 studies (gonarthrosis)</td>
<td>Eufllexxa, Orthovisc, Hyalgan, Supartz, Synvisc</td>
<td>No adverse events</td>
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<td>Callegari et al. 2011&lt;sup&gt;148&lt;/sup&gt;</td>
<td>RCT</td>
<td>30 subjects with stenosing tenosynovitis of finger flexor</td>
<td>2 groups: - group A: corticosteroids + HA - group B: open surgery</td>
<td>1 ml 0.8% HA (Sinovial Mini) + methyl prednisolone acetate 40 mg/1 ml (Depo-medrol) - pain at injection site - joint swelling</td>
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<td>Chang et al. 2013&lt;sup&gt;216&lt;/sup&gt;</td>
<td>Systematic review</td>
<td>9 studies (ankle osteoarthritis)</td>
<td>Not specified</td>
<td>- post-injection pain - increase in volume of inguinal lymph nodes - localized pruritus - dissecans osteochondritis (4 months after treatment)</td>
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<td>Chevalier et al. 2010&lt;sup&gt;202&lt;/sup&gt;</td>
<td>RCT</td>
<td>253 patients with gonarthrosis</td>
<td>2 groups: - arthrocentesis + infiltration of HA - arthrocentesis + injection saline solution</td>
<td>6 ml of Hylan G-F 20 (Synvisc-One) - pain at injection site - joint stiffness - intraarticular effusion - joint swelling</td>
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<tr>
<td>Lee et al. 2011&lt;sup&gt;158&lt;/sup&gt;</td>
<td>RCT</td>
<td>43 subjects with gonarthrosis</td>
<td>2 groups: - HA + 30 mg ketorolac (3 weeks), followed by HA alone (2 weeks) - HA alone for 5 weeks</td>
<td>2.5 ml (1%) of Hyal (MW: 940-1020 kDa) - pain at injection site (HA+ketorolac group)</td>
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<td>Day et al. 2004&lt;sup&gt;108&lt;/sup&gt;</td>
<td>RCT multicentric study</td>
<td>223 patients with gonarthrosis</td>
<td>2 groups: - HA in saline solution - only saline solution</td>
<td>25 mg of ARTZ (extract from cock’s crest, MW 6.2×105-11.7×105 Da) - pain at injection site</td>
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<tr>
<td>Diracoglu et al. 2009&lt;sup&gt;222&lt;/sup&gt;</td>
<td>RCT</td>
<td>63 patients with bilateral gonarthrosis</td>
<td>2 groups: - HA - placebo</td>
<td>Hylan G-F 20 (Synvisc) - No adverse events</td>
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To be continued
<table>
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<tr>
<th>Authors</th>
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<td>Espallargues et al. 2003</td>
<td>Systematic review</td>
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<td>(gonarthrosis)</td>
<td>Hylan G-F 20, pain at injection site, muscle cramps, hemorrhoids, impatience</td>
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<td>Fernández López et al. 2006</td>
<td>Systematic review</td>
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<td>(coxarthrosis)</td>
<td>Not specified, No adverse events</td>
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<td>Filardo et al. 2012</td>
<td>RCT</td>
<td>109</td>
<td>patients with knee chondropathy or gonarthrosis</td>
<td>Hyalubrix (HA with MW &gt; 1500 KDa), pain at injection site</td>
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<td>Fuchs et al. 2005</td>
<td>RCT</td>
<td>60</td>
<td>patients with chronic non radicular lumbar pain</td>
<td>10 mg of Ostenil® mini, highly purified HA, from bacterial fermentation, in 1 ml of saline solution</td>
<td>No adverse events</td>
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<td>Fuchs et al. 2006</td>
<td>RCT</td>
<td>56</td>
<td>patients with rhizarthrosis</td>
<td>10 mg/1 ml of Ostenil® mini (1,2 MDa), lipotimia, pain at index finger, sciatica, pulmonary carcinoma</td>
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<td>Oh et al. 2011</td>
<td>RCT</td>
<td>80</td>
<td>subjects submitted to rotator cuff surgical repair</td>
<td>5 g of HA / carboxymethylated cellulose (CMC): Guardix-Sol®</td>
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<td>Ishijima et al. 2014</td>
<td>RCT</td>
<td>200</td>
<td>patients with gonarthrosis</td>
<td>25 mg of high MW HA (2700 kDa), Chugai Pharmaceutical Co., joint stiffness</td>
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<td>Jørgensen et al. 2010</td>
<td>RCT</td>
<td>337</td>
<td>patients with gonarthrosis</td>
<td>2 ml of sodium hyaluronate (Hyalgan, 10 mg / ml), pain at injection site</td>
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<td>Jüni et al. 2007</td>
<td>RCT</td>
<td>660</td>
<td>patients with gonarthrosis</td>
<td>2 ml of Synvisc, Orthovisc and Ostenil, joint effusion, redness at injection site, septic arthritis, anaphylactic shock</td>
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<tr>
<td>Lee et al. 2006</td>
<td>RCT</td>
<td>146</td>
<td>subjects with gonarthrosis</td>
<td>Hyruan Plus (high MW 3000 kD), Hyal (medium MW 750 kD), pain at injection site, localized pruritus, urticaria, myalgia, paresthesias</td>
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<td>Leighton et al. 2014</td>
<td>RCT</td>
<td>442</td>
<td>subjects with gonarthrosis</td>
<td>60 mg/3 ml of Durolane, pain at injection site, arthralgia, joint stiffness, joint swelling</td>
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*To be continued*
### I.S.Mu.L.T. Hyaluronic acid injections in musculoskeletal disorders guidelines

*Continue from Table XVIII.*

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<td>Lundsgaard et al. 2008&lt;sup&gt;225&lt;/sup&gt;</td>
<td>RCT</td>
<td>251 subjects with gonarthrosis</td>
<td>3 groups: - 2 ml of HA - 20 ml saline solution - 2 ml saline solution</td>
<td>2 ml of Hyalgan (10.3 mg/ml)</td>
<td>No adverse events I</td>
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<td>Maheu et al. 2011&lt;sup&gt;226&lt;/sup&gt;</td>
<td>RCT</td>
<td>276 patients with gonarthrosis</td>
<td>2 groups: - 20 ml of medium MW HA (F60027) - 16 mg of high MW HA (Hylan G-F20)</td>
<td>20 mg of F60027 (Structorial) 16 mg of Hylan G-F20</td>
<td>pain at injection site I</td>
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<td>Medina et al. 2006&lt;sup&gt;220&lt;/sup&gt;</td>
<td>Systematic review</td>
<td>7 studies (gonarthrosis)</td>
<td>-</td>
<td>Artzal, Synvisc, Hylagan, Durolane, Suplasyn, NRD101</td>
<td>allergic manifestations: - sweating - pallor - feeling of thoracic or epigastric oppression - cyanotic skin - hypotension</td>
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<td>Migliore et al. 2009&lt;sup&gt;102&lt;/sup&gt;</td>
<td>RCT</td>
<td>42 subjects with coxarthrosis</td>
<td>2 groups: - 4 ml HA derived from bacterial fermentation - 4 ml mepivacaine 2%</td>
<td>4 ml of Hyalubrix (60 mg)</td>
<td>pain at injection site I</td>
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<tr>
<td>Munteanu et al. 2011&lt;sup&gt;140&lt;/sup&gt;</td>
<td>RCT</td>
<td>151 patients with osteoarthritis of first metatarsophalangeal joint</td>
<td>Participants randomly allocated to receive up to 1 ml intraarticular injection of both Hylan G-F20 or placebo</td>
<td>Hylan G-F 20 (Synvisc)</td>
<td>cellulitis at injection site I</td>
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<td>Navarro-Sarabia et al. 2011&lt;sup&gt;114&lt;/sup&gt;</td>
<td>RCT</td>
<td>306 subjects with gonarthrosis</td>
<td>2 groups: - HA - saline solution</td>
<td>2.5 ml (1%) of medium MW (900000 Da) sodium hyaluronate, obtained from fermentation of Streptococcus zoopidemicus (Adant)</td>
<td>allergic reaction not specified I</td>
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<td>Neustadt et al. 2005&lt;sup&gt;209&lt;/sup&gt;</td>
<td>RCT multicenter</td>
<td>327 patients with gonarthrosis</td>
<td>3 groups: - 4 injections of high MW HA (O4) - 3 HA and 1 arthrocentesis (O3A1) - 4 arthrocentesis (A4)</td>
<td>2 ml / 30 mg of highly purified high MW HA (Orthovisc, 1-2.9 MDa)</td>
<td>- pain at injection site - arthralgia - hematoma/ecchymosis at injection site - rhinopharyngitis - headache - vertebral pain - heart attack - gastrointestinal bleeding</td>
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<tr>
<td>Oliveras-Moreno et al. 2008&lt;sup&gt;226&lt;/sup&gt;</td>
<td>RCT</td>
<td>41 subjects with pain at temporomandibular joint (Wilkes stage II)</td>
<td>2 groups: - HA - methocarbamol + paracetamol</td>
<td>1 ml of sodium hyaluronate 1% (Ostenil mini)</td>
<td>No adverse events I</td>
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<td>Özgen et al. 2012&lt;sup&gt;78&lt;/sup&gt;</td>
<td>RCT</td>
<td>24 subjects with tendinitis of supraspinatus</td>
<td>2 groups: - HA - physical means</td>
<td>2 ml/16 mg of G-F 20 with a MW of 6x106</td>
<td>No adverse events I</td>
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<td>Palmieri et al. 2013&lt;sup&gt;159&lt;/sup&gt;</td>
<td>RCT</td>
<td>62 patients with bilateral gonarthrosis</td>
<td>3 groups: - 66 mg of HA - 49.5 mg of HA + 5 mg of diclofenac</td>
<td>66 mg/2 ml of HA (Variofill®)</td>
<td>No adverse events I</td>
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*To be continued*
Continue from Table XVIII.

<table>
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<tr>
<th>Study</th>
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<th>Intervention Details</th>
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<td>Petrella et al.</td>
<td>RCT</td>
<td>98 subjects with gonarthrosis</td>
<td>3 groups: - HA (Hydros) - HA + triamcinolone acetonide 10 mg (Hydros TA) - HA (Synvisc-One)</td>
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<td>2 ml of HA (Hyalgan®)п pain at injection site</td>
</tr>
<tr>
<td>Qvistgaard et al.</td>
<td>RCT</td>
<td>101 patients with coxarthrosis</td>
<td>3 groups: - 1ml/40 mg methylprednisolone + 2 fake injections + 3 injections HA (2 ml) - 3 injections of saline solution (2 ml)</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>2 ml of HA (Hyalgan®)п pain at injection site</td>
</tr>
<tr>
<td>Reichenbach et al.</td>
<td>Systematic review</td>
<td>13 studies (gonarthrosis)</td>
<td>Artzal, Orthovisc, Hyalgan, Ostenil, Bio-Hy - pain at injection site - joint swelling</td>
</tr>
<tr>
<td>Richette et al.</td>
<td>RCT</td>
<td>122 patients with symptomatic coxarthrosis</td>
<td>2 groups: - HA - saline solution</td>
</tr>
<tr>
<td>Saito et al.</td>
<td>Systematic review</td>
<td>5 studies (knee rheumatoid arthritis)</td>
<td>Not specified - pain at injection site</td>
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<tr>
<td>Saito et al.</td>
<td>Systematic review</td>
<td>19 studies (chronic shoulder pain)</td>
<td>NRD 101, Artz (900 kD), SLM-10 (1900 kD), Hyalart, Subenyl (1900 kD), Orthovisc (1000-2900 kD), Hyalgan (500-730 kD) - pain at injection site - joint swelling</td>
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<tr>
<td>Shi et al.</td>
<td>Cochrane review</td>
<td>11 studies (temporo-mandibular joint disorders)</td>
<td>- discomfort at injection site - joint swelling</td>
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<tr>
<td>Stahl et al.</td>
<td>RCT</td>
<td>52 patients with grade II rhizarthrosis</td>
<td>2 groups: - methylprednisolone acetate - HA</td>
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<tr>
<td>Strand et al.</td>
<td>RCT</td>
<td>379 patients with gonarthrosis</td>
<td>2 groups: - HA - PBS</td>
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<tr>
<td>Tang 2012</td>
<td>RCT</td>
<td>162 patients with knee Kashin-Beck disease</td>
<td>2 groups: - Intra-articular HA - meloxicam per os</td>
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<tr>
<td>Tikiz et al.</td>
<td>RCT</td>
<td>43 patients with coxarthrosis</td>
<td>2 groups: - Low MW HA - High MW HA</td>
</tr>
</tbody>
</table>

To be continued
## References

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158. Lee SC, Rha DW, Chang WH. Rapid analgesic onset of intra-articular hyaluronic acid compared with ketorolac in osteoarthritis of the


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