

Hyaluronic acid vs corticosteroids in symptomatic knee osteoarthritis: a mini-review of the literature

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Summary

Introduction. Although intra-articular injections of hyaluronic acid (HA) are common non-operative measures used in clinical practice in the management of symptomatic osteoarthritis, there is a great controversy on their efficacy and safety compared to corticosteroids (CSs).

Efficacy. Conflicting results have been reported in clinical trials and meta-analysis due to methodological differences in study design, along with collection, analysis, and interpretation of data. Even if some studies reported small or no differences of HA compared with CSs (or inferred that HA is not more effective than saline as a placebo), in general CSs have shown to be superior in the short term (especially on pain control), while better results have been reported with HA at subsequent evaluations, but with only a moderate effect after 26 weeks.

Safety. Mild or moderate adverse events have generally been reported after HA injections, the most common being injection site pain. HA is generally considered safe compared to CSs or saline. Furthermore, HA has shown to be safe also after a previous course of injections.

Conclusions. Conflicting results have been reported on the efficacy and safety of HA. Guidelines are controversial and in most of the cases “uncertain” recommendations are provided due to inconclusive evidence in literature. However, HA does not seem to have significantly higher side effects when compared to saline or CSs injections, and provides better medium-term control of symptoms in patients with mild to moderate knee osteoarthritis.

KEY WORDS: knee; osteoarthritis; hyaluronic acid; injection.

Introduction

Intra-articular injections are common non-operative measures used in clinical practice in the management of symptomatic osteoarthritis with corticosteroids (CSs) and hyaluronic acid (HA) being the two most commonly injected substances (1). Although widely used in daily practice, there is a great controversy on the management of osteoarthritis via injections. In fact, although guidelines from many international societies recommend CSs as the gold standard (2-5), many adverse events have been described (6, 7). On the other hand, even if there is increasing evidence that HA injections give at least the same results, avoiding the side effects reported with CSs (8-17), international guidelines in most of the cases are controversial or inconclusive on HA injections (2-5, 18-21).

The aim of the present study was to report a mini-review of the literature on the comparison between HA and CSs injections in the non-operative management of symptomatic knee osteoarthritis, focusing on efficacy, adverse events, and safety.

Rationale: CSs vs HA

CSs have both anti-inflammatory and immunosuppressive effects acting directly on nuclear steroid receptors and interrupting the inflammatory and immune cascade. CSs reduce vascular permeability and inhibit accumulation of inflammatory cells, phagocytosis, production of neutrophil superoxide, metalloprotease, and metalloprotease activator, and prevent the synthesis and secretion of several inflammatory mediators (22-24).

HA is a non-sulfated glycosaminoglycan, and a natural component of various animal and human tissues (25). HA could bind to specific receptors, triggering cytokine release and stimulation of cell cycle proteins, and stimulating cell migration and proliferation (26). Molecular weight and concentration of HA could be reduced in patients with osteoarthritis (27-29), thus resulting in an increased susceptibility of cartilage to breakdown. The mechanisms of action of HA injections have not been completely clarified, but exogenous HA is thought to enhance endogenous HA synthesis, stimulate chondrocyte metabolism and synthesis of cartilage matrix components, and inhibit chondrodegenerative enzymes; thus reducing the inflammatory process (30-32). Many different HA are commercially available, classified according to their chemical structure (low molecular weight, high molecular weight, cross-linked, and reticulated), having different biological and biomechanical activities, and different residency time.

Clinical studies: CSs vs HA

Comparing the efficacy of CSs and HA in patients with symptomatic knee osteoarthritis, conflicting results have been reported, both in clinical trials and meta-analysis.

In general, while CSs have shown to be more effective (especially on pain control) in the short term (<1 month), better results have been reported with HA at subsequent evaluations, providing only a moderate effect after 26 weeks (8, 12, 17, 33-39). Furthermore, the efficacy of repeated injections of HA, after a previous course of either HA or CSs, has also been proved (37, 40). However, other studies neglected the efficacy of HA (41-44), reporting only small or no differences compared with CSs.

The efficacy HA has also been compared to saline injections. Saline has a great placebo effect when injected into the joint (45) and, also in this case, conflicting results have been reported. While some studies inferred that HA is not more effective than saline (9, 11, 46), three recent systematic reviews and meta-analysis (39, 47, 48), showed that HA provided better control of pain and dysfunction compared to saline, especially for US-approved HA (47).

The highly conflicting results reported in clinical trials are mainly due to adoption of different HA (some of which are not US-approved), the inconsistent methodology adopted, different end-points, different outcomes, and statistical tests used.

The inconsistent results reported in meta-analysis and guidelines are mainly due to the adoption of different inclusion and exclusion criteria, leading to some papers to be included in certain meta-analysis and excluded from others. Furthermore, heterogeneity, methodological errors, and confusion on effect size interpretation have also been reported (34, 38).

There is a great debate on the need to include and analyze "all the available evidence" (20) (including also lower level-of-evidence studies and unpublished data, in order to reduce publication bias), or only "the best available evidence" (49) (including only level-of-evidence-1 studies or giving high quality studies a greater weight, in order to avoid the results to be biased by lower level-of-evidence studies with small sample size and poor methodology). In fact, it has been reported that lower level-of-evidence studies tend to show greater differences (bigger effect size) between HA and CSs, while high level-of-evidence studies with good methodology and strong statistical analysis of data tend to show small or no differences (50).

Adverse events and safety

Mild or moderate adverse events have generally been reported after intra-articular injections, the most common being injection site pain (51). The incidence of those events is very broad, depending on different methodologies adopted by different Authors.

Although CSs are considered the gold standard substance to be injected into the joint in patients with symptomatic osteoarthritis (2, 3, 5), severe adverse events have been reported, such as suppression of cartilage proteoglycan synthesis, worsening of cartilage lesions, degenerative lesions in normal cartilage, and skin discoloration (6, 7).

HA is generally considered safe compared to CSs or saline (17, 35, 40-42, 52). Furthermore, HA is considered safe also after a previous course of HA injections (35, 37, 40). Despite this evidence, the safety profile of intra-articular HA injections has recently been questioned (43). It should be noted that serious adverse events were not related to treatment, unpublished and unverifiable data were included, and incorrect statistical parameters were used. When those issues were addressed, HA proved to be safe and effective (34, 46, 53).

Conclusions

Conflicting results have been reported in clinical studies and meta-analysis on the efficacy and safety of HA. Guidelines are controversial and "uncertain" recommendations are provided in most of the cases due to inconclusive evidence in literature. However, HA does not seem to have significantly higher side effects when compared to saline or CSs injections, and provides better medium-term control of symptoms in patients with mild to moderate knee osteoarthritis.

More studies are needed to better clarify the controversies on this topic, along with a homogeneous methodology in study design, and collection, analysis, and interpretation of data.

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