

# Intra-articular Injections of Hyaluronic Acid and Other Drugs in the Knee Joint

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**Abstract** *Background:* Degenerative osteoarthritis of the knee (OA) affects 35% of persons older than 65 years. If pain persists after non-invasive treatment, some intra-articular drugs can be tried before surgical treatment. *Questions/Purposes:* The purpose of this article is to review the literature after 2006 with the aim of answering two questions: (1) Are intra-articular injections of corticosteroids (CS), hyaluronic acid (HA) and platelet-rich plasma (PRP) effective in painful knee OA? and (2) Which of these drugs is more effective? *Methods:* The search engines were MedLine and the Cochrane Library. The keywords used were: knee, osteoarthritis, and intra-articular injections. Eight hundred and forty-four articles were found but only 142 had been published after 2006. Of those, only 14 were selected and reviewed because they were strictly focused on the topic and the questions of this article. *Results:* The clinical efficacy of intra-articular injections of HA and CS in patients with knee OA has been demonstrated. Pain reduction after three to five weekly injections of HA lasts between 5 to 13 weeks (sometimes up to 1 year). Pain reduction is less durable after CS injections (2 to 3 weeks). Recent reports indicate that PRP could have a better performance than HA in younger patients. *Conclusions:* Three to five weekly intra-articular injections of HA are recommendable in patients with knee OA before surgical treatment. CS injections have a very short effect. The efficacy and duration of PRP injections require further studies.

Level of Evidence: Level IV therapeutic study. See levels of evidence for a complete description.

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## Introduction

Degenerative osteoarthritis of the knee (OA) is a major source of knee pain and affects 35% of persons older than 65 years [12]. Non-invasive treatment is commonly indicated in the early radiological phases of OA by means of relative rest, oral anti-inflammatory drugs, oral analgesics, and physical therapy. If pain persists, intra-articular injections of a number of drugs may be indicated before surgical treatment. These typically include hyaluronic acid (HA), corticosteroids (CS), and platelet-rich plasma (PRP). Two systematic reviews have been published so far on the efficacy of intra-articular injections of HA and CS [3] [4].

The purpose of this article is to summarize the systematic reviews and the MedLine literature after 2006 with the aim of answering two questions: (1) Are intra-articular injections of HA, CS and PRP effective in painful knee OA? and (2) Which of these treatments is more effective?

## Methods

A review has been performed on role of intra-articular injections of HA, CS, and PRP in patients with degenerative OA of the knee. The search engines were MedLine (PubMed) and the Cochrane Library. The keywords used were: knee, osteoarthritis, and intra-articular injections. One hundred and forty-two articles were found after 2006, but only 14 were selected and reviewed because they were deeply focused on the topic.

## Results

Intra-articular injections of corticosteroids appear to be effective in providing short-term pain relief in knees affected

by OA. In a systematic review, Bellamy et al. [3] documented pain reduction within 2 to 3 weeks in patients with knee OA treated with intra-articular injections of CS. At 4 to 24 weeks post-injection, there was lack of evidence of effect on pain. Triamcinolone hexacetonide was more effective than betamethasone. Therefore, the short-term benefit of intra-articular CS is clear.

There are multiple studies that support the use of HA injections for relief of painful symptoms of knee OA and suggest a longer duration of action than that seen with CS. Bellamy et al. [4] found that intra-articular injections of HA are effective in patients with knee OA especially at the 5 to 13 week post injection period. In a randomized, double-blind, multicenter, placebo-controlled study, Huang et al. [7] showed that five weekly intra-articular injections of HA relieved pain, and improved function in patients with OA. Foti et al. [6] demonstrated that HA reduces pain, improves knee range of motion, and increases quality of life in patients with knee OA. Altman et al. also found that repeat injections of HA are effective, safe, and well tolerated. The AMELIA study [10] compared repeated injections of HA against placebo assessing efficacy and safety and searched for an effect on disease progression over 40 months. The results of AMELIA showed that intra-articular injections of HA improved knee OA symptoms for up to 1 year. In a meta-analysis, Bannuru et al. [2] assessed the therapeutic trajectory of HA vs placebo. The main conclusion was that HA is efficacious by 4 weeks, reaches its maximal effectiveness at 8 weeks and lasts up to 24 weeks. In a phase III, double-blind multicenter, randomized study [11], Sinovial (highly purified intra-articular injection of HA) and Synvisc (G-F20) were found to be equivalent. Maheu et al. [9] found F60027 (medium molecular weight hyaluronan product—F60027, Structovial) and Hylan G-F20 (Synvisc) equally effective in relieving pain in patients with knee degenerative OA.

Other studies have compared HA with PRP. In a prospective, cohort study with a control group, Spaková et al. [14] analyzed patients with initial stages of knee OA. One group of patients was treated using three intra-articular injections of PRP, and the other group of patients was treated with three injections of HA. The results obtained support the use of autologous PRP in the treatment of the initial stages of knee OA. However, the authors recognized that further studies are needed to confirm these preliminary results.

In a prospective comparative study, Filardo et al. [5] compared two different approaches to PRP production as intra-articular injection treatments for patients with knee OA. One group was treated with three injections of PRP prepared with a single-spinning procedure (PRGF), the other group with three injections of PRP obtained with a double-spinning approach. Similar results were found in both groups, with a significant clinical improvement with respect to the basal level. The best results were obtained in younger patients with lesser degrees of disease.

#### *Which One Is More Effective (CS, HA, or PRP)?*

In comparisons of CS and HA products performed by Bellamy et al. [3, 4], no significant differences were found at 1 to

4 weeks post injection. Between 5 and 13 weeks post injection, HA products were more effective than CS.

However, in a prospective randomized study [13], it was found that the clinical effects of HA and CS are comparable and that both drugs are useful.

In another prospective comparative study, Kon et al. [8] compared the efficacy of PRP and two types of intra-articular injections of HA. One group was treated with three injections of autologous PRP. A second group was treated with injections of high-molecular weight HA. The third group was treated with low-molecular weight (LW) HA. At 2 months, the PRP and LW HA groups showed a similar improvement, with better results compared with the high-molecular weight HA group. At 6 months, better results were found in the PRP group. PRP and LW HA treatments offered similar results in patients aged over 50 years.

## Discussion

Knee OA affects 35% of persons older than 65 years [12]. If pain persists after oral anti-inflammatory or analgesic medications and physical therapy are tried, then intra-articular injections of a number of drugs may be indicated before surgical treatment, mainly corticosteroids (CS), hyaluronic acid (HA), and platelet-rich plasma (PRP).

The clinical effects of intra-articular injections of HA and CS have been shown to be similar. However, the duration of pain relief has been shown to be longer with HA than with CS [1] [2–7] [9–11]. In some preliminary reports, PRP has shown a better performance than intra-articular injections of HA in younger patients with degenerative OA of the knee [5] [8] [14].

In conclusion, current evidence supports the practice of administration of three to five weekly intra-articular injections of HA in patients with knee OA before surgical treatment. Their efficacy may last up to 1 year. However, CS injections have a very short effect and their use is not recommended for long-term management of this disease. Intra-articular injections of PRP may be a promising alternative but future well-designed studies are needed before PRP can be accepted into current practice.

**Disclosures** The author certifies that he has no commercial associations (e.g., consultancies, stock ownership, equity interest, patent/licensing arrangements, etc.) that might pose a conflict of interest in connection with the submitted article.

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