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Review

Evidence and recommendations for use of intra-articular injections for knee osteoarthritis

Christelle Nguyen [a,b,*], Marie-Martine Lefèvre-Colau [a,c], Serge Poiraudeau [a,c], François Rannou [a,b]

[a] Université Paris Descartes, PRES Sorbonne Paris Cité, Service de Rééducation et de Réadaptation de l'Appareil Locomoteur et des Pathologies du Rachis, Hôpital Cochin, Assistance Publique – Hôpitaux de Paris, Paris, France
[b] Université Paris Descartes, PRES Sorbonne Paris Cité, Laboratoire de Pharmacologie, Toxicologie et Signalisation Cellulaire, INSERM UMR-S 1124, UFR Biomédicale des Saints Pères, Paris, France
[c] Université Paris Descartes, PRES Sorbonne Paris Cité, INSERM UMR-S 1153 et Institut Fédératif de Recherche sur le Handicap, Paris, France

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ABSTRACT

Pharmacological treatments are widely recommended in international guidelines for management of osteoarthritis (OA). However, the use of intra-articular (IA) therapies of diverse active drugs remains controversial. We critically reviewed studies of the efficacy and safety of IA injections of corticosteroids (CS), hyaluronic acid (HA), platelet-rich plasma (PRP), and botulinum toxin A (BTA) and evidence-based international recommendations for their use in treating knee OA. The process of article selection was unsystematic. Articles were selected on the basis of authors' expertise, self-knowledge, and reflective practice. Only studies assessing knee OA were included. IA CS and HA injections were conditionally to fully recommended for treating knee OA. No recommendations have been formulated for IA PRP or BTA. The evidence remains inconsistent and controversial for the use of IA therapies for knee OA. The characteristics of and selection criteria for the OA population that would likely benefit from these therapies need to be identified. Accurately phenotyping and selecting patients is mandatory in future randomized controlled trials. Therefore, efficacy and safety meta-analyses should be performed, as should qualitative and sensitivity analyses of published trial results.

1. Introduction

Pharmacological treatments, including acetaminophen and non-steroidal anti-inflammatory drugs, are widely recommended in national and international guidelines for managing knee osteoarthritis (OA) in primary care settings [1,2]. However, patients with knee OA often have comorbidities, which raise concerns about the risk/benefit ratio of these widely prescribed drugs [3]. Therefore, intra-articular (IA) therapies might be an alternative and safe treatment for these patients.

However, the efficacy of IA therapies of diverse active drugs remains controversial among organizations because of important differences in the interpretation of evidence. Indeed, recommendations are usually based on the results of systematic reviews and meta-analysis of randomized controlled trials (RCTs). These reviews are often inconclusive regarding the benefits of these treatments and are limited by the heterogeneity and quality of the included studies. Furthermore, concerns have been raised about the risk/benefit profile of IA drugs.

Here, we review studies of the efficacy and safety of IA injections of corticosteroids (CS), hyaluronic acid (HA), platelet-rich plasma (PRP), and botulinum toxin A (BTA) and evidence-based international recommendations for their use in treating knee OA.

2. Methods

The process of selecting articles related to knee OA for this critical narrative review was not systematic. Individual trials, systematic reviews and meta-analyses included in the latest American College of Rheumatology (ACR) and Osteoarthritis Research Society International (OARSI) international guidelines were searched, as was MEDLINE *via* PubMed from inception to December 2015 for additional guidelines, trials, systematic reviews and meta-analyses. The following MeSH terms were used:

* Corresponding author at: Service de Rééducation et de Réadaptation de l'Appareil Locomoteur et des Pathologies du Rachis, 27, Rue du Faubourg Saint-Jacques, 75014 Paris, France. Tel.: +33 1 58 41 29 45; fax: +33 1 58 41 25 38.
E-mail address: christelle.nguyen2@aphp.fr (C. Nguyen).

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injection, knee osteoarthritis, corticosteroids, hyaluronic acid, platelet-rich plasma, and botulinum toxin. Articles were selected on the basis of authors' expertise, self-knowledge, and reflective practice.

3. Results

3.1. CS injection

Although OA is generally considered a degenerative joint disorder, there is evidence that a low-grade inflammation also occurs at some phases of the disease [4], which provides sound rationale for the use of drugs targeting local inflammation. CSs are potent anti-inflammatory agents that act by a variety of mechanisms on different cellular levels. IA CS has been used for knee OA for over 50 years [5] and is available in both crystalline and non-crystalline forms. The crystalline triamcinolone and the non-crystalline prednisolone and methylprednisolone are used most frequently. Although the 2012 ACR [1] and 2014 OARSI guidelines [2] both recommend participation in exercise programs as well as weight loss (for overweight patients) as first-line treatments for all patients with symptomatic knee OA, the recommendations largely differ in the use of IA CS [1,2]. ACR guidelines include a conditional, weak recommendation for the use of IA CS in patients unresponsive to basic treatment [1]. Conversely, in OARSI guidelines, IA CS is considered an appropriate treatment, whatever the OA subtype and comorbidities [2]. This recommendation is based on 2 systematic reviews, published before 2010, that supported clinically significant short-term decreases in pain [6,7]. The quality of evidence was rated good. However, no effect size for pain was available [2].

The 2015 update of a 2006 Cochrane review [7] included 14 new trials, for a total of 27 trials [8]. Studies included were RCTs or quasi-RCTs, with a control group receiving sham or no intervention. The median prednisolone equivalent dose across all trials was 50 mg, and the median number of CS injections was one. Trials randomized a median of 76 participants (range 16–205). The meta-analysis found CS more effective for pain reduction than control interventions (standardized mean difference [SMD] −0.40, 95% CI −0.58 to −0.22), which corresponds to a difference in pain scores of 1.0 cm on a 10-cm visual analog scale (VAS) [8]. When results were stratified by length of follow-up, benefits were moderate at 1–2 weeks (SMD −0.48, 95% CI −0.70 to −0.27), small to moderate at 4–6 weeks (SMD −0.41, 95% CI −0.61 to −0.21), and small at 13 weeks (SMD −0.22, 95% CI −0.44 to 0.00), with no effect found at 26 weeks (SMD −0.07, 95% CI −0.25 to 0.11) [8]. In addition, CS injection was more effective for improving function than the control intervention (SMD −0.33, 95% CI −0.56 to −0.09) [8]. Adverse events could not be accurately assessed. Little to no evidence was found for an association with CS dosage, ultrasound guidance, local anesthetic, crystalline preparation, or type of control intervention [8]. However, the authors found a moderate to large degree of between-trial heterogeneity, and most of the identified trials were considered small, and the quality of evidence for the major outcomes was graded "low" [8]. Interestingly, analysis of pain and function stratified by funding source, independent or not of industry, did not show any differences. No hierarchy could be clearly established between corticosteroids in terms of efficacy according to their half-life, onset of action or duration. Therefore, the choice of the corticoid mainly relies on the physician's practice and the availability of the product.

Finally, a systematic review and network meta-analysis of pharmacological treatment for knee OA that included 129 trials (32,129 participants) [9] found that for treating OA-related knee pain at 3 months, the effect size (ES) was superior for IA CS than IA placebo (ES = 0.32, 95% CI 0.16–0.47), oral placebo (ES = 0.61, 95% CI 0.32–0.89), oral acetaminophen (ES = 0.42, 95% CI 0.12–0.73) and all other oral treatments [9] and was among the highest of all the pharmacological treatments assessed.

3.2. HA injection

The clinical benefit of IA HA on knee OA may rely on 2 mechanisms: [1] mechanical viscosupplementation of the joint (allowing lubrication and shock absorption), and [2] the re-establishment of joint homeostasis by inducing endogenous HA production, which continues long after the exogenous injection has left the joint. However, international guidelines are even more inconsistent for the use of IA HA than IA CS for knee OA. The 2014 OARSI guidelines recommended IA HA injection with a degree of uncertainty for knee-only OA and not appropriate for multiple-joint OA [2]. This recommendation was based on a recent systematic review demonstrating a small but significant efficacy of IA HA for knee OA pain by week 4, with a peak at week 8 (reaching moderate clinical significance) and residual benefit until 24 weeks [10]. Another review found moderate benefits of IA HA for pain and physical function in knee OA [11]. A third review comparing IA HA and IA CS found that IA HA provided greater benefit at 12 and 26 weeks [6]. Conversely, the 2012 ACR guidelines contain no recommendations regarding the use of IA HA as first-line treatment. IA HA injections for knee OA were conditionally recommended only for patients with inadequate response to initial therapy by the technical expert panel [1].

In a systematic review and network meta-analysis of pharmacological treatment for knee OA by Bannuru et al., the ES for IA CS (ES = 0.63, 95% CI 0.39–0.88) was the highest among all the pharmacological treatments assessed [9]. In the most recently updated systematic review and meta-analysis, including only trials considered to have low risk of bias (adequate randomization and concealment, and double-blind design), 8 RCTs (2199 randomized patients) met the inclusion criteria [12]. At 3 months, IA HA significantly reduced pain intensity (SMD −0.21, 95% CI −0.32 to −0.10) and improved function (SMD −0.12, 95% CI −0.22 to −0.02) as compared with placebo. The authors concluded that IA HA provided a moderate but real benefit for patients with knee OA [12]. Experimental data suggest a differential action by HA molecular weight (MW). Consistently, some authors found that HA MW may affect its efficacy and safety, with the highest MW more efficient than low MW HA [13]. However, the studies included were heterogeneous, publication bias was high and these conclusions were not supported by other studies. Another meta-analysis even suggested more frequent post-injection reactions with high rather than low MW HA [14]. In clinical practice, HA LW is most commonly used. In trials with low risk of bias, the number of IA HA injections varied from 1 injection for 1 cycle to 5 injections for 4 cycles [12]. However, trials directly comparing different regimens of injections are lacking, and till date, we lack evidence of an effect of number of joint injections. One can assume that increased number of injections might increase the risk for serious adverse events [11]. Seven of the 8 trials included in this meta-analysis received industry funding, and the authors of the meta-analysis disclosed competing interests [12]. However, stratified analysis by funding source has not been performed.

3.3. PRP injection

IA "biological therapies" have generated intense interest as possible modifiers of cartilage biology. PRP derived from autologous blood with a high concentration of activated platelets in a small volume of plasma, which can release a host of mediators and growth factors that act during the initial phase of tissue healing and regeneration. Several growth factors are released, such as