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Cochrane in *CORR*

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Cochrane in *CORR*®: Intra-articular Corticosteroid For Knee Osteoarthritis

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(Jüni P, Hari R, Rutjes AWS, Fischer R, Silletta MG, Reichenbach S, da Costa BR. Intra-articular corticosteroid for knee osteoarthritis. Cochrane Database of Systematic Reviews 2015, Issue 10. Art. No.: CD005328. DOI: 10.1002/14651858.CD005328.pub3.)

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Cochrane Reviews are regularly updated as new evidence emerges and in response to feedback, and The Cochrane Library (http://www.thecochranelibrary.com) should be consulted for the most recent version of the review.

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Importance of the Topic

Knee osteoarthritis (OA) affects more than 9 million adults aged 45 years or older in the United States [6]. It is the most-common cause of knee pain in this population and imposes substantial global health and economic burdens. By the year 2020, OA will become the fourth-leading cause of disability globally [9]. One estimate suggests that 10% of individuals older than 55 years of age have knee OA, and of those 25% are severely limited by knee pain [8]. As the population continues to age, the incidence of knee OA will continue to increase, further burdening an already-strained healthcare system [3].

The majority of patients with knee OA are treated without surgery, using some combination of oral and topical anti-inflammatory medications, patient weight loss, physiotherapy, and various knee injectables. The goals of nonsurgical treatment include symptom relief and improved function. Nonsurgical management can help to delay knee replacement in young patients for whom knee replacement would not be expected to be a lifelong solution, and for older patients to try to minimize their exposure to surgical risk. Intra-articular corticosteroid injections are widely used for nonoperative management of knee OA symptoms. This Cochrane Review of randomized or quasi-randomized control trials evaluated the benefits and harms of intraarticular corticosteroids compared with sham or no intervention in people with knee OA in terms of pain, physical function, quality of life, and safety.

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Upon Closer Inspection

Of the 26 included trials in this Cochrane Review, 19 compared corticosteroids to a sham injection and seven compared corticosteroids to no treatment. It has become increasingly recognized that sham interventions themselves have therapeutic benefits. With the advent of network meta-analysis techniques, this placebo effect can be quantified and compared to other placebo effects [1]. While some clinicians minimize the importance of those phenomena, we would counsel against doing so. The placebo effect of intra articular injections has been demonstrated in some cases to exceed that of the therapeutic effect of oral anti-inflammatory medications [2]. Bannuru and colleagues [1] performed a network meta-analysis of 149 randomized controlled trials evaluating the effects of alternative placebo types on pain outcomes in knee OA. The study identified IA placebo (effect size, 0.29 [95% CI, 0.09 to 0.49]) and topical placebo (effect size, 0.20 [95% CI, 0.02

to 0.38]) had substantially greater effect size in comparison to oral placebo [1]. This effect size corresponds to approximately a 22-point decrease and a 20-point decrease on a 0 to 100 pain scale, respectively. Thus, studies comparing corticosteroid to sham or placebo injection may not demonstrate as large an effect of the active treatment due to the placebo effect of injection itself.

When pooling outcomes across studies comparing corticosteroid to placebo interventions and those that compared to no treatment, the differential treatment effect of placebo interventions may result in heterogeneity that must be considered via subgroup analysis. Study heterogeneity is the variability between reported study outcomes and may be due to differences in compared groups with respect to patient population, intervention or presence of cointerventions, comparators, or outcomes assessed. The presence of heterogeneity between studies is explored and quantified using both a statistical test (chi-square test) for heterogeneity and the I^2 statistic [4]. I^2 values are commonly interpreted according to the Cochrane Handbook where 50% heterogeneity is substantial and requires explanation [4]. This Cochrane Review identified I^2 to be 68%, suggesting a large degree of between trial variability. This may be explained by differences with respect to comparator (placebo vs. no treatment) or cointerventions (viscosupplementation) which was not explored in this review.

Take-home Messages

This Cochrane Review found intra-articular cortisone injections to be more beneficial than placebo (or than no treatment) with respect to pain reduction (standardized mean difference [SMD] -0.40, 95% CI -0.58 to -0.22) as well as functional improvement (SMD -0.33, 95% CI -0.56 to -0.09) [6]. The improvements in pain were relatively short lived, as one might expect (<6 months), and the effects decreased over time. There were no substantial differences between groups with respect to side effects or major adverse events. The long-term use of intra-articular cortisone has been questioned following a randomized controlled trial published in *JAMA* evaluating repeated (four times per year over 2 years) IA injection of 40 mg of corticosteroids on progression of cartilage loss and knee pain in comparison to saline injections [7]. The study found greater volumetric cartilage loss as assessed via MRI in patients treated with intra-articular corticosteroid [7]. While MRI assessment may not be an entirely reliable method of cartilage assessment, and the effect size they observed seemed small (0.11 mm after eight corticosteroid injections over a 2-year period), the study findings still suggest clinicians be cautious with respect longer term repeated intra-articular corticosteroid administration. We also note that study could not evaluate the short-term efficacy of corticosteroids (that is, during the first 12 weeks), given the first followup assessment in that *JAMA* study took place 12 weeks after the initial injection.

We believe the clinical implications of the results of this Cochrane Review may be unclear given the small differences between groups and considerable heterogeneity in findings. However, this may be the result of a lack of consideration of the intra-articular delivery effect itself. This effect has been quantified in a recent network meta-analysis, which confirmed not only intra-articular therapies such as cortisone to be the most efficacious in comparison to oral treatments, but the actual placebo effect from the intra-articular injection to be greater than that of oral anti-inflammatory medications [2]. When evaluating the effect of intra-articular therapies, it is critical to consider this additive variable in order to not underestimate the clinical impact of the intervention.

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