



## PRACTICE

## UNCERTAINTIES

# Is there a place for intra-articular corticosteroid injections in the treatment of knee osteoarthritis?

John W Orchard *adjunct professor*

School of Public Health, University of Sydney, New South Wales 2006, Australia

## What you need to know

- Intra-articular corticosteroid injections possibly improve pain and function in the short term (<8 weeks) in patients with osteoarthritis of the knee, but the evidence is of low quality, and any benefit is not usually sustained beyond 3 months
- Emerging evidence suggests a possible small risk of joint deterioration and worsening symptoms over the long term with intraarticular corticosteroid injections
- Consider the severity of pain, feasibility of other treatment options including exercise, and the patient's preferences regarding risks and benefits when planning treatment

The prevalence of end-stage knee osteoarthritis requiring joint replacement is increasing globally.<sup>1</sup> Some of this increase is due to increasing obesity and worsening lifestyle factors such as poor physical activity. It also requires us to evaluate whether standard treatments for mild to moderate osteoarthritis are effective.

Intra-articular corticosteroid, also referred to as corticosteroid injection, is widely prescribed for osteoarthritis of the knee. Guidelines, such as those produced by the National Institute for Health and Care Excellence (NICE),<sup>2</sup> have traditionally supported its use,<sup>3</sup> but reviews of efficacy indicate a high degree of uncertainty.<sup>4,5</sup> On average, a patient might have symptomatic knee osteoarthritis for 30 years. It is uncertain how the long term safety or harms of corticosteroid injection balance against the likelihood of short term pain improvement.

## What is the evidence of uncertainty?

Systematic reviews indicate low quality evidence that intra-articular corticosteroid injections may provide short term pain relief and a small improvement in physical function for up to six weeks in knee osteoarthritis compared with placebo.<sup>4,6</sup> Patients with more severe disease are likely to experience greater improvement.<sup>7</sup> The benefits are not seen to last beyond three months in trials,<sup>4</sup> although individual patients may report longer periods of symptom relief. There is considerable heterogeneity

between trials. While corticosteroid injections have been found to be safe in the short term, long term harms have not been well assessed. Recent cohort studies suggest possible risk of progression of osteoarthritis and worsening symptoms in patients prescribed intra-articular corticosteroid.<sup>8,9</sup>

Table 1 describes the findings of key studies.

## Search strategy

- I searched PubMed in February 2019 using the terms (corticosteroid OR corticosteroids OR triamcinolone OR betamethasone OR methylprednisolone OR dexamethasone) AND (injection OR intra-articular) AND knee osteoarthritis
- This search revealed 559 initial papers, of which I prioritised systematic reviews, randomised trials, and long term safety studies for the initial review
- A key reference is a high-quality Cochrane review on the topic published in 2015.<sup>4</sup> Further key studies after this were added and are summarised in table 1.

## Benefits of intra-articular corticosteroid injection

A Cochrane review of corticosteroid injection for knee osteoarthritis in 2015 (27 randomised controlled trials, 1767 patients) concluded there was low quality evidence of improvement in pain and function compared with placebo over a 1-6 week period.<sup>4</sup> The number of patients needed to treat to gain additional benefit was eight, and average pain improvement was one point on a 10 point scale lasting up to six weeks.<sup>4</sup> The quality of studies was consistently low. The single trial at low risk of bias showed no benefit.

A high quality, well powered, placebo controlled randomised trial (140 patients) published subsequently<sup>7</sup> found no clinical difference in pain reduction with corticosteroid injection every three months compared with placebo for knee osteoarthritis at any stage over a two year follow-up. Measurements were made three months after each injection and so could have missed short term improvements.

john.orchard@sydney.edu.au

This is one of a series of occasional articles that highlight areas of practice where management lacks convincing supporting evidence. The series advisers are Sera Tort, clinical editor, and David Tovey, editor in chief, the Cochrane Library. To suggest a topic for this series, please email us at [uncertainties@bmj.com](mailto:uncertainties@bmj.com)

A recent systematic review and meta-analysis reported uncertain effect sizes beyond one year for pain improvement for all pharmacological treatments for knee osteoarthritis compared with placebo. Limited evidence from four trials suggests that intermittent corticosteroid injection was not associated with pain improvement in the long term.<sup>5</sup>

Patients with severe pain may experience greater improvement in short term pain (for up to four weeks) with corticosteroid injection compared with placebo, as shown by a meta-analysis of individual patient data (7 randomised controlled trials, 620 patients).<sup>6</sup> However, this meta-analysis combined data for patients with knee osteoarthritis and hip osteoarthritis.

## Risks of intra-articular corticosteroid injection

The Cochrane review did not find any evidence of harm from corticosteroid injection in the short term (<6 months). Long term harms were not assessed.

The McAlindon trial mentioned above reported a small (−0.1 mm) but statistically significant deterioration in knee cartilage depth in the corticosteroid injection group on imaging.<sup>7</sup> Cartilage depth and quality is a radiological indicator of worsening disease in osteoarthritis, although its association with clinical progression is not established. An earlier study<sup>10</sup> did not find similar disease progression in terms of joint space reduction on x ray after two years with similar corticosteroid injection regimen. This study was smaller in size (68 patients) and used a less sensitive form of imaging.

Recent cohort studies indicate worsening of pain, stiffness, and function with intra-articular corticosteroid at two year follow-up<sup>8</sup> as well as joint deterioration and progression to total knee replacement.<sup>9</sup> Repeated intra-articular injections of corticosteroids exhibited greater risk of disease progression, but this does not rule out joint deterioration with a single injection.<sup>9</sup> A retrospective study using a national insurance database in the United States highlights possible increased risk of infection after knee surgery in patients who had received a corticosteroid injection in the same knee within three months before surgery.<sup>11 12</sup> A recent case series reported adverse joint events on imaging in 8% (36/459) of patients with hip and knee osteoarthritis who had received at least one intra-articular corticosteroid injection in the preceding year.<sup>13</sup> This study has several limitations but warrants further investigation into risks of disease worsening.

## Is existing research likely to resolve this uncertainty?

For long established treatments that are part of the “standard of care,” there is disagreement as to how much evidence is required to support their continued use. It is not clear if the burden of proof is to show net benefit (in order to retain) or to show net harm (in order to discard). Expert guidelines often tend to favour a “retain” stance but pure evidence-based medicine tends to favour a “reject where net benefit not clear” stance.

I have not searched trial registries for ongoing studies on this topic. In my opinion, further research must include high quality randomised controlled trials and observational studies with longer term follow-up (2, 5, or 10 years) to better delineate the likelihood of short term improvement (up to six weeks) and medium and long term risks (two years onwards).

## What should we do in light of this uncertainty?

Intra-articular corticosteroid injection possibly offers a small and transient improvement in symptoms of knee osteoarthritis, which must be offset against some risk of disease worsening in the long term.

Most of the uncertainty relates to the ability of the clinician and patient to weigh up the risks and benefits and to consider whether the short term or long term outcome is more important for a particular patient. There is possibly a place for corticosteroid injections in frail elderly patients, for example, who have severe pain from knee osteoarthritis but are unsuitable for joint replacement. However, for younger and middle aged patients with an expectation of minimising disease progression, longer term risk-benefit profile is generally more important, although short term improvement may occasionally be important in younger patients, such as before an overseas holiday.

## Other treatments for knee osteoarthritis

The evidence for the benefit of exercise and weight loss in osteoarthritis continues to accrue.<sup>2 14 15</sup> Moderate load exercise programmes are the mainstay of management of mild to moderate knee osteoarthritis. Encourage graduated increase of moderate, low impact exercise and advise the patient to refrain from high doses of high impact exercise, which can worsen symptoms. Offer referral to physiotherapy for designing a structured exercise programme. Knee replacement may be required in severe and end stage osteoarthritis in suitable patients.<sup>16</sup> Concerns of harms associated with opioids and the lack of efficacy of knee arthroscopy<sup>17</sup> make these poor options.

### What patients need to know

- Osteoarthritis is a lifelong condition, although symptoms of pain and stiffness can fluctuate over time
- Moderate exercise is the mainstay of treatment for mild to moderate osteoarthritis of the knee
- Cortisone injections may give a small degree of symptom relief in the short term (about 6 weeks), but symptoms are likely to return and studies have not shown benefits beyond the short term
- There is emerging evidence from individual studies of possible cartilage deterioration and worsening of symptoms with repeated injections over two years
- Ask your doctor about the treatment options to develop a shared management plan considering the severity of your symptoms and your preferences

### Education into practice

- Think of a patient you have seen with knee osteoarthritis. Based on reading this article, how would you discuss the risks and benefits of intra-articular corticosteroid injections with your patient?
- Have patients with osteoarthritis at your practice been given detailed information about exercise planning under instruction of a health professional?
- For patients at your practice who were advised cortisone injection for knee osteoarthritis, is there a documented discussion of the risks and benefits before treatment?

### How patients were involved in the creation of this article

A patient reviewer kindly reviewed this article for *The BMJ*. She asked to clarify the risk of disease progression with injection as most patients are not aware of it. She also suggested considering the treatment advice for different age groups. I have accordingly elaborated on these in the article. I also agree with her suggestion for more research in this area so patients may be informed and opt for another treatment such as exercise over corticosteroid injections. I am grateful for her input.

Competing interests: I have read and understood BMJ policy on declaration of interests and have no relevant interests to declare.

Provenance and peer review: Commissioned, based on an idea from the author; externally peer reviewed.

- 1 Pabinger C, Lothaller H, Geissler A. Utilization rates of knee-arthroplasty in OECD countries. *Osteoarthritis Cartilage* 2015;23:1664-73. 10.1016/j.joca.2015.05.008 26028142
- 2 National Institute for Health and Care Excellence. Management of osteoarthritis, 2019. <http://pathways.nice.org.uk/pathways/osteoarthritis>.
- 3 Royal Australian College of General Practitioners. Guideline for the management of knee and hip osteoarthritis. 2nd ed. RACGP, 2018. <https://www.racgp.org.au/download/Documents/Guidelines/Musculoskeletal/guideline-for-the-management-of-knee-and-hip-0a-2nd-edition.pdf>.
- 4 Jüni P, Hari R, Rutjes AW, et al. Intra-articular corticosteroid for knee osteoarthritis. *Cochrane Database Syst Rev* 2015;(10):CD005328.26490760
- 5 Gregori D, Giacobelli G, Minto C, et al. Association of pharmacological treatments with long-term pain control in patients with knee osteoarthritis: a systematic review and meta-analysis. *JAMA* 2018;320:2564-79. 10.1001/jama.2018.19319 30575881
- 6 van Middelkoop M, Arden NK, Atchia I, et al. The OA Trial Bank: meta-analysis of individual patient data from knee and hip osteoarthritis trials show that patients with severe pain exhibit greater benefit from intra-articular glucocorticoids. *Osteoarthritis Cartilage* 2016;24:1143-52. 10.1016/j.joca.2016.01.983 26836288
- 7 McAlindon TE, LaValley MP, Harvey WF, et al. Effect of intra-articular triamcinolone vs saline on knee cartilage volume and pain in patients with knee osteoarthritis: a randomized clinical trial. *JAMA* 2017;317:1967-75. 10.1001/jama.2017.5283 28510679
- 8 Liu SH, Dubé CE, Eaton CB, Driban JB, McAlindon TE, Lapane KL. Longterm effectiveness of intraarticular injections on patient-reported symptoms in knee osteoarthritis. *J Rheumatol* 2018;45:1316-24. 10.3899/jrheum.171385 29907665
- 9 Zeng C, Lane NE, Hunter DJ, et al. Intra-articular corticosteroids and the risk of knee osteoarthritis progression: results from the Osteoarthritis Initiative. *Osteoarthritis Cartilage* 2019;27:855-62. 10.1016/j.joca.2019.01.007 30703543
- 10 Raynaud JP, Buckland-Wright C, Ward R, et al. Safety and efficacy of long-term intraarticular steroid injections in osteoarthritis of the knee: a randomized, double-blind, placebo-controlled trial. *Arthritis Rheum* 2003;48:370-7. 10.1002/art.10777 12571845
- 11 Cancienne JM, Werner BC, Luetkemeyer LM, Browne JA. Does timing of previous intra-articular steroid injection affect the post-operative rate of infection in total knee arthroplasty? *J Arthroplasty* 2015;30:1879-82. 10.1016/j.arth.2015.05.027 26071248
- 12 Cancienne JM, Gwathmey FW, Werner BC. Intraoperative corticosteroid injection at the time of knee arthroscopy is associated with increased postoperative infection rates in a large medicare population. *Arthroscopy* 2016;32:90-5. 10.1016/j.arthro.2015.09.003 26553960
- 13 Kompel AJ, Roemer FW, Murakami AM, Diaz LE, Crema MD, Guermazi A. Intra-articular corticosteroid injections in the hip and knee: perhaps not as safe as we thought? *Radiology* 2019;293:656-63. 10.1148/radiol.2019190341 31617798
- 14 Franssen M, McConnell S, Harmer AR, Van der Esch M, Simic M, Bennell KL. Exercise for osteoarthritis of the knee. *Cochrane Database Syst Rev* 2015;1:CD004376.25569281
- 15 Abbott JH, Wilson R, Pinto D, Chapple CM, Wright AAMOA Trial team. Incremental clinical effectiveness and cost effectiveness of providing supervised physiotherapy in addition to usual medical care in patients with osteoarthritis of the hip or knee: 2-year results of the MOA randomised controlled trial. *Osteoarthritis Cartilage* 2019;27:424-34. 10.1016/j.joca.2018.12.004 30553932
- 16 Skou ST, Roos EM, Laursen MB, et al. A randomized, controlled trial of total knee replacement. *N Engl J Med* 2015;373:1597-606. 10.1056/NEJMoa1505467 26488691
- 17 Thurlund JB, Juhl CB, Roos EM, Lohmander LS. Arthroscopic surgery for degenerative knee: systematic review and meta-analysis of benefits and harms. *BMJ* 2015;350:h2747. 10.1136/bmj.h2747 26080045

Published by the BMJ Publishing Group Limited. For permission to use (where not already granted under a licence) please go to <http://group.bmj.com/group/rights-licensing/permissions>

## Table

Table 1 | Summary of evidence from key recent high quality papers

Study	Focus	Key findings	Limitations	Conclusion
Juni 2015 <sup>4</sup> Cochrane review (27 RCTs, 1767 patients)	Short term efficacy and safety assessed by multiple placebo-controlled RCTs	Intra-articular corticosteroids (IAC) appeared to be more beneficial in pain reduction than control interventions, a difference in pain scores of 1 out of 10. The number needed to treat for an additional beneficial outcome is 8 (95% CI 6 to 13). Benefits are moderate at 1-2 weeks, small at 13 weeks with no evidence of an effect at 26 weeks. There is no evidence of short term harm compared to placebo	The quality of studies was consistently low (high risk of bias)	IAC is safe in the short term and may provide small-moderate short term benefits. Long term harms were not assessed as most studies were limited to 26 weeks follow-up.
McAlindon 2017 <sup>7</sup> RCT	Medium-term (3 months to 2 years) efficacy and safety (140 patients)	Intra-articular triamcinolone injection every 3 months resulted in greater cartilage volume loss detected on MRI at 2 years than did saline for a mean change in index compartment cartilage thickness of -0.21 mm vs -0.10 mm (between group difference -0.11mm, 95% CI -0.20 to -0.03mm). There was no clinically important difference in pain (-1.2 vs -1.9, between group difference 0.6, 95% CI -1.6 to 0.3).	Measurements were only made 3 months after each injection and could possibly have missed short term improvements of IAC over placebo.	IAC provided no benefit over placebo in time frames from 3 months to 2 years, but was associated with progressive cartilage deterioration
Liu 2018 <sup>8</sup> Cohort study (412 patients)	Long term effectiveness (2 years) as assessed by symptoms compared to controls	Compared to non-users participants initiating corticosteroid injection experienced worsening of pain (yearly worsening: 1.24 points, 95% CI 0.82-1.66 on the WOMAC 20 point scale), along with worsening of stiffness and physical functioning after adjusting for potential confounders.	Cohort design rather than RCT is less powerful at eliminating confounders	IAC was associated with worsening symptoms over 2 years follow up
Gregori 2018 <sup>5</sup> Systematic review of all pharmacological interventions for knee osteoarthritis (33 interventions, 47 RCTs, 22037 patients)	Long term pain control (>12 months)	Intermittent IAC injections were not associated with pain improvement in the long term. Combination with hyaluronic acid injection had moderately beneficial but variable effect on pain.	Very few studies examine medium to long term effect of IACs alone	Based on limited evidence, IAC was not associated with pain improvement beyond 12 months
Zeng 2019 <sup>9</sup> Cohort study (148 IACs initiators, 536 comparators)	Radiographic progression of knee osteoarthritis with IAC compared to controls (propensity-score matched)	Compared to non-users, hazard ratios (HRs) of joint structure worsening over 48 months from IAC initiation and continuous IACs were 3.02 (95% CI, 2.19-4.16) and 4.67 (95% CI, 2.92-7.47), respectively.	Cohort design rather than RCT is less powerful at eliminating confounders	Corticosteroid injection was associated with increased risk of structural deterioration and progression to knee replacement

RCT = randomised controlled trial. IAC = intra-articular corticosteroid. CI = confidence interval. MRI = magnetic resonance imaging. WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.