Bellamy N, Campbell J, et al. Intraarticular corticosteroid for treatment of osteoarthritis of the knee. Cochrane Database of Systematic Reviews 2006, Issue 2. Art. No.: CD005328.

Design: Meta-analysis of randomized clinical trials

Study question: How safe and effective are intra-articular (IA) steroids in treating osteoarthritis (OA) of the knee?

PICOS:

- Patients: Adults diagnosed with OA of the knee using the criteria of the American College of Rheumatology, or on the basis of detailed clinical and/or radiographic information
- Interventions: All IA corticosteroid preparations used for treatment of OA in adults
- Comparison interventions:
    - Placebo
    - Active treatment such as joint lavage
    - IA hyaluronic acid
    - Other IA steroids or different doses of IA steroids
- Outcomes:
    - Pain
    - Physical function
    - Patient global assessment
    - Joint imaging for studies lasting more than one year
- Study types: Randomized controlled trials only with published data on outcome measures, without language restrictions

Study selection:

- Databases included MEDLINE through January 2006, EMBASE through mid-2003, and the Cochrane Central Register through Issue 2 of 2003
    - These databases were supplemented by hand searches of bibliographic references and by abstracts from conference proceedings, as well as hand searches of numerous orthopedic and rheumatology journals
- One author selected articles and extracted data while a second author verified the work of the first
- Trial methodology (risk of bias) was assessed according to method of randomization, description as double blind, description of withdrawals and dropouts, allocation concealment, and appropriate method of blinding
- Effect measures were reported as relative risks for dichotomous outcomes (such as reporting or not reporting improvement) and as mean differences for continuous outcomes (such as mean pain scores using a VAS scale from 0-100)

Results:

- 28 RCTs with 1973 patients met the selection criteria
    - 13 of these compared IA steroid versus placebo
    - 10 compared IA steroid with hyaluronic acid injection
    - 6 trials compared IA steroid against another IA steroid
    - 3 trials compared IA steroid against joint lavage
- A total of 350 separate analyses were done, but only 16 analyses attempt to combine outcome data from two or more studies in a meta-analysis; the other 334 are reports of single outcomes from single studies
    - Of the 16 meta-analyses in the report, 5 combine data from 3 studies and 11 combine data from 2 studies; none combine data from 4 or more studies
- For the comparison of IA steroid versus placebo, one meta-analysis of 3 studies with 161 patients showed less pain with IA steroid one week after injection (21.91 points on a 100 point VAS; 95% confidence interval from 13.89 to 29.93 points)
    - For pain relief after one week, only single studies were available, and in each of these, the 95% confidence interval included the null value of no effect
    - For global improvement after one week, outcomes from 3 studies with 158 patients were combined to estimate that patients who had IA steroid were 1.44 times as likely as those injected with placebo to have a positive response (95% CI 1.13 to 1.82); for global improvement later than one week, the differences between steroid and placebo were no longer statistically significant
- For the comparison of IA steroid versus joint lavage, numerous single studies reported a large number of comparisons, but no differences between steroid and lavage were discovered
- For the comparison of IA methylprednisolone versus IA hyaluronic acid, data from 3 studies with 170 patients were combined
    - Both interventions had equal pain scores 1 to 4 weeks after injection
    - Hyaluronic acid had lower pain scores than IA steroid 5 to 13 weeks after injection (7.73 points on a 100 point VAS, 95% CI between 2.64 and 12.81)
    - For the number of patients with moderate or severe pain while bearing a load, 2 studies with 130 patients showed that steroid and hyaluronic acid injection were equivalent 1 to 4 weeks after injection, but that hyaluronic acid had fewer patients with pain on load-bearing 5 to 13 weeks after injection (risk for hyaluronic acid was 62% that of IA steroid, with 95% CI from 45% 5o 85%)
    - For moderate or greater rest pain, IA steroid and hyaluronic acid were equivalent 1 to 4weeks after injection, but at 5 to 13 weeks after injection, the risk with hyaluronic acid was 39% of the risk with steroid (95% CI from 19% to 78%)
    - For range of motion, hyaluronic acid had about 5 degrees greater flexion than IA steroid at 1 to 4 weeks and again at 5 to 13 weeks post injection

- For the comparison of different IA steroid preparations, one study reported a difference in the number of patients with pain one week following injection, with triamcinolone more effective than betamethasone (43% with pain versus 76% with pain), with similar comparisons at 2 and 4 weeks after injection
- For combination treatment, IA steroid plus hyaluronic acid was compared with hyaluronic acid alone in one study with 40 patients
    - This study made 36 data comparisons on outcomes for various WOMAC subscales at various time points, with small differences favoring the combination for 4 endpoints, but with fewer withdrawals in the group having only hyaluronic acid injection

Authors' conclusions:

- Limited conclusions can be drawn because of sparse data for most comparisons
- IA steroid is likely to be more effective than IA placebo one week after injection, and possibly at 2 to 3 weeks, but no evidence of benefit is apparent after 4 weeks
- IA steroid versus hyaluronic acid suggests that the effect of hyaluronic acid lasts longer than for IA steroid, with clinical benefits of hyaluronic acid being detectable 5 to 13 weeks post injection
- No generalizations regarding different IA steroid preparations are warranted with the available data
- The value of combinations of steroid with hyaluronic acid merits further evaluation, even though most of the variables in the single study of a combination were not significantly different
- There is a lack of standardization of reporting standards for outcome assessments, assessment times, and trial durations, with consequent reductions in the usefulness of trials of IA steroids

Comments:

- The large number of total comparisons (350 in all), the vast majority of which are single endpoints from single studies, creates an unwieldy analysis in which about 17 (one in twenty) would be expected to be "statistically significant" in one or another direction
- The presentation of the results is also lengthy and consists of reporting outcomes from study after study, without a thematic organization to give an overall picture of the effectiveness of steroid injection
- It would appear that some outcomes with two or more studies could have been combined in a reasonable meta-analysis, but the authors declined to do so, without explaining what influenced the decision to do meta-analyses on some outcomes but not on others, imposing extra efforts on the reader

    - For example, on page 98 of the document, in Analysis 1.16, steroid versus placebo, outcome 16, global assessment: number of patients preferring treatment, risk ratios from three studies are presented, but no subtotal summary is done: a risk ratio of 2.22 can be computed with low heterogeneity, but this is buried on page 12 of the text and is easily overlooked when a visual forest plot fails to show the summary of data
- Thus, the overall summary of current data might have been done much more simply; while the authors were confronted with a situation in which there is no standardization of how to measure and report outcomes of treatment, the scattered nature of the reporting is duplicated in the scattered presentation of the results section
- The comparisons of IA steroid with hyaluronic acid are problematic, since the effectiveness of hyaluronic acid is quite uncertain with current data from other sources
- However, the report does support evidence that an IA steroid injection is likely to have a rapid but transient analgesic effect in knee OA compared to placebo

Assessment: Not a high quality meta-analysis, but adequate for good evidence that steroid injection in the setting of knee osteoarthritis produces rapid but short-lasting pain relief compared to placebo, likely to last at least one week but not likely to last 4 weeks or longer