CME

Intra-articular steroid injections for painful knees

Systematic review with meta-analysis

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ABSTRACT

OBJECTIVE Do intra-articular steroid injections relieve the pain of osteoarthritis (OA) of the knee?

DATA SOURCES MEDLINE, Cochrane, and Internet databases were searched for randomized controlled trials.

STUDY SELECTION Five randomized controlled trials involving 312 patients were found.

SYNTHESIS One week after injection, treated patients were less likely to have continuing pain and had significantly lower scores on a visual analogue scale (VAS) for pain. Three to 4 weeks after injection, treated patients still had significantly less pain, but their VAS scores were no longer significantly lower than scores in the control group. Six to 8 weeks after injection, neither pain reduction nor VAS scores were significantly different between groups.

CONCLUSION Intra-articular corticosteroid injection results in clinically and statistically significant reduction in osteoarthritic knee pain 1 week after injection. The beneficial effect could last for 3 to 4 weeks, but is unlikely to continue beyond that.

RÉSUMÉ

OBJECTIF L'injection intra-articulaire de stéroïdes est-elle efficace pour soulager la douleur dans l'arthrose du genou?

SOURCE DES DONNÉES On a consulté les bases de données MEDLINE et Cochrane ainsi que l'Internet pour repérer des essais randomisés.

CHOIX DES ÉTUDES Cinq essais randomisés portant sur 312 patients ont été retenus.

SYNTHÈSE Une semaine après l'injection, les patients étaient moins susceptibles de souffrir de douleurs constantes et leur score de douleur sur une échelle visuelle analogique (EVA) était significativement plus bas. Trois à 4 semaines après l'injection, les patients accusaient encore un réduction significative de la douleur, mais leurs scores EVA n'étaient plus significativement inférieurs à ceux des patients témoins. Six à 8 semaines après l'injection, il n'y avait plus de différence significative entre les groupes, ni pour le soulagement subjectif ni pour les scores EVA.

CONCLUSION Dans l'arthrose du genou, une réduction significative de la douleur est observée une semaine après l'administration intra-articulaire d'un corticostéroïde. Cet effet bénéfique pourrait durer de 3 à 4 semaines, mais il est peu probable qu'il se prolonge au-delà.

This article has been peer reviewed.
Cet article a fait l'objet d'une évaluation externe.
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A 60-year-old man with osteoarthritis (OA) in his knee has had a lot of pain recently. You were planning to inject his knee with a corticosteroid "depo" preparation and mentioned this to a colleague. She immediately said she thought there was no evidence that intra-articular injections of corticosteroids "worked" for OA.

You have been injecting knees and other joints with steroids for many years, and your clinical impression is that it often seemed to help. Your "evidence," however, is experiential, and you have never checked the literature for studies on this treatment. Neither has your colleague.

For a 60-year-old man with painful OA of the knee, will intra-articular injection of a depo-corticosteroid preparation decrease pain without causing serious side effects?

METHODS

Literature search

We searched MEDLINE from 1966 to December 2002 using PubMed and Ovid; the Cochrane Library, including the database of systematic reviews and the register of controlled trials; and EMBASE. We also used the Internet search engine **Google.com**. Search terms used were osteoarthritis, knee, corticosteroid or glucocorticoids, and intra-articular or intraarticular. The search was limited to studies done on human adults, randomized controlled trials, systematic reviews, and guidelines. There were no language limits. Randomized controlled trials (RCTs) and systematic reviews were primarily sought, but articles of related interest were considered. In this first search, we found three RCTs,[1-3] a nonsystematic review,[4] and two reports of complications from knee injections.[5,6]

One RCT[1] was used to seek further articles with the "Related articles" feature of PubMed. This feature does not use the limits that were set, so 161 articles were found. Of these, three were RCTs.[7-9] Manual checking of references in the review article and the RCTs identified two RCTs published in 1981[10] and 1996,[11] and several papers published in the 1950s reporting on use of non-depo formulations (hydrocortisone acetate) of steroids.[12,13]

We did not find a completed review on OA treatment using corticosteroid injection by the Cochrane Collaboration. There is, however, a protocol description[14] in the Cochrane database.

The Internet search using **Google.com** found two potential sources of additional information: the American College of Rheumatology's OA treatment guidelines[15] and the EULAR's (European League Against Rheumatism) recommendations for management of knee OA.[16] No additional primary studies were found in their reference lists.

Inclusion criteria

Both RCTs and systematic reviews that looked specifically at intra-articular steroid injection for OA of the knee were considered. We included all studies that compared the newer, long-acting, potent forms of depo-corticosteroid (eg, triamcinolone hexacetonide, methylprednisolone, betamethasone, and cortivazol) with placebo. **Table 1**[1,3,7,8,11] gives information on the five studies selected. Studies done in the 1950s were not included because they were either not controlled trials or they used short-acting hydrocortisone acetate rather than the longer-acting depo formulations now available. Studies comparing two different types of intra-articular steroids were not included unless there was also a placebo arm.

Critical appraisal of selected articles

Those assessing the articles were not blinded to author or citation source, but were not acquainted with any of the authors of the articles included in the review. The critical appraisal process considered the validity of the methods, the results, and how well the results could be applied to clinical practice.[17,18] Details of methods, descriptions of patients studied, and intervention and control

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Table 1. Summaries of articles in this review

STUDY	DESIGN	PATIENTS	TREATMENT GROUP	CONTROL GROUP	OUTCOMES MEASURED
Friedman and Moore[3] 1980	Double-blind, randomized, placebo-controlled trial with intention to treat	34 patients older than 40 years with history, physical examination, and laboratory test results consistent with OA. Treatment and control groups were similar in mean age, duration of knee pain, and pain score before treatment	N = 17; 17 analyzed. 20 mg of triamcinolone hexacetonide	N = 17; 17 analyzed. 1 mL of solution used in steroid preparation without steroid	Continuation of pain at 1 and 8 weeks; pain score on VAS at 1 and 4 weeks
Dieppe et al[8] 1993	Double-blind, randomized, placebo-controlled trial with intention to treat. 1-week crossover design	16 patients (24 knees): 13 women, three men. Mean age was 65 years. Mean duration of OA was 6 y ± 4.5 y. Radiographic grading of OA was moderate-to-severe in all cases	N = 12; 12 analyzed. Intra-articular 20 mg of triamcinolone hexacetonide followed by placebo	N = 12; 2 analyzed. Placebo (1 mL of 0.9% saline) followed by 20 mg of triamcinolone hexacetonide	Continuation of pain; pain score on VAS at 1 week
Gaffney et al[7] 1995	Single-blind, randomized, placebo-controlled trial with intention to treat	Patients at a general rheumatology clinic with evidence of knee OA. Treatment and control groups were similar in age, sex, symptom duration, radiologic scores, and history of previous steroid injection	N = 42; 42 analyzed. 20 mg of intra-articular triamcinolone hexacetonide	N = 42; 42 analyzed. Placebo (1 mL of 0.9% saline) intra-articular	Continuation of pain; pain score on VAS at 1 and 6 weeks
Jones and Doherty[11] 1996	Double-blind, randomized, placebo-controlled trial with intention to treat. Crossover design. Order of injection (methylprednisolone first or placebo first) was randomized	60 hospital-referred patients (23 men, 37 women) who met American College of Rheumatology criteria for knee OA (clinical and radiographic). Mean age was 70.6 y (range 51-89 y)	N = 60; 59 analyzed. 40 mg of methylprednisolone followed 8 weeks later by placebo (1 mL of 0.9% saline)	N = 60; 59 analyzed. Placebo followed 8 weeks later by methylprednisolone	Failure to achieve 15% reduction in pain; pain score on VAS at 3 and 8 weeks
Ravaud et al[1] 1999	Double-blind, randomized, placebo-controlled trial with intention to treat	53 patients in placebo and treatment arms. 45 other patients were used in two other arms that used knee lavage as part of the intervention. All patient groups were similar in demographic and clinical parameters	N = 25; 25 analyzed. 3.75 mg of intra-articular cortivazol	N = 28; 28 analyzed. Placebo (1.5 mL of 0.9% saline) intra-articular	Failure to achieve 30% reduction in pain at 1, 4, and 12 weeks; pain score on VAS at 1 and 4 weeks

OA—osteoarthritis, VAS—visual analogue scale.

procedures were assessed. Absolute risk reduction (ARR) and number needed to treat (NNT) for event-based outcomes were calculated for each study when sufficient data were provided.

When mean scores were used as outcomes, differences between the scores and 95% confidence intervals (CI) of these differences were calculated if standard deviations (SD) were given by the author. If SDs were not provided, *P* values given by the authors were used. A meta-analysis was conducted using the RevMan software available from the Cochrane Collaboration website (**http://www.cochrane.org/cochrane/revman41.htm**).

For the meta-analysis, we considered both dichotomous and continuous outcomes. Target levels of pain reduction differed from study to study (**Table 2**[1,3,7,8,11]); however, in combining the results, we considered only whether the target level set by the investigators had been achieved. Continuous outcomes were patients' assessments of level of pain on a visual

Table 2. Summary of results: *Event-related and pain-measure outcomes.*

	EVENT-RELATED OUTCOMES				PAIN-MEASURE OUTCOMES ON CONTINUOUS SCALE				
STUDY (STEROID USED)	EVENT	RRR %	ARR %	NNT (RANGE)	OUTCOME	WHEN MEASURED AFTER INJECTION	TREATMENT GROUP	CONTROL GROUP	*P*
Friedman and Moore[3] 1980 (triamcinolone)	Knee pain 1 wk after injection	59	17	6 (2-~)	VAS score (1-10)	1 wk	2.3	3.6	.005
	Knee pain 8 wk after injection	0	0	~	VAS score (1-10)	8 wk	2.8	2.6	NS
Dieppe et al[8] 1993 (triamcinolone)	Pain unchanged at 1 wk	69	38	3 (2-8)*	Change in VAS score (placebo-first group)	1 wk	3.2	1.2	< .05
					Change in VAS score (steroid-first group)	1 wk	3.9	1.1	< .05
Gaffney et al[7] 1995 (triamcinolone)	Continuation of knee pain at 1 wk	59	31	3 (2-9)*	VAS score (0-100)	1 wk	21.7	43.1	< .05
	Continuation of knee pain at 6 wk	5	2.3	43 (4-~)	VAS score (0-100)	6 wk	35.8	42.9	NS
Jones and Doherty[11] 1996 (methylprednisolone)	Failure to achieve 15% reduction in pain at 3 wk	38	32	3 (2-6)*	VAS score (0-100)	3 wk	52.6	58.5	< .05
					VAS score (0-100)	8 wk	52.6	59.4	NS
Ravaud et al[1] 1999 (cortivazol)	Failure to achieve 30% reduction in pain at 4 wk	52	39	3 (2-7)*	VAS score (0-100)	1 wk	33.7	53	< .05
	Failure to achieve 30% reduction in pain at 4 wk	38	27	4 (2-78)*	VAS score (0-100)	4 wk	42.8	54	NS*
	Failure to achieve 30% reduction in pain at 12 wk	32	23	4 (2-~)					

AAR—absolute risk reduction, NNT—number needed to treat, NS—not significant, RRR—relative risk reduction, VAS—visual analog scale.
**P < .05.*

analogue scale (VAS) using ranges of either 0 to 10 cm or 0 to 100 mm. For the meta-analysis of VAS scores, we were not able to include the Friedman and Moore[3] and Dieppe et al[8] studies because SDs were not given, and, for the Jones and Doherty[11] study, we estimated SDs from the interquartile ranges in the figures. Timing of measurement of outcomes was fairly consistent among studies. Four of the five studies measured outcomes at 1 week, two at 3 to 4 weeks, and two at 6 to 8 weeks. One study also measured outcomes at 12 weeks.

RESULTS

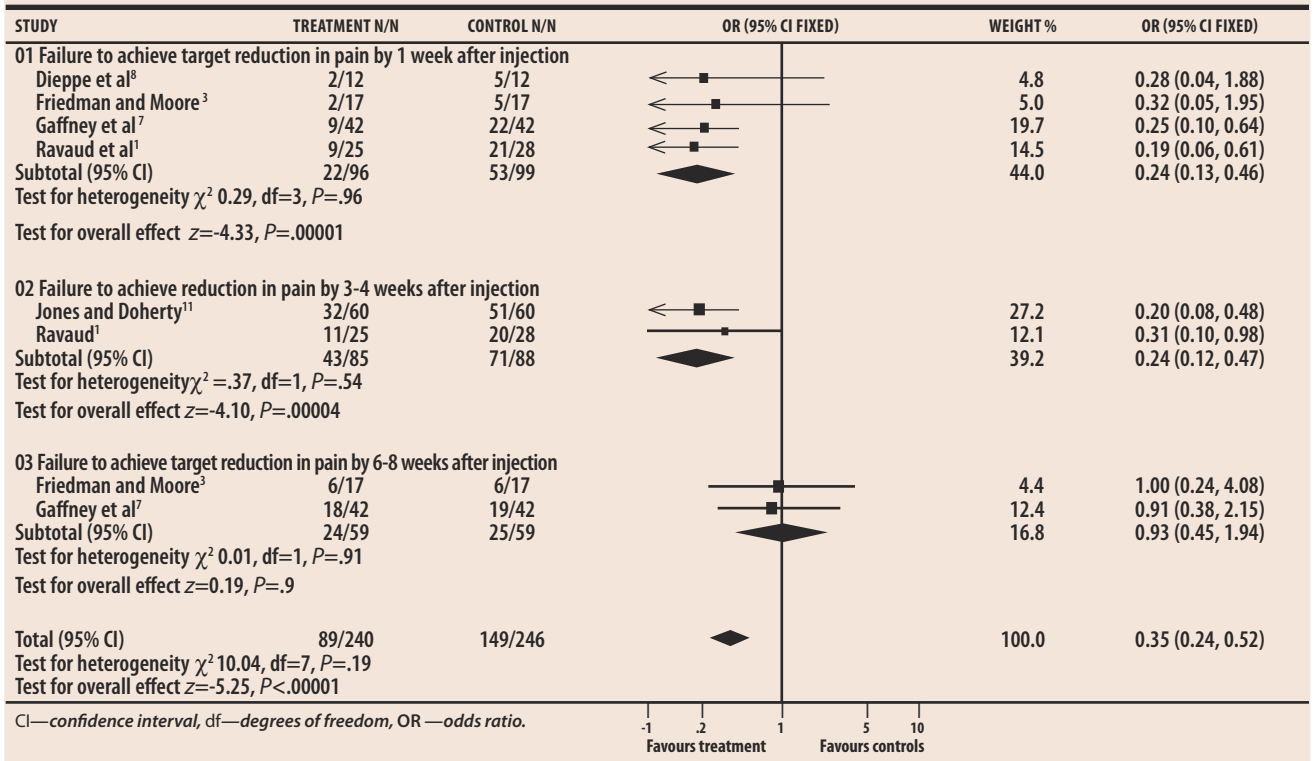
A summary of results of the five studies is shown in **Table 2**.[1,3,7,8,11] Meta-analysis results are shown in **Figure 1**.[1,3,7,8,11] **Figure 1A** shows results of a meta-analysis of the effect of intra-articular corticosteroid injection. **Figure 1B** shows similar results, except each bar represents scores on a VAS pain scale. Tests of heterogeneity are non-significant, indicating data can be pooled.

At 1 week, treated patients were more likely to have achieved the level of pain reduction investigators thought was clinically significant; they scored significantly lower on the VAS. At 3 to 4 weeks, achievement of target pain reduction remained significant, but the difference in VAS scores was no longer significant. At 6 to 8 weeks, there was no difference in achievement of target pain reduction or in VAS score between treatment and control groups.

None of the articles included in the review used a local anesthetic in combination with a steroid in

Figure 1. Meta-analysis of outcomes: *A) Dichotomous, B) Continuous. By convention, the proportion of patients who failed to achieve target reduction in pain is used for analysis. Each bar represents estimates from one study at one follow-up time. Bars entirely left of the vertical line indicate statistically significant benefit from steroid injection. Diamond shapes indicate odds ratios and 95% confidence interval estimates of pooled data for that follow-up time.*

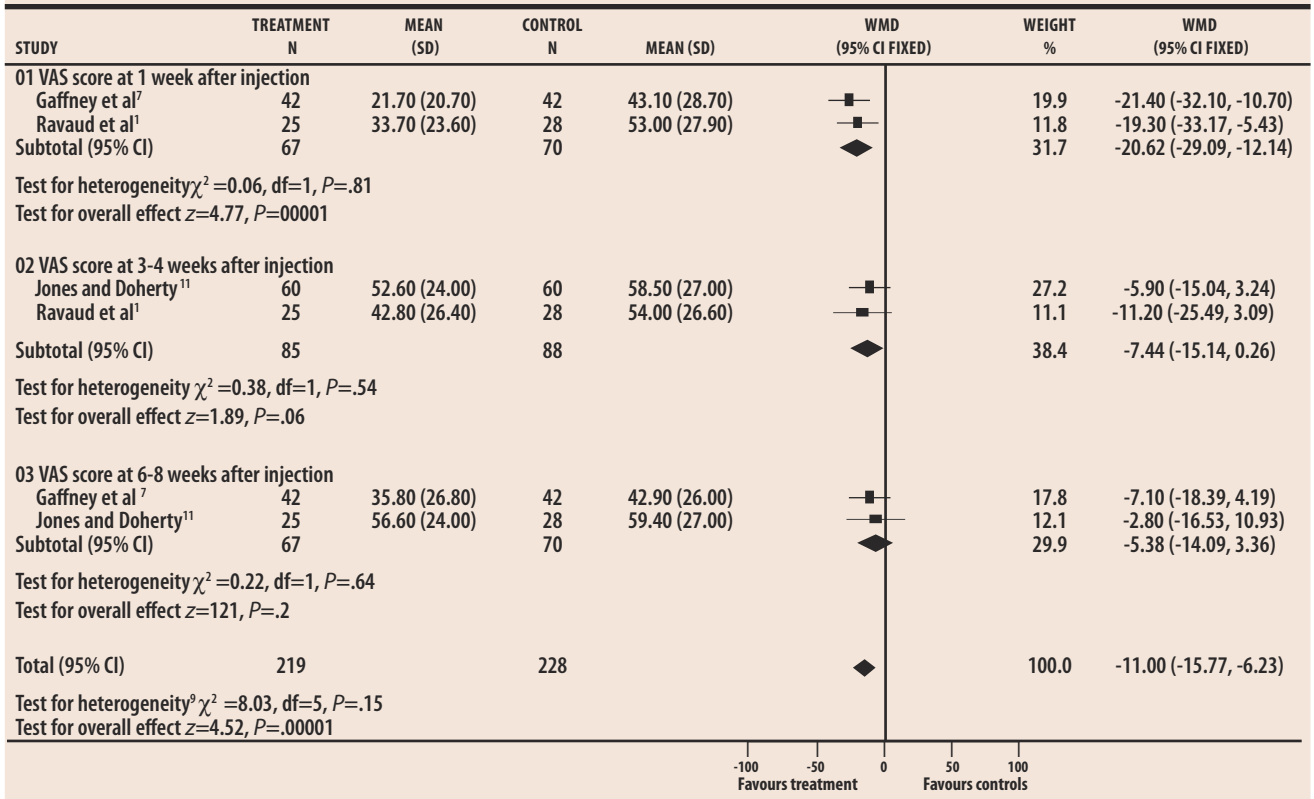
A



STUDY	TREATMENT N/N	CONTROL N/N	OR (95% CI FIXED)	WEIGHT %	OR (95% CI FIXED)
01 Failure to achieve target reduction in pain by 1 week after injection					
Dieppe et al[8]	2/12	5/12		4.8	0.28 (0.04, 1.88)
Friedman and Moore[3]	2/17	5/17		5.0	0.32 (0.05, 1.95)
Gaffney et al[7]	9/42	22/42		19.7	0.25 (0.10, 0.64)
Ravaud et al[1]	9/25	21/28		14.5	0.19 (0.06, 0.61)
Subtotal (95% CI)	22/96	53/99		44.0	0.24 (0.13, 0.46)
Test for heterogeneity χ^2 0.29, df=3, *P*=.96					
Test for overall effect *z*=-4.33, *P*=.00001					
02 Failure to achieve reduction in pain by 3-4 weeks after injection					
Jones and Doherty[11]	32/60	51/60		27.2	0.20 (0.08, 0.48)
Ravaud[1]	11/25	20/28		12.1	0.31 (0.10, 0.98)
Subtotal (95% CI)	43/85	71/88		39.2	0.24 (0.12, 0.47)
Test for heterogeneity χ^2 =.37, df=1, *P*=.54					
Test for overall effect *z*=-4.10, *P*=.00004					
03 Failure to achieve target reduction in pain by 6-8 weeks after injection					
Friedman and Moore[3]	6/17	6/17		4.4	1.00 (0.24, 4.08)
Gaffney et al[7]	18/42	19/42		12.4	0.91 (0.38, 2.15)
Subtotal (95% CI)	24/59	25/59		16.8	0.93 (0.45, 1.94)
Test for heterogeneity χ^2 0.01, df=1, *P*=.91					
Test for overall effect *z*=0.19, *P*=.9					
Total (95% CI)	89/240	149/246		100.0	0.35 (0.24, 0.52)
Test for heterogeneity χ^2 10.04, df=7, *P*=.19					
Test for overall effect *z*=-5.25, *P*<.00001					

CI—*confidence interval,* df—*degrees of freedom,* OR —*odds ratio.*

B



STUDY	TREATMENT N	MEAN (SD)	CONTROL N	MEAN (SD)	WMD (95% CI FIXED)	WEIGHT %	WMD (95% CI FIXED)
01 VAS score at 1 week after injection							
Gaffney et al[7]	42	21.70 (20.70)	42	43.10 (28.70)		19.9	-21.40 (-32.10, -10.70)
Ravaud et al[1]	25	33.70 (23.60)	28	53.00 (27.90)		11.8	-19.30 (-33.17, -5.43)
Subtotal (95% CI)	67		70			31.7	-20.62 (-29.09, -12.14)
Test for heterogeneity χ^2 =0.06, df=1, *P*=.81							
Test for overall effect *z*=4.77, *P*=00001							
02 VAS score at 3-4 weeks after injection							
Jones and Doherty[11]	60	52.60 (24.00)	60	58.50 (27.00)		27.2	-5.90 (-15.04, 3.24)
Ravaud et al[1]	25	42.80 (26.40)	28	54.00 (26.60)		11.1	-11.20 (-25.49, 3.09)
Subtotal (95% CI)	85		88			38.4	-7.44 (-15.14, 0.26)
Test for heterogeneity χ^2 =0.38, df=1, *P*=.54							
Test for overall effect *z*=1.89, *P*=.06							
03 VAS score at 6-8 weeks after injection							
Gaffney et al[7]	42	35.80 (26.80)	42	42.90 (26.00)		17.8	-7.10 (-18.39, 4.19)
Jones and Doherty[11]	25	56.60 (24.00)	28	59.40 (27.00)		12.1	-2.80 (-16.53, 10.93)
Subtotal (95% CI)	67		70			29.9	-5.38 (-14.09, 3.36)
Test for heterogeneity χ^2 =0.22, df=1, *P*=.64							
Test for overall effect *z*=121, *P*=.2							
Total (95% CI)	219		228			100.0	-11.00 (-15.77, -6.23)
Test for heterogeneity[9] χ^2 =8.03, df=5, *P*=.15							
Test for overall effect *z*=4.52, *P*=.00001							

the treatment arm, as is common in practice. This was probably because the investigators wanted to ensure they were measuring only the effects of the steroids.

As for harm, none of the investigators in the five trials reported adverse consequences of intra-articular injections, and few adverse effects are reported in the literature. Creamer[4] in his 1999 review reported that iatrogenic infection occurred at a rate of 1:14 000 to 1:50 000. Evidence of accelerated deterioration of the joint due to repeated injections is very weak[4-6]; most authors believe it is an effect of the disease and not the injections.[4,5,19] Patients report the procedure itself to be painful or very painful about 20% of the time.[1]

To ensure we were up-to-date, we did another MEDLINE search just before we submitted this article. We found an RCT looking at the safety and efficacy of triamcinolone over the long term published in February 2003.[20] Patients were given either 40 mg of triamcinolone or saline into affected knees every 3 months for 2 years. They received a total of eight injections each. Pain scores improved in both groups during the 2-year period and were similar in both groups at 1 year and 2 years. Range of motion of the knee was better in the triamcinolone group at 1 year but not at 2 years. Treated patients had less pain at night and marginally less stiffness in knees at 2 years.

The importance of this study is that radiologic examination did not show any difference in deterioration in the triamcinolone group compared with placebo. Also, there were no adverse local or systemic affects. This study has not been included in the meta-analysis because it used multiple injections and did not measure outcomes in the short term (1 to 12 weeks). Its purpose was to evaluate the long-term effect of multiple injections in the knee. We include it here for the sake of completeness and because it reinforces our conclusion that adverse effects are rare.

DISCUSSION

Treatment effects were consistent among the five studies (**Table 2**[1,3,7,8,11]). The four studies that measured effect at 1 week show a significant reduction in pain (assessed on a VAS) compared with placebo. Three of the studies showed an effect at 1 week when patients' subjective assessments of pain relief were used or when a predetermined clinically significant level of pain reduction was used. No study showed an effect of triamcinolone beyond 1 week. Methylprednisolone, however, showed a continuing effect at 3 weeks, and cortivazol at 4 weeks. The meta-analysis confirms the general impression of the study results: that intra-articular steroid injections are useful in reducing pain for up to 4 weeks.

Clinical application

These studies were all performed in a secondary care environment by rheumatologists, who also gave the injections. Patients all had moderate-to-severe OA. Before treating patients with intra-articular steroids, primary care physicians should consider whether they are comfortable and experienced in doing intra-articular injections and whether patients' disease is similar to that of people who have been shown to benefit from this treatment. Pain relief is likely to be short lived; it will likely last for a week and probably for a month, but not beyond that. A short-term effect can sometimes be useful (eg, to control severe pain while waiting for non-steroidal anti-inflammatory drugs [NSAIDs] to work, in situations where patients need rapid and substantial relief of pain for an upcoming activity, and when pain is affecting health due to sleep interruption). Osteoarthritic patients who have gastrointestinal side effects from NSAIDs might well be good candidates for steroid injection.

Alternative interpretations of the data

It is likely that the effect of treatment is real because of the consistency of results from study to study. The studies overall appear well done, especially the recent ones. The effect seems short

lived, however, and in several situations, CIs suggest that intra-articular steroids could increase pain for some people. On balance, there seems a greater likelihood of benefit than of harm within the first month; but then a decreasing effect over time could lead to increased pain. Patients' informed choice will be important in making the decision to use intra-articular steroids.

Limitations

We believe the results of this meta-analysis provide a valid assessment of the effect of intra-articular steroids for treatment of knee OA. The following methodologic limitations should be kept in mind, however. We did not contact experts in the field to seek out unpublished data; assessments were done by only two reviewers who were not blinded to the source of the articles; and the five studies selected used slightly different end points or targets for successful pain reduction (we accepted these targets and combined them in a single outcome of successful or failed treatment). Differences in effect were not large.

Bottom line

This systematic review with meta-analysis supports the recommendations of American[19] and international[20] authorities that intra-articular injection of corticosteroids provides short-term relief of the pain of OA of the knee. Intra-articular corticosteroids result in a clinically and statistically significant reduction in knee pain 1 week after injection that continues for 3 to 4 weeks. Adverse events were rarely reported. The procedure should be used for patients with moderate-to-severe OA. Physicians using this treatment should be aware of its limitations. Patients should be informed of the benefits and possible adverse effects of intra-articular injection, and decisions on whether to inject should be made jointly by physicians and patients.

Competing interests

None declared

EDITOR'S KEY POINTS

- Family physicians are often asked to inject knees with steroids to relieve pain from chronic osteoarthritis. This systematic review and meta-analysis pools results of five randomized controlled trials of pain reduction. Results were consistent among trials.
- Intra-articular steroid injections reduce pain significantly for 3 to 4 weeks, but not much longer than that. Side effects appear to be minimal.
- Family physicians who offer this treatment can use this information to discuss the benefits and drawbacks of injection with their patients.

POINTS DE REPÈRE DU RÉDACTEUR

- Les patients qui souffrent d'arthrose du genou demandent souvent au médecin de famille des injections intra-articulaires. Cette revue systématique avec méta-analyse regroupe les résultats de cinq essais randomisés portant sur le soulagement de la douleur. Ces essais ont donné des résultats concordants.
- L'injection intra-articulaire de stéroïdes procure un soulagement significatif qui dure de 3 à 4 semaines, mais pas beaucoup plus. Les effets indésirables semblent minimes.
- Le médecin de famille qui offre ce type de traitement peut utiliser cette information pour discuter avec le patient des avantages et inconvénients de l'injection.

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