Injectable Corticosteroids in Modern Practice

Brian J. Cole, MD, MBA, and H. Ralph Schumacher, Jr, MD

Abstract

Long-lasting, crystalline suspensions of injectable corticosteroids have been used to treat joint and soft-tissue disorders for many years; they decrease inflammation by reducing local infiltration of inflammatory cells and mediators. Depot formulations differ in their characteristics. Compounds with low solubility are thought to have the longest duration of action but may cause tissue atrophy when used in soft tissues. Intra-articular corticosteroids are commonly used to treat osteoarthritis and inflammatory arthritis: meta-analyses confirm their benefit in reducing pain and symptoms. Intra-articular corticosteroid injections have been shown to be safe and effective for repeated use (every 3 months) for up to 2 years, with no joint space narrowing detected. Fewer clinical trials are available for extra-articular uses for injectable corticosteroids, although there is evidence of efficacy in a variety of soft-tissue conditions. The accuracy of injections affects outcomes. Postinjection flare, facial flushing, and skin and fat atrophy are the most common side effects. Systemic complications of injectable corticosteroids are rare.

J Am Acad Orthop Surg 2005;13:37-46

First used for arthritic joints more than 50 years ago, injectable corticosteroids remain a mainstay of treatment of many causes of acute joint or soft-tissue pain. In a survey, 51% of rheumatologists stated that they used injectable corticosteroids frequently; an additional 42% used them at least some of the time.[1] The results of using injectable corticosteroids, however, have not been rigorously evaluated. Controlled trials with these agents have been few, and much of the evidence concerning both efficacy and safety remains anecdotal. This may be because these drugs are indeed assumed to be effective as well as because of the difficulty in measuring subjective outcomes, such as pain or swelling.

Despite the scarcity of high-quality clinical trial data, a large body of literature is available related to injectable corticosteroids. Depot formulations vary in their physical and pharmacologic characteristics, particularly with regard to their solubility and retention of crystals at the site of injection. Understanding the different formulations, the factors that affect outcome, and the common complications is necessary to use injectable corticosteroids appropriately for both intra-articular and soft-tissue conditions.

Mechanism of Action

The pathways by which injectable depot corticosteroids mediate symptom relief are not completely understood, and they may differ from the mechanisms associated with systemic corticosteroids. Local action of decreasing inflammation in synovial tissues is believed to be the primary effect of depot corticosteroids. The effect is particularly profound on edema as well as the number of lymphocytes, macrophages, and mast cells.[2] Other studies have found reductions in inflammatory cells in joints after corticosteroid injections, although this may be preceded by a mild initial inflammatory response immediately following the injection.[3]

In addition to local effects, intra-articular corticosteroids may elicit dose-related systemic effects. Marked improvements in inflammatory markers, such as erythrocyte sedimentation rate (ESR) and C-reactive protein level, can occur in patients with rheumatoid arthritis (RA) who receive intra-articular treatment with corticosteroids. Effects of intra-articular corticosteroids are frequently observed on noninjected involved joints, further suggesting the importance of systemic effects. However, the effect on noninjected joints is variable, ranging from no response to complete response.

Commonly Used Depot Corticosteroids

Corticosteroids are available in several different formulations, includ-

Dr. Cole is Director, Rush Cartilage Restoration Center, Rush University Medical Center, Chicago, IL. Dr. Schumacher is Chief of Rheumatology, VA Medical Center, Philadelphia, PA.

ing pills, ointments, and soluble and depot parenteral formulations. Of these, only depot formulations are suitable for injecting joints. Depot formulations tend to remain at the injected site for a long period of time and display mainly local effects. Water-soluble formulations, such as dexamethasone, diffuse rapidly from the injected regions and exert mostly systemic effects. Nevertheless, soluble formulations are useful for certain extra-articular conditions of the upper extremities, such as car-

pal tunnel syndrome and trigger finger.

The choice of depot corticosteroid is based on a variety of considerations, including the availability, cost, versatility, and pharmacokinetics of the agent. In a survey of members of the American College of Rheumatology (ACR), the most commonly used depot corticosteroids were methylprednisolone acetate (35%), triamcinolone hexacetonide (31%), and triamcinolone acetonide (22%).[4] Other available preparations include hy-

drocortisone acetate, betamethasone sodium phosphate, betamethasone acetate, and prednisolone tebutate. Because many facilities keep only one or two depot corticosteroids on hand, the versatility of an agent can play a key role in its use. The ability of methylprednisolone acetate to be used for both joint and soft-tissue injections likely contributes to its widespread use[5-10] (Table 1).

Pharmacokinetics

In general, the pharmacokinetics

Table 1
Characteristics of Depot Corticosteroids*

Generic Name	Solubility (% wt/vol)[5]	Crystal Structure[6]	Serum Half-Life (days)	Peak Plasma Concentration (ng/mL)	Average Duration of Action (days)[†]	Fluorinated
Betamethasone sodium phosphate and betamethasone acetate	NA	Betamethasone acetate: 10 to 20 μm, rod-shaped with blunted ends, negative birefringence; difficult to distinguish from sodium urate crystals	6.3[7]	10.8 (after 7-mg injection in one knee[7])	Approximately 9[8,9]	Yes
Hydrocortisone acetate	0.002	NA	NA	NA	6-40[9]	No
Methylprednisolone acetate	0.001	Small, pleomorphic, tendency to agglutinate, strong birefringence	5.8	11.8 (dose not specified)	7-84[10]	No
Prednisolone tebutate	0.001	Small, pleomorphic with a branched and irregular configuration, positive birefringence	NA	NA	10-15[8,9]	No
Triamcinolone acetonide	0.004	Very similar to methylprednisolone acetate, but with a slightly increased tendency to agglutinate and slightly stronger birefringence	3.2-6.4[7]	Approximately 11 (after 40-mg injection into one knee)[7]	14[8,9]	Yes
Triamcinolone hexacetonide	0.0002	15 to 60 μm, rod-shaped, negative birefringence; difficult to distinguish from sodium urate crystals	4.6[7]	Approximately 3 (after 40-mg injection into one knee)[7]	8-90+[10]	Yes

NA = not available.

* Unless otherwise noted, information is derived from the manufacturer's prescribing information.

[†] Most studies were short-term. Estimates of duration of pain relief were, in many cases, based on clinical impression.

of depot corticosteroids are not as well studied as those of intravenous formulations, and conventional pharmacokinetic parameters, such as peak plasma concentrations and serum half-life, may not be relevant to the local actions of depot formulations. The serum half-life influences the systemic effects associated with injected corticosteroids, but its impact on local activity with intra-articular use is less clear and probably is negligible.

Solubility

Solubility is a key issue because compounds with lower solubility may maintain effective synovial levels for a longer time and produce lower systemic levels than would compounds with greater solubility. In a comparison of triamcinolone acetonide and triamcinolone hexacetonide, Derendorf et al[7] found that total absorption amount was similar between the two compounds. However, the absorption rates were markedly different, with triamcinolone hexacetonide released more slowly than triamcinolone acetonide, resulting in lower peak plasma levels. A lower systemic level of corticosteroids is generally viewed as a favorable feature because of potential reductions in systemic toxicity. However, lower plasma levels also may result in reduced effects on inflammation at noninjected sites. Although compounds with low solubility are well suited for intra-articular injections, they may not be appropriate for soft-tissue injections because of associated side effects, particularly atrophy of surrounding tissues.[5]

Crystal Structure

Direct examinations of corticosteroid crystals have been performed. In one study, corticosteroid formulations were injected into rat subcutaneous air pouches 24 hours after injection with either normal saline or monosodium urate (MSU) crystals to stimulate inflammation. In air pouches injected with normal saline, betamethasone acetate crystals disappeared from the fluid within 24 hours, whereas triamcinolone hexacetonide crystals were still present at 48 hours, and prednisolone tebutate crystals lasted throughout the 7-day study.[11] In rat air pouches injected with MSU crystals, betamethasone resulted in a rapid but mild decrease in inflammation. Triamcinolone hexacetonide and prednisolone tebutate dramatically suppressed inflammation at 7 days, but their use also resulted in atrophy and necrosis of the membranes. All three corticosteroid preparations resulted in an increase in MSU crystals on the synovial surface and in the number of tissue deposits of MSU (tophi-like formations).[11] This study thus highlights the different properties of various injectable corticosteroid formulations and the potential impact of these characteristics on both efficacy and side effects.

In humans, depot corticosteroid crystals have been detected in synovial fluid for up to 1 month after joint injection.[3,6] The crystal structures of different preparations vary (Table 1), and light microscopy may not always be able to differentiate between corticosteroid crystals and other crystals involved in inflammatory arthritis, such as MSU, calcium pyrophosphate dihydrate, and hydroxyapatite.[3]

Duration of Action

The reported ranges for duration of action vary widely between different corticosteroids and sometimes even for the same corticosteroid. Although some data suggest that decreased solubility correlates with a sustained clinical effect, this is not necessarily always the case. In one clinical trial, triamcinolone hexacetonide, a compound with lower solubility, showed a less durable clinical effect when injected into osteoarthritic knees than did a more soluble compound, methylprednisolone acetate.[12] This finding also is supported by data from a meta-analysis[13] and suggests that understanding of the mechanism of action of these agents is incomplete.

Chemical Structure and Considerations

The addition of a fluorine group to the base corticosteroid molecule can increase absorption and activity, but it may also result in increased side effects.[14] However, patients who experience adverse reactions to a fluorinated compound may be able to tolerate a nonfluorinated compound.

Chemical incompatibility between injectable corticosteroids and other agents can result in flocculation. Injectable corticosteroids are often combined with local anesthetics because injecting both agents not only provides immediate pain relief but also can verify that the site injected was the source of pain.[15] In some cases, combinations of corticosteroids and anesthetics are available from the manufacturer. If not, the mixture should be carefully inspected for the formation of precipitates before injection.

Intra-articular Injections

Uses

The most common and best-studied use of injectable corticosteroids is for joint disorders. ACR guidelines support the value of these treatments of acute knee pain in osteoarthritis[16] and for joints affected by RA.[17] Other joint conditions that may respond to corticosteroid injections include juvenile RA, crystal deposition diseases (ie, gout and pseudogout), systemic lupus erythematosus and mixed connective tissue disease, acute traumatic arthritis, psoriatic arthritis, ankylosing spondylitis, and arthritis associated with inflammatory gastrointestinal disorders. The main goal of treatment is to relieve pain and control synovitis in affected joints. An associated benefit of reducing synovitis may be increased ability to exercise and improve muscle strength.

Intra-articular injections also have been useful in controlling pain and decreasing rehabilitation time after arthroscopic knee surgery.[18,19] Following diagnostic knee arthroscopy, the addition of methylprednisolone to intra-articular injections of bupivacaine plus morphine, compared with a saline injection and bupivacaine/morphine injection, resulted in significant benefits in pain reduction during leg lift ($P = 0.0001$ and $P = 0.006$, respectively), flexion to 90° ($P = 0.001$ and $P = 0.002$), and walking up and down stairs ($P = 0.0001$ and $P = 0.008$).[18] Injection of intra-articular triamcinolone acetonide after arthroscopic knee surgery also resulted in significantly lower pain scores ($P < 0.05$ to $P < 0.01$) and significantly fewer requests for rescue analgesia (0% versus 53%; $P < 0.001$) compared with saline.[19]

Clinical Trial Data

Few controlled long-term studies are available assessing the duration of pain relief after intra-articular corticosteroid injection. Variations in findings range from 1 week with only marginal benefit relative to placebo[20] to dramatic pain relief lasting up to 13 weeks.[10] Two recent meta-analyses have tried to reconcile these data for osteoarthritis of the knee.[13,21] The meta-analysis by Arroll and Goodyear-Smith[21] included 10 placebo-controlled randomized trials, published between 1958 and 2003, in which improvement of symptoms was included as an outcome. Jadad quality scores, which provide an estimate of the overall quality of each study on a scale of 0 (lowest quality) to 5 (highest quality), ranged from 2 to 5.[22] All six studies that examined symptom improvement at 2 weeks reported greater improvement in patients who received intra-articular corticosteroids compared with placebo, and the pooled data were highly significant for the overall effect ($P < 0.00001$). The two methodologically sound studies that examined improvement at 16 to 24 weeks also found sig-

nificant benefits associated with intra-articular corticosteroids ($P = 0.009$), but long-term improvements may require higher doses (50 mg equivalent of prednisone). Five studies reported changes in pain on a visual analog scale (VAS) 2 weeks after treatment, and the pooled data from these studies found a statistically significant effect in favor of treatment ($P = 0.00001$).[21]

The meta-analysis by Godwin and Dawes[13] examined five randomized placebo-controlled trials published between 1980 and 1999 that reported pain outcomes on a VAS. All five studies also were included in the meta-analysis of Arroll and Goodyear-Smith.[21] Pooled data indicated that treated patients were more likely than placebo patients to achieve clinically significant pain reduction at 1 week and at 3 to 4 weeks. By 6 to 8 weeks, no significant reductions in pain were observed. The pain relief appeared to vary depending on the compound used. None of the three studies using triamcinolone hexacetonide showed an effect on pain beyond 1 week. In contrast, methylprednisolone showed a significant effect on pain at 3 weeks, and cortivazol (a corticosteroid not approved for use in the United States) continued to reduce pain at 4 weeks.[13]

A recent trial that compared methylprednisolone acetate and triamcinolone hexacetonide supported the sustained effect of methylprednisolone acetate in patients with knee osteoarthritis.[12] In 57 randomly assigned patients, both methylprednisolone acetate and triamcinolone hexacetonide resulted in significant ($P < 0.01$) differences in VAS-measured pain reduction at 3 weeks (change from baseline of 13.7 and 32.9 mm, respectively). However, at 8 weeks, only methylprednisolone showed a significant ($P < 0.05$) effect on pain scores (change from baseline of 18.3 and 7.6 mm, respectively). Similar results were obtained with Lequesne index scores, a measure of symptom severity and dis-

ability. Neither corticosteroid mediated significant reductions in stair climbing time.[12]

Raynauld et al[23] reported that repeated intra-articular corticosteroid injections into the knee were safe and effective for up to 2 years. In this double-blind trial, 66 patients were randomized to receive triamcinolone acetonide or saline into the study knee every 3 months for up to 2 years. Assessments of the primary outcome—progression of joint space narrowing—revealed no significant differences between treatment groups in mean joint space width at 1 and 2 years. Patients who received intra-articular corticosteroids showed a significant ($P = 0.05$) improvement in range of motion compared with placebo at 1 year. Other parameters, including pain, stiffness, and physician's and patient's global assessments, were not statistically different between treatment groups at 1 and 2 years. However, area-under-the-curve analyses for knee pain at night and knee stiffness found a significant difference ($P = 0.05$ for both) over 2 years in favor of patients receiving intra-articular corticosteroids. This study thus supports the safety of long-term corticosteroid injections and their ability to improve clinical symptoms over the course of 2 years.[23]

Fewer data are available on the use of intra-articular corticosteroids in the treatment of joints affected by RA. However, some studies suggest that the duration of pain relief may be longer than for osteoarthritis. In a retrospective study, a sustained clinical remission occurred in 75% of injected joints during the 7-year follow-up. However, these patients also were receiving systemic therapy with disease-modifying antirheumatic drugs.[24]

Although the literature indicates that many patients respond to intra-articular corticosteroid therapy, there are no consistent data on the duration of pain relief after injection. Individual patients respond differently, and specific agents also may vary in their effects. Study design, injection tech-

nique, the condition being treated, and type and frequency of outcome assessments also may contribute to the wide disparities observed. A trial of this therapy is needed to determine effectiveness in any given patient.

Practical Considerations

One of the factors that may affect the variability in response to intra-articular injections is placement of the needle. A radiographic study of injections into various joints found that 56 (52%) of 108 injections were definitely intra-articular; the others either were extra-articular or the location could not be clearly determined from the radiograph.[25] More accurate placement resulted in better clinical outcome. Improvements in joint inflammation were observed in 59% of patients whose injections were intra-articular compared with 37% of patients whose injections were extra-articular.[25] A more recent study that focused exclusively on intra-articular injections into the knee found a higher accuracy rate of 75%, with entry through the lateral midpatellar portal resulting in the highest rate of correct placement (93%).[26]

The generally accepted recommendation for frequency of intra-articular injections is no more than once every 3 months into the same joint.[17] However, this is more an empiric recommendation than an evidence-based one and likely was originally founded on concerns of possible arthropathy.

Some studies suggest that synovial fluid aspiration should accompany intra-articular injections. Successful aspiration of synovial fluid at the time of corticosteroid injection is significantly ($P < 0.01$) associated with treatment response[27] and with significant ($P = 0.001$) reductions in relapses in the 6 months after the injection.[28] The explanation for this phenomenon may have to do with a decrease in symptoms (ie, pain, stiffness) because of reductions in the effusion or to reduced dilution of the injection. Suc-

cessful aspiration also confirms that the injection was intra-articular.

The combination of intra-articular corticosteroids plus joint lavage may provide modest short-term benefits. Compared with patients who received lavage alone, significantly ($P = 0.004$) more patients treated with intra-articular methylprednisolone acetate and lavage met Osteoarthritis Research Society International response criteria at 4 weeks (33% versus 58%, respectively).[29] However, no significant differences were observed at other time points (2, 8, 12, or 24 weeks) or with other outcomes, including pain and stiffness.[29] The short-term nature of this benefit may explain why other studies have not detected additional improvements when these techniques are combined.

Although one controlled study found that resting the joint after injection is helpful,[30] another study did not find such a benefit.[31] These differing conclusions probably can be explained by the different time course of assessments. The authors of the study that did not find a benefit conducted assessments at baseline, 48 hours, and 10 months. They did not detect any changes in pain or tenderness, swelling, or range of motion in rheumatoid joints rested for 48 hours after injection compared with nonrested joints.[31] In contrast, the authors of the study that found a benefit to resting joints examined patients for up to 24 weeks after injection. Patients who did not rest joints and those who rested joints for a minimum of 24 hours after injection showed similar improvements at 3 weeks. Improvements in pain and stiffness were generally maintained over 24 weeks in patients in the rested group but not in those in the nonrested group. At 24 weeks, the rested group showed notable improvements in median areas under the curve in pain score, stiffness score, knee circumference, walking time, and C-reactive protein measures compared with the nonrested group.[30] This study suggests that

the benefits of resting joints may not be immediately apparent but can be notable during the recovery period. Clinical experience provides further support for the benefits of resting joints after injection of intra-articular corticosteroids.[24]

Extra-articular Injections

Uses

Corticosteroid injections are also useful in treating a variety of nonarticular disorders, particularly overuse syndromes (eg, tendinitis, bursitis, ligament sprain, tenosynovitis), acute athletic injuries, and nerve compression syndrome. Rather than entering the joint, extra-articular injections are targeted to the area surrounding the joint (periarticular), into tendons (eg, lateral epicondylitis), or above tendons (eg, subacromial space above the rotator cuff). Table 2 shows the most common uses of corticosteroid injections among orthopaedic surgeons.[32]

The effects of injectable corticosteroids in nonarticular locations are not completely understood. In some cases, intramuscular injections of relatively soluble corticosteroids may relieve polyarticular inflammation through systemic absorption and provide benefits for weeks.[5] However, inflammation is not always associated with tendinopathies; when present, inflammation may be necessary for the healing process. Corticosteroids may act through different mechanisms to mediate symptom relief of noninflammatory conditions.

Clinical Trial Data

There are few controlled clinical trial data of nonarticular uses of corticosteroids on which to base treatment decisions.[33,34] In a systematic review by Smidt et al,[33] 13 randomized controlled trials were identified in which corticosteroid injections were used in patients with lateral epicondylitis. All but one of the studies

had poor internal validity scores, thus limiting the conclusions that could be drawn from pooled data. Nevertheless, the data indicate that corticosteroid injections resulted in superior short-term (<6 weeks) outcomes in pain and global improvement compared with injections with local anesthetics or with conservative treatment. Comparisons with placebo were made in only two studies, and the data were inconsistent. Of the six studies that examined intermediate (6 weeks to 6 months) or long-term (>6 months) outcomes, none found significant differences in favor of corti-

costeroid injections. The authors suggest that high-quality studies with longer follow-up periods are needed to resolve the role of injectable corticosteroids in lateral epicondylitis.[33]

The use of corticosteroids in the treatment of trigger finger is supported by two randomized controlled studies.[35,36] In both, a single injection of a local anesthetic in combination with either methylprednisolone acetate[35] or betamethasone[36] successfully treated trigger finger in about 60% of patients, whereas local anesthetic alone improved the condition in about 20% of patients. A retrospective study of 235 patients with 338 primary trigger fingers provided further evidence for the use of injectable corticosteroids for this condition.[37] In this study, 49% of fingers showed resolution or improvement after a single injection; an additional 23% improved after two injections. Corticosteroid injections also may be effective in the treatment of de Quervain's tenosynovitis.[38,39] In a prospective study, approximately 90% of patients responded to treatment.[38]

Carpal tunnel syndrome also may respond to corticosteroid injections. In a Cochrane review of five randomized trials, Marshall et al[40] concluded that corticosteroid injections were more effective than placebo in relieving symptoms for up to 1 month. Corticosteroid injections also provided greater clinical improvement than did oral corticosteroids for up to 3 months after treatment. In one randomized trial, 30 patients received oral placebo for 10 days along with a single methylprednisolone acetate injection into the carpal tunnel; another 30 patients received oral prednisolone daily for 10 days along with a single saline injection.[41] Compared with the oral prednisolone group, the group receiving methylprednisolone injections experienced significant improvements in symptoms at 8 and 12 weeks ($P = 0.002$ and $P = 0.004$, respectively). Further time points were not assessed.

In another randomized trial of patients with carpal tunnel syndrome, methylprednisolone acetate plus lidocaine was compared with lidocaine alone.[42] At 1 month, 77% of patients in the corticosteroid group (23/30) did not require further treatment, compared with 20% of the patients in the lidocaine-only group (6/30). Although some of the responders began to experience symptoms over time, at 12 months, 50% of the corticosteroid group (15/30) still did not require further treatment compared with 7% of the lidocaine-only group (2/30). A lower rate of long-term responses was reported in a recent prospective study of 73 patients.[43] In this study, 10% of patients remained asymptomatic 1 year after receiving three betamethasone injections into the carpal tunnel and wearing a wrist splint for 9 weeks. Patients with recent mild to moderate symptoms seemed to have better responses to corticosteroid injections than did those with long-lasting or more severe symptoms.

Buchbinder et al[34] performed a Cochrane review of corticosteroid injections for shoulder pain. Pooled data indicated that subacromial corticosteroid injection was superior to placebo in treating rotator cuff disease but was comparable to nonsteroidal anti-inflammatory drugs. For adhesive capsulitis, a possible short-term benefit of corticosteroid injections was suggested, but there were insufficient data for pooling, and more high-quality studies are required.[34]

A review of the treatment of anserine bursitis identified two studies involving corticosteroid injections and concluded that this is the only treatment modality with proven success in treating this condition.[44] In one trial, corticosteroid injections resulted in notable reductions in pain compared with naproxen (corticosteroid, 70% significantly improved and 30% resolved; naproxen, 58% and 5%, respectively).

The use of injectable corticosteroids to treat trochanteric bursitis has

not been assessed in a randomized trial. However, an open observational study of a single injection of betamethasone mixed with lidocaine has been conducted.[45] More than three fourths (77%) of patients reported pain relief at 1 week after injection, and 61% continued to report improvement in pain at week 26. These data suggest that corticosteroid injections can provide long-lasting benefit for trochanteric bursitis.

Practical Considerations

As with intra-articular injections, the accuracy of needle placement can be a key factor in the outcome of soft-tissue disorders. In one study that used radiographic contrast material to track injection accuracy during local corticosteroid injections to the shoulder, only 14 (37%) of 38 procedures were found to be accurately placed. Subacromial injections (29% accurate placement) were more difficult than glenohumeral injections (42%).[46] Outcomes in patients who received accurately placed injections were superior to outcomes in those whose injections were inaccurately placed (Fig. 1). Significant ($P < 0.05$) differences in changes from baseline between the two groups were found in stiffness, loss of function, flexion, and abduction.

Use of sonography could increase the accuracy of injection location and thereby improve outcomes. In a study in which blinded subacromial corticosteroid injections were compared with ultrasonography-guided injections in patients with painful shoulders, the group receiving guided injections had significantly greater improvements in pain scores ($P < 0.001$) and in shoulder function ($P = 0.012$) at 6 weeks compared with the group receiving blinded injections.[47]

Safety

The excellent overall safety record of injectable corticosteroids is acknowl-

edged in the 2002 ACR update of the *Guidelines for the Management of Rheumatoid Arthritis*: "Glucocorticoid injection of joints and periarticular structures is safe and effective when administered by an experienced physician."[17] This statement reflects a large body of clinical data. A recent prospective evaluation of 1,147 intra-articular and periarticular corticosteroid injections with methylprednisolone acetate found a very low rate of complications, with transient injection pain the most common (6.7% of patients).[48] The only long-term effects persisting beyond 6 months involved two cases of subcutaneous lipodystrophy, which were attributed to insufficient depth of injection.

As with all procedures, however, in certain instances, corticosteroid injections should not be used. Absolute contraindications to corticosteroid injections include a suspected or known joint infection, the presence of a prosthetic joint, or a fracture in the joint being injected. Caution should be used in patients with joint instability, coagulopathy, or overlying cellulitis or infection.[5]

Side Effects

The most common side effects of corticosteroid injections are postinjection flare, facial flushing, and skin or fat atrophy.[49] The frequency of these events depends on the compound and dose administered, the route of administration, and how closely patients are followed after the procedure. Postinjection flare, typically marked by pain in the injected joint or at the site of injection, affects 1% to 10% of patients. In most cases, adverse reactions occur later the same day; a lag time of 24 to 48 hours was reported by about 10% of affected patients in one study.[48] Postinjection pain and flares may be caused by the needle puncture but more commonly are thought to result from chemical synovitis in response to the injected crystals.[6] In most cases, analgesic therapy or ice packs adequately control discomfort, and symptoms subside within 48 hours.[48]

Facial flushing occurs in up to 15% of patients and is particularly common in women. The onset is usually within a few hours of injection, and symptoms may linger for 3 to 4
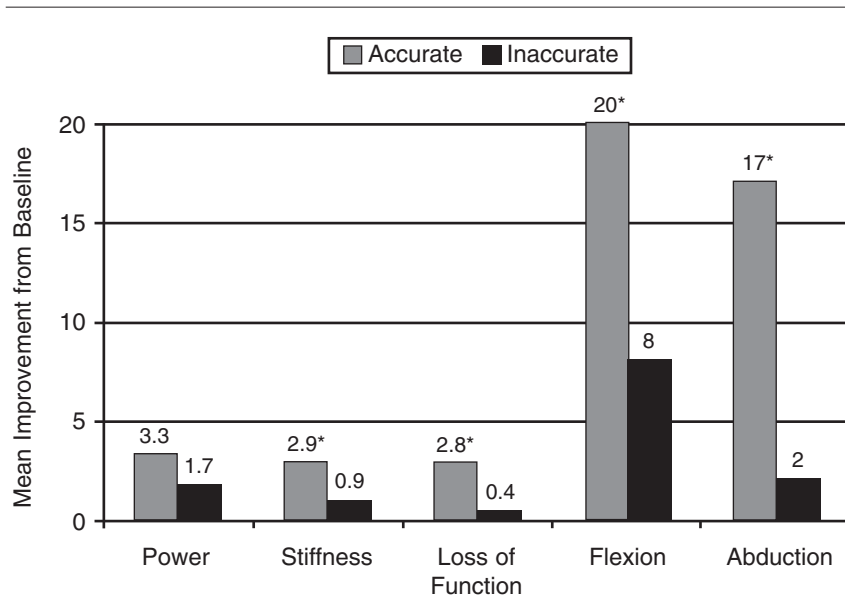
Figure 1 Mean improvement from baseline in clinical outcomes of patients with shoulder symptoms who received either accurately or inaccurately placed corticosteroid injections. There were significant differences in four of five outcome parameters (* = $P < 0.05$).[46]

days.[49] Skin or fat atrophy after injection (Fig. 2) may be more common with less soluble agents, such as the triamcinolone compounds.[49] In the prospective study of methylprednisolone acetate complications by Kumar and Newman,[48] 4 (0.6%) of 672 patients reported subcutaneous lipodystrophy. Effects lasted beyond 6 months in two patients.

Of the less common side effects, joint sepsis is of the greatest concern, with reported incidences ranging from 1 in 3,000 to 1 in 50,000.[50] Current rates may be even lower because of improved sterile technique and the availability of corticosteroid preparations in prefilled syringes, which reduces handling. In a survey of 191 orthopaedic surgeons, rheumatologists, and general practitioners, only 12.6% had ever encountered septic arthritis after corticosteroid injection of the knee, and only 3% had encountered it more than once.[50]

Case reports have documented the occurrence of tendon ruptures in patients after corticosteroid injections.[51] These appear to be associated with injections placed directly within tendons, which may accelerate degeneration of the already damaged tissue.

Although animal studies have suggested that corticosteroid injections may have deleterious effects on articular cartilage, studies in humans have not shown similar results. In a trial in which patients with osteoarthritis of the knee received triamcinolone acetonide 40 mg or placebo injections every 3 months for up to 2 years, no difference in loss of joint space was observed at the 1- or 2-year follow-up evaluations.[23] In another study of patients with RA, joint arthroplasty surgery was no more common during a 7-year follow-up in a joint that received four or more intra-articular injections per year than in those that received less frequent injections.[52] In children with chronic arthritis, treatment of joints with intra-articular triamcinolone hexacetonide did not appear to affect cartilage integrity.[53]
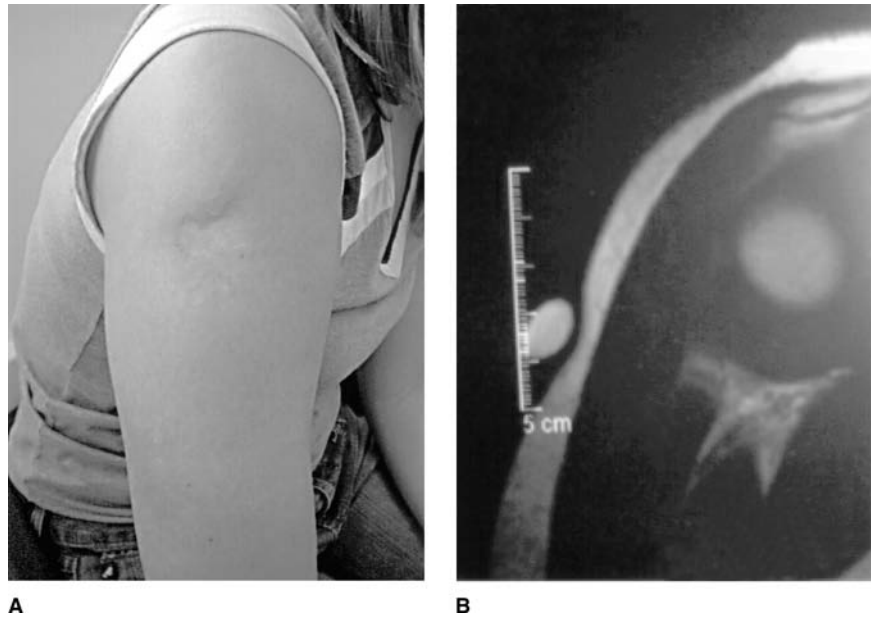
Figure 2 **A,** Right shoulder of an 18-year-old woman after a corticosteroid injection into the subcutaneous fat resulted in localized fat atrophy. **B,** Coronal T1-weighted MRI scan with gelatin capsule against region of fatty atrophy demonstrating marked volume loss in subcutaneous fat.

Systemic Effects

Systemic effects of injectable corticosteroids are influenced by the agent used, dose, frequency, and number of joints injected.[49] Systemic effects from corticosteroid injections are generally milder than with oral or intravenous formulations. Although osteoporosis is a known side effect of systemic glucocorticoids, a study of the effect of intra-articular triamcinolone acetonide on markers of bone metabolism found no net effects on bone resorption and only a transient effect on bone formation.[54] Furthermore, improvements in mobility may help counteract osteoporotic effects.

Corticosteroid-induced myopathy is a possible consequence of therapy, but it has not been reported after intra-articular injections. Corticosteroid-induced myopathy is more common with fluorinated corticosteroids (triamcinolone and dexamethasone) than with nonfluorinated compounds (hydrocortisone and methylprednisolone)[14] (Table 1).

The ability of intra-articular injections to suppress the hypothalamic-pituitary-adrenal (HPA) axis is well documented.[55-57] Suppression is usually mild and transient. In one study in which 11 patients received intra-articular injections of methylprednisolone acetate, 9 showed an average 21.5% reduction in serum cortisol levels 24 hours after injection. By 72 hours after injection, eight had returned to normal physiologic cortisol levels.[56] However, prolonged HPA axis suppression (5 to 7 weeks[57] and 11 weeks[55] after the last injection) has been reported, in one case accompanied by Cushing's syndrome.[55] Corticosteroid-associated HPA axis suppression could pose a particular problem during situations involving physical stress, such as surgery.

Corticosteroids can increase hepatic glucose synthesis and antagonize insulin effects, resulting in worsening of preexisting glucose intolerance.[14] Transient increases in blood glucose levels may be seen in patients receiving corticosteroid injections. However-

er, in a study in which patients with diabetes received soft-tissue injections of methylprednisolone acetate for rheumatic complaints, no significant changes were detected in fasting or predinner blood glucose readings during the 14 days after injection.[58]

Summary

Injectable corticosteroids can provide dramatic relief of pain and symptoms, although often this effect lasts for no more than a few weeks. Other benefits of injectable corticosteroid therapy include allowing the patient to regain mobility and to participate more fully in rehabilitation programs.[17] Systemic effects are uncommon, and local adverse effects usually are mild and transient.

A large body of clinical trial data supports the efficacy of intra-articular corticosteroid injections, particularly for patients with knee osteoarthritis. Intra-articular corticosteroids also appear to effectively control pain in rheumatoid joints and after arthroscopic knee surgery. Evidence supporting the use of injectable corticosteroids for soft-tissue disorders is less well established, although the efficacy of these compounds in the treatment of trigger finger, carpal tunnel syndrome, and anserine bursitis seems clear. Nevertheless, the experience of many clinicians suggests that injectable corticosteroids can play an important role in the management of other soft-tissue complaints, as well.

Despite their long history of use, questions remain concerning injectable corticosteroids. Reports on the comparative effectiveness and safety of different preparations in various conditions are largely anecdotal, and controlled high-quality studies of these agents in comparison with other therapies for soft-tissue disorders are needed. Factors affecting the durability of treatment effect are incompletely understood. An improved understanding of the mechanisms by which injectable corticosteroids relieve symptoms, particularly in non-inflammatory conditions, could be useful in designing more effective therapeutic agents and in providing optimal patient care.

References

1. Hochberg MC, Perlmutter DL, Hudson JI, Altman RD: Preferences in the management of osteoarthritis of the hip and knee: Results of a survey of community-based rheumatologists in the United States. *Arthritis Care Res* 1996;9:170-176.
2. Pasquali Ronchetti I, Guerra D, Taparelli F, et al: Morphological analysis of knee synovial membrane biopsies from a randomized controlled clinical study comparing the effects of sodium hyaluronate (Hyalgan) and methylprednisolone acetate (Depomedrol) in osteoarthritis. *Rheumatology (Oxford)* 2001;40:158-169.
3. Gordon GV, Schumacher HR: Electron microscopic study of depot corticosteroid crystals with clinical studies after intra-articular injection. *J Rheumatol* 1979;6:7-14.
4. Centeno LM, Moore ME: Preferred intraarticular corticosteroids and associated practice: A survey of members of the American College of Rheumatology. *Arthritis Care Res* 1994;7:151-155.
5. Genovese MC: Joint and soft-tissue injection: A useful adjuvant to systemic and local treatment. *Postgrad Med* 1998;103:125-134.
6. Kahn CB, Hollander JL, Schumacher HR: Corticosteroid crystals in synovial fluid. *JAMA* 1970;211:807-809.
7. Derendorf H, Mollmann H, Gruner A, Haack D, Gyselbg G: Pharmacokinetics and pharmacodynamics of glucocorticoid suspensions after intra-articular administration. *Clin Pharmacol Ther* 1986;39:313-317.
8. Caldwell JR: Intra-articular corticosteroids: Guide to selection and indications for use. *Drugs* 1996;52:507-514.
9. Gray RG, Gottlieb NL: Intra-articular corticosteroids: An updated assessment. *Clin Orthop* 1983;177:235-263.
10. Bain LS, Balch HW, Wetherly JM, Yeadon A: Intraarticular triamcinolone hexacetonide: Double-blind comparison with methylprednisolone. *Br J Clin Pract* 1972;26:559-561.
11. Rull M, Clayburne G, Sieck M, Schumacher HR: Intra-articular corticosteroid preparations: Different characteristics and their effect during inflammation induced by monosodium urate crystals in the rat subcutaneous air pouch. *Rheumatology (Oxford)* 2003;42:1093-1100.
12. Pyne D, Ioannou Y, Mootoo R, Bhanji A: Intra-articular steroids in knee osteoarthritis: A comparative study of triamcinolone hexacetonide and methylprednisolone acetate. *Clin Rheumatol* 2004;23:116-120.
13. Godwin M, Dawes M: Intra-articular steroid injections for painful knees: Systematic review with meta-analysis. *Can Fam Physician* 2004;50:241-248.
14. Nesbitt LT Jr: Minimizing complications from systemic glucocorticosteroid use. *Dermatol Clin* 1995;13:925-939.
15. Schumacher HR Jr: Aspiration and injection therapies for joints. *Arthritis Rheum* 2003;49:413-420.
16. American College of Rheumatology Subcommittee on Osteoarthritis Guidelines: Recommendations for the medical management of osteoarthritis of the hip and knee: 2000 update. *Arthritis Rheum* 2000;43:1905-1915.
17. American College of Rheumatology Subcommittee on Rheumatoid Arthritis Guidelines: Guidelines for the management of rheumatoid arthritis: 2002 update. *Arthritis Rheum* 2002;46:328-346.
18. Rasmussen S, Lorentzen JS, Larsen AS, Thomsen ST, Kehlet H: Combined intra-articular glucocorticoid, bupivacaine and morphine reduces pain and convalescence after diagnostic knee arthroscopy. *Acta Orthop Scand* 2002;73:175-178.
19. Wang JJ, Ho ST, Lee SC, Tang JJ, Liaw WJ: Intraarticular triamcinolone acetonide for pain control after arthroscopic knee surgery. *Anesth Analg* 1998;87:1113-1116.
20. Friedman DM, Moore ME: The efficacy of intraarticular steroids in osteoarthritis: A double-blind study. *J Rheumatol* 1980;7:850-856.
21. Arroll B, Goodyear-Smith F: Corticosteroid injections for osteoarthritis of the knee: Meta-analysis. *BMJ* 2004;328:869.
22. Jadad AR, Moore RA, Carroll D, et al: Assessing the quality of reports of randomized clinical trials: Is blinding necessary? *Control Clin Trials* 1996;17:1-12.

23. Raynauld 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;48:370-377.

24. McCarty DJ, Harman JG, Grassanovich JL, Qian C: Treatment of rheumatoid joint inflammation with intrasynovial triamcinolone hexacetonide. *J Rheumatol* 1995;22:1631-1635.

25. Jones A, Regan M, Ledingham J, Pattrick M, Manhire A, Doherty M: Importance of placement of intra-articular steroid injections. *BMJ* 1993;307:1329-1330.

26. Jackson DW, Evans NA, Thomas BM: Accuracy of needle placement into the intra-articular space of the knee. *J Bone Joint Surg Am* 2002;84:1522-1527.

27. Gaffney K, Ledingham J, Perry JD: Intra-articular triamcinolone hexacetonide in knee osteoarthritis: Factors influencing the clinical response. *Ann Rheum Dis* 1995;54:379-381.

28. Weitoft T, Uddenfeldt P: Importance of synovial fluid aspiration when injecting intra-articular corticosteroids. *Ann Rheum Dis* 2000;59:233-235.

29. Smith MD, Wetherall M, Darby T, et al: A randomized placebo-controlled trial of arthroscopic lavage versus lavage plus intra-articular corticosteroids in the management of symptomatic osteoarthritis of the knee. *Rheumatology (Oxford)* 2003;42:1477-1485.

30. Chakravarty K, Pharoah PD, Scott DG: A randomized controlled study of post-injection rest following intra-articular steroid therapy for knee synovitis. *Br J Rheumatol* 1994;33:464-468.

31. Chatham W, Williams G, Moreland L, et al: Intraarticular corticosteroid injections: Should we rest the joints? *Arthritis Care Res* 1989;2:70-74.

32. Hill JJ Jr, Trapp RG, Colliver JA: Survey on the use of corticosteroid injections by orthopaedists. *Contemp Orthop* 1989;18:39-45.

33. Smidt N, Assendelft WJ, van der Windt DA, Hay EM, Buchbinder R, Bouter LM: Corticosteroid injections for lateral epicondylitis: A systematic review. *Pain* 2002;96:23-40.

34. Buchbinder R, Green S, Youd JM: Corticosteroid injections for shoulder pain. *Cochrane Database Syst Rev* 2003;1:CD004016.

35. Lambert MA, Morton RJ, Sloan JP: Controlled study of the use of local steroid injection in the treatment of trigger finger and thumb. *J Hand Surg [Br]* 1992;17:69-70.

36. Murphy D, Failla JM, Koniuch MP: Steroid versus placebo injection for trigger finger. *J Hand Surg [Am]* 1995;20:628-631.

37. Newport ML, Lane LB, Stuchin SA: Treatment of trigger finger by steroid injection. *J Hand Surg [Am]* 1990;15:748-750.

38. Anderson BC, Manthey R, Brouns MC: Treatment of De Quervain's tenosynovitis with corticosteroids: A prospective study of the response to local injection. *Arthritis Rheum* 1991;34:793-798.

39. Richie CA III, Briner WW Jr: Corticosteroid injection for treatment of de Quervain's tenosynovitis: A pooled quantitative literature evaluation. *J Am Board Fam Pract* 2003;16:102-106.

40. Marshall S, Tardif G, Ashworth N: Local corticosteroid injection for carpal tunnel syndrome. *Cochrane Database Syst Rev* 2002;4:CD001554.

41. Wong SM, Hui AC, Tang A, et al: Local vs systemic corticosteroids in the treatment of carpal tunnel syndrome. *Neurology* 2001;56:1565-1567.

42. Dammers JW, Veering MM, Vermeulen M: Injection with methylprednisolone proximal to the carpal tunnel: Randomised double blind trial. *BMJ* 1999;319:884-886.

43. Graham RG, Hudson DA, Solomons M, Singer M: A prospective study to assess the outcome of steroid injections and wrist splinting for the treatment of carpal tunnel syndrome. *Plast Reconstr Surg* 2004;113:550-556.

44. Alvarez-Nemegyei J, Canoso JJ: Evidence-based soft tissue rheumatology IV: Anserine bursitis. *JCR: Journal of Clinical Rheumatology* 2004;10:205-206.

45. Shbeeb MI, O'Duffy JD, Michet CJ Jr, O'Fallon WM, Matteson EL: Evaluation of glucocorticosteroid injection for the treatment of trochanteric bursitis. *J Rheumatol* 1996;23:2104-2106.

46. Eustace JA, Brophy DP, Gibney RP, Bresnihan B, FitzGerald O: Comparison of the accuracy of steroid placement with clinical outcome in patients with shoulder symptoms. *Ann Rheum Dis* 1997;56:59-63.

47. Naredo E, Cabero F, Beneyto P, et al: A randomized comparative study of short term response to blind injection versus sonographic-guided injection of local corticosteroids in patients with painful shoulder. *J Rheumatol* 2004;31:308-314.

48. Kumar N, Newman RJ: Complications of intra- and peri-articular steroid injections. *Br J Gen Pract* 1999;49:465-466.

49. Lanyon P, Doherty M: Intra-articular therapy, in Firestein GS, Panayi GS, Wollheim FA (eds): *Rheumatoid Arthritis: Frontiers in Pathogenesis and Treatment*. Oxford, England: Oxford University Press, 2000, pp 361-369.

50. Charalambous CP, Tryfonidis M, Sadiq S, Hirst P, Paul A: Septic arthritis following intra-articular steroid injection of the knee: A survey of current practice regarding antiseptic technique used during intra-articular steroid injection of the knee. *Clin Rheumatol* 2003;22:386-390.

51. Smith AG, Kosygan K, Williams H, Newman RJ: Common extensor tendon rupture following corticosteroid injection for lateral tendinosis of the elbow. *Br J Sports Med* 1999;33:423-424.

52. Roberts WN, Babcock EA, Breitbach SA, Owen DS, Irby WR: Corticosteroid injection in rheumatoid arthritis does not increase rate of total joint arthroplasty. *J Rheumatol* 1996;23:1001-1004.

53. Huppertz HI, Tschammler A, Horwitz AE, Schwab KO: Intraarticular corticosteroids for chronic arthritis in children: Efficacy and effects on cartilage and growth. *J Pediatr* 1995;127:317-321.

54. Emkey RD, Lindsay R, Lyssy J, Weisberg JS, Dempster DW, Shen V: The systemic effect of intraarticular administration of corticosteroid on markers of bone formation and bone resorption in patients with rheumatoid arthritis. *Arthritis Rheum* 1996;39:277-282.

55. O'Sullivan MM, Rumfeld WR, Jones MK, Williams BD: Cushing's syndrome with suppression of the hypothalamic-pituitary-adrenal axis after intra-articular steroid injections. *Ann Rheum Dis* 1985;44:561-563.

56. Lazarevic MB, Skosey JL, Djordjevic-Denic G, Swedler WI, Zgradic I, Myones BL: Reduction of cortisol levels after single-intra-articular and intramuscular steroid injection. *Am J Med* 1995;99:370-373.

57. Reid DM, Patel S, Reid IW, Eastmond CJ, Rennie JA: Hypothalamic-pituitary-adrenal (HPA) axis function in patients receiving long-term intra-articular corticosteroids. *Clin Rheumatol* 1983;2:159-161.

58. Slotkoff AT, Clauw DJ, Nashel DJ: Abstract: Effect of soft tissue corticosteroid injection on glucose control in diabetics. *Arthritis Rheum* 1994;37(suppl 9):S347.