Topical Review

Corticosteroids: Review of the History, the Effectiveness, and Adverse Effects in the Treatment of Joint Pain

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Background: Corticosteroids have been used for the past 70 years in the treatment of various musculoskeletal conditions. This includes its use for joint pain such as rheumatoid arthritis and osteoarthritis.

Objectives: A narrative review of the literature from its initial discovery to the present day to summarize the research of corticosteroids for joint pain to determine the safety and effectiveness of this commonly used and prescribed medication.

Methods: A review of the literature was performed regarding the effectiveness and side effects of corticosteroids for joint and osteoarthritis conditions.

Results: The current evidence would suggest that the use of corticosteroids provides moderate short-term benefit for reducing pain and improving functioning. These benefits generally last several weeks without long-term effectiveness. In addition to its limited short-term effectiveness, there are multiple potential adverse effects including toxicity to articular cartilage and numerous systemic side effects such as increases in blood glucose levels, a reduction in immune function, and an increased risk of infections.

Limitations: English only articles were reviewed. No attempt was made to perform a formal statistical or meta-analysis.

Conclusions: The current evidence would suggest that the use of corticosteroids provides moderate evidence for short-term pain reduction and improvement in function. There are multiple potential adverse effects, such as toxic damage to articular cartilage, as well as numerous systemic side effects, including a reduction in immune function and an increased risk of infection, of which physicians need to be aware.

Key words: Cortisone, corticosteroids, arthritis, joint, pain, adverse effects, immune function, infections

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Since its initial discovery and introduction 70 years ago, cortisone has become a widely used medication both orally and in injection form for the treatment of a variety of musculoskeletal conditions. This ranges from spinal conditions, such as radiculopathy, to tendinopathies, as well as various conditions involving joints, such as degenerative arthritis. Despite the historical use of cortisone, the scientific evidence is limited to short-term improvements in pain with great discrepancy in other potential clinical benefits. In addition, there are multiple negative effects of corticosteroids both at local sites when injected as well as systemically with both oral and injected methods. The purpose of this paper is to provide a narrative review of the history of cortisone from its discovery through the current evidence regarding its effectiveness and adverse effects in the treatment of joint pain.

Cortisone was first discovered in the 1920s through animal research at the Mayo Clinic (1). A decade later, a group of endocrinologists at the Mayo Clinic, led by Dr. Edward C. Kendall, began investigating the chemical and physiologic components of the adrenal cortex to better understand this hormone. In 1934, the first compounds were separated and given the names Compounds A to D. Subsequently, in 1935 the other 2 compounds were isolated and named Compounds E and F (2). Part of the initial motivation of this research, beyond medical advancement, were the rumors that German pilots were using Compound E to enhance their abilities to fly. Initial studies were limited to mice because the samples were being isolated from the adrenal gland itself, and it was not until a partnership with Merck & Co. to synthesize the compounds that adequate research occurred (3). Compound E was found to have marked effects on muscular activity, carbohydrate metabolism, and physiologic resistance to cold, stress, and toxic substances. These preliminary findings were encouraging and led to a small study where Kendall and his colleagues injected 14 rheumatoid arthritis patients with Compound E, resulting in rapid alleviation of symptoms. However, the effects wore off after the injections were discontinued (2). These findings won Kendall the Nobel Prize in Physiology and Medicine in 1950 (2) and resulted in continued investigation by other researchers into the potential applications of this new drug.

The findings of Compound E, now known as cortisone, were echoed in a study by Steinbrocker et al (4), which showed improvement in patients with inflammatory processes (rheumatoid arthritis and lupus erythematosus), metabolic processes (gout), degenerative (osteoarthritis), irritative and traumatic (tendinitis and frozen shoulder), as well as neurovascular mechanism (reflex dystrophy). At this time, the authors acknowledged that the exact mechanism was still unknown but appeared to act on multiple pathways including, but not limited to, anti-inflammatory, analgesic, and antiallergic. Steinbrocker and his colleagues (4) saw promise, stating that "these new substances may make a helpful place... in some stubborn conditions which are relatively self-limiting" because of the prompt relief and shortening of clinical course. However, they also recognized that there are still "questions and problems regarding their adequacy and possible hazards" (4) in the use of cortisone for chronic conditions.

Soon after the benefits of Compound E were becoming more accepted, Hollander et al (5-8) began investigating Compound F, or as it later became known, hydrocortisone. These researchers chose to investigate Compound F because preliminary data were suggestive that this component of adrenal hormones had the greatest anti-inflammatory effects and because the systemic effects of Compound E were limiting their benefit. One of Hollander's colleagues, Thorne (5), shared anecdotal data of injecting the knees of rheumatoid arthritis patients, which resulted in clinical improvement without the side effects noted in trials of oral administration. This appears to be the first case of intraarticular injections and inspired Hollander to inject 26 rheumatoid arthritis patients with Compound F; the patients acted as the experimental and control groups because, in each patient, one knee was injected and the other observed (5). The results showed a decrease in joint temperature and a synovial fluid cell count drop. The success in the small group led to a larger trial of 700 injections into 129 arthritic joints (rheumatoid and osteoarthritis) (8). Most of the injections were into the knee, but the ankles, elbows, wrists, hips, shoulders, and metacarpophalangeal joints were also targeted. One-third of the rheumatoid arthritis patients had symptomatic improvement within 3 days, lasting 8 days on average (maximum 10 weeks), while 36/39 patients with osteoarthritis had improvements within 24 hours, lasting 3 weeks on average, with some patients experiencing 6 months of relief. In addition to the benefits, the researchers found there to be no systemic side effects, no infections, and no local side effects. Despite the apparent success, Hollander (5,8) noted that this is not a curative, but palliative practice to be used in tandem with general therapy and that "time will tell whether this method of utilizing hydrocortisone is of… practical value."

Acknowledging Compound F's shortcomings, Hollander and his colleagues (5-8) worked with Merck & Co. to attempt to find a longer-lasting solution in the form of a higher, less soluble ester. The researchers tested tertiary butyl acetate compared to the standard formulation in patients with rheumatoid and osteoarthritis. The data were promising, showing greater symptomatic alleviation in 65% of patients with an average improvement of symptoms for 16 days (vs 9 days in the control) (6). After 10 years of collecting data, Hollander and colleagues (7) published a retrospective review of the previous decade's use of hydrocortisone. The indications included all forms of arthritis, bursitis, and tendinitis. For the various conditions, the researchers followed patients for several years. In 100 patients

with rheumatoid arthritis, 48 still required periodic injections over weeks or months, 31 did not require injections, 8 did not have an adequate response, and the remaining 13 passed away or were lost to follow-up. In 100 patients with knee osteoarthritis, 24 continued to receive injections every 1 to 3 months, 59 were no longer bothered, and 11 did not have an adequate response. He also noted that patients with hip osteoarthritis received some benefit, though less than in the knee, which he attributed to the difficulty of successfully injecting a hip in comparison to the knee. Through this collection, the only side effects encountered were symptom exacerbation, infection of the site, and joint instability in joints receiving repeated injections, with the only contraindication being an infection at the site (it is noted that "reinjection into a chronically inflamed joint has been repeated up to 142 times with continued palliation and without apparent harmful effect") (7). Despite this success, Hollander highlights that hydrocortisone should be used in adjunct to regular treatment, suggesting that "rehabilitation may be accelerated" but that the "arthritic process may advance…[while] symptoms are relieved" (7). This overwhelming success in the preliminary studies resulted in the widespread use of hydrocortisone injections and likely contributed to today's continued use in a myriad of conditions.

Consequently, the objectives of this manuscript are to provide a narrative review of the literature from its initial discovery to the present day to summarize the research of corticosteroids for joint pain to determine the safety and effectiveness.

Methods

For this narrative review, multiple databases were searched including PubMed and Google Scholar searches using key words of cortisone, corticosteroids, joint pain, arthritis, evidence, effectiveness, side effects, and adverse effects. Thus, the articles containing the discovery, adverse effects, and effectiveness, along with clinical uses, were reviewed and summarized. The manuscripts were reviewed by the senior author for accuracy. No quality assessment or risk of bias were performed.

Results

The Mechanism

Corticosteroids exert most functionality through interactions with globally-expressed receptors. Once in the body, the steroids circulate in a free form or bound to corticosteroid-binding globulin, also known as transcortin. The free form can diffuse passively through the plasma membrane to bind to intracellular glucocorticoid receptors, whereas the bound form interacts with ligand-dependent transcription factors. Once bound within the cell, corticosteroids can regulate gene expression through transcriptional, post-transcriptional, and post-translational mechanisms (9).

Though corticosteroids have multiple functions, the focus of this paper is on the anti-inflammatory effect, which seems to correlate with dose and duration of treatment. The mechanism is multifactorial but is ultimately most dependent on 2 mechanisms of action: (1) the inhibition of cytokine, chemokine, and adhesion molecule production and (2) the antagonism of the action of proinflammatory cytokines, including interleukin-1 and tumor necrosis factor. These actions are achieved through inhibition of transcription factors AP-1 and NFkB through several mechanisms that vary based on cell type. In some cells, inhibition occurs through direct protein interactions, resulting in decreased transcriptional activity; for instance, some corticosteroids inhibit Janus kinase signal transduction and activation transcription pathways that are usually initiated by IL-2 and interferon-gamma. In other cells, inhibition occurs through induction of inhibitory molecules such as lipocortin-1 (a phospholipase A2 inhibitor which blocks eicosanoid generation and cyclooxygenase-2 induction). Through these mechanisms, corticosteroids inhibit vasodilation and vascular permeability, resulting in decreased plasma exudation, erythema, and swelling (9).

The administration of corticosteroids also affects white cell response. For example, corticosteroids cause neutrophilic leukocytosis. Though the exact mechanism is not completely understood, it is hypothesized that corticosteroids alter adhesion molecules of neutrophils or the endothelial surface (E-selectin and ICAM-1), which prevents neutrophils from reaching the inflammatory site. Additionally, there is a decrease in circulating levels of eosinophils, basophils, monocytes, and lymphocytes (decrease in T more than B and CD4 more than CD8) in response to corticosteroids. Again, it is not completely understood, but research has shown that there is down regulation of lymphocyte adhesion molecules (such as LFA-1 and CD2) through action at corticosteroid receptors. There is also evidence of nongenomic effects of corticosteroids related to cell membrane redistribution and changes to the cellular adhesion molecules themselves, as well as redistribu-

tion of lymphocytes to bone marrow, spleen, skin, and regional lymph nodes (9).

The Evidence for Corticosteroids in the Treatment of Osteoarthritis

As described previously, corticosteroids have anti-inflammatory effects that allow for their benefit in inflammatory conditions. However, the mechanism of benefit in osteoarthritis is still unknown. A recent study used enzyme-linked immunosorbent assay (ELISA) and Western Blot in order to understand a potential mechanism. Ultimately, it was hypothesized that corticosteroids protect against osteoarthritis through inhibition of IL-6 and IL-8, suppression of NF-κB and STAT3, and reduction of collagen I, MMP-1, and MMP-13 expression (10). Though the mechanism is still unclear, this pathology is likely the most studied and most targeted by corticosteroids. There is data evaluating oral steroids, intraarticular injections, and intramuscular injections (11,12); as a result, there is enough data for it to be reviewed by joints: hip, knee, and other joints.

The Hip

The American College of Rheumatology recommends that ICS (ICS) of the hip be used in patients whose symptoms are not adequately managed by acetaminophen and be administered no more than every 3 months (13). Similarly, the 2017 American Academy of Orthopedic Surgeons guidelines identified ICS as an intervention with strong evidence in the management of improving function and reducing short-term pain for symptomatic patients with hip osteoarthritis. Strong evidence is defined as having 3 high strength studies (< 1 flaw in prognostic studies, < 2 in other study types per reviewers) (14); 3 studies were identified for demonstrating beneficial effects. One randomized, double-blind, placebo study compared fluoroscopic injection of bupivacaine to bupivacaine and a corticosteroid in 52 patients. The researchers demonstrated at least a 20% decrease in Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) lasting up to 3 months (15). A second study compared the use of a single, ultrasound-guided injection of normal saline, hyaluronic acid, or methylprednisolone acetate in 77 patients with moderate-severe hip osteoarthritis; response was assessed with the Numerical Rating Scale, WOMAC, and ultrasound to assess for synovitis. Again, corticosteroids were found to be highly efficacious, especially in the first week, but with a tapering response to the 8 week mark. Additionally, it was demonstrated that ultrasound-detected synovitis can be used as a biomarker of response to injection (16). The third study, a double-blind, randomized controlled trial, compared ultrasound-guided injections of saline, hyaluronic acid, and corticosteroids; pain on walking was the primary data point studied. Results demonstrated steroids having a significant effect at days 14 and 28, but no difference by 3 months, and it was indicated that steroids were beneficial in patients with and without effusions (17).

Previous studies of corticosteroid injections found limited success in the hip; in a 1954 review, anecdotes exchanged between colleagues revealed a success rate of 47% of such injections (18). A meta-analysis not included in the American Academy of Orthopedic Surgeons guidelines assessed short-term (up to 4 weeks), mid-term (closest to 3 months), and long-term (closest to 12 months) effects of intraarticular glucocorticoid injections for hip and knee osteoarthritis. Pain scores (various scales) and "inflammatory signs" were the outcomes assessed. Overall, for patients with hip osteoarthritis, it was found that the injections reduced pain in the short- and mid-term (especially in patients with severe pain at baseline), but had no effect in the long-term (19). A subsequent analysis attempted to assess variability within ICS by evaluating steroid type, dose, and volume. Few articles assess these particular variables but it was concluded that methylprednisolone acetate and triamcinolone seem to have similar effectiveness with pain and functional improvements lasting from one to 6 months, that a higher dose correlates with a more prolonged effect (for 40 mg vs 80 mg methylprednisolone, persistent pain/functional improvement lasted up to 6 vs 12 weeks, respectively), and that volume (1 mL triamcinolone + 2 mL bupivacaine vs same + 6 mL sterile water) had no effect on pain, stiffness, or function at 3 months (20).

Though the short-term benefits are evident from these studies, there are also reported complications of ICS in hip osteoarthritis. Rapid destructive osteoarthritis occurs when there is rapid and progressive chondrolysis (serial radiographs demonstrating > 2 mm in one year or 50% joint space narrowing in one year) leading to severe osteoarthritis; it most commonly occurs in older women. The incidence of this pathology is unknown but is estimated to be up to 16%. Case reports have detailed individual incidents, but one retrospective analysis reviewed 109 patients (129 injections) who received a single, fluoroscopic-guided intraarticular injection of 1 mL of triamcinolone with a concentration

of 40 mgs/mL. Of these patients, 23 went on to develop rapid destructive osteoarthritis (21% incidence). Of those patients, 91% proceeded to total hip arthroplasty (median time of 10.2 months) compared to 31% of the nonrapid destructive osteoarthritis patients receiving total hip arthroplasty (median time 24.9 months) (21,22). This suggests that there could be a relationship between the incidence of rapid destructive osteoarthritis, as well as progression to total hip arthroplasty, in patients who receive intraarticular corticosteroid injections. It is therefore important to assess the impact of these injections on patients who undergo total hip arthroplasty.

Finally, one study demonstrated an increased risk of infection and early revision in patients who received ≥ 1 ICS in the year leading up to total hip arthroplasty (23).

The Knee

One of the first studies assessing the use of intraarticular corticosteroids in the knee was in 1954 when Bornstein et al (18) studied the use of hydrocortisone in patients with rheumatoid arthritis and osteoarthritis. The methodology was not as standardized as today's studies, but it was reported that most of the osteoarthritis injections were in the knees. Results revealed that patients with rheumatoid arthritis had a more sustained effect, 7% of osteoarthritis patients had both subjective and objective improvement, and 52% were failures (18). Another early study was performed by Miller et al (24), who compared the effects of hydrocortisone injections to placebo, saline, Novocain (pH 5.9), and Novocain (pH 5.7) in patients with radiologically proven primary osteoarthritis. Although the assessment was more subjective than in recent studies, the authors concluded that at 6 weeks and 6 months, there was no discernable difference in the patient condition (24). A survey in the 1990s found that > 95% of rheumatologists sometimes use and 53% frequently used corticosteroid injections in the treatment of osteoarthritis. Yet, at that time, a review of 5 studies on this treatment, using an 8-point quality rating system, revealed that none had a score greater than 3/8 for design, suggesting that the findings were not strong enough to base our clinical utilization of the treatment (25). More recently, the American Academy of Orthopedic Surgeons evaluated the effectiveness of corticosteroid injections for its 2013 guidelines (26). In its evaluation, 4 placebo comparison studies met the criteria for evaluation (minimum treatment period of 4 weeks), but only one demonstrated results superior to the placebo (26). Individual randomized controlled trials and reviews reveal that corticosteroid injections do provide some benefit to patients, though it is typically seen short-term. A previously mentioned meta-analysis evaluated short-, mid-, and long-term effects of intraarticular glucocorticoid injections for the hip and knee; for knee osteoarthritis patients, pain reduction was found in the short-term (especially in patients with severe pain at baseline), insignificant pain reduction at mid-term, and no effect in the long-term (19). Another study found that, by 4 weeks post-corticosteroid injection, the difference in pain was no longer significant compared to placebo (27). These findings were echoed by another review which found moderate improvement in pain at 1 – 2 weeks, small to moderate at 4 – 6 weeks, small improvement at 13 weeks, and none at 26 weeks. This study also found improvement in functional WOMAC only in weeks 1 – 6 post-injection (20). The Cochrane Review assessed 28 trials comparing ICS to several treatment modalities, including placebo (30). When compared to placebo, there was significant reduction in pain that persisted for up to 3 weeks (NNT of 3 to 4), but from 4 weeks and beyond the evidence shows mild benefit. Echoed through each study is the benefit seen in these injections in the short-term, but with other modalities needed for long-term management (28,29). In these studies, there was also limited data on the impact of corticosteroid injections on patient function (30). A previous review of randomized controlled trials had similar findings; the only study showing prolonged benefit (at 24 months) in night pain and stiffness was a randomized, double-blind, placebo-controlled study that allowed for reinjection every 3 months (31,32). Some studies have demonstrated that bone marrow lesions are associated with symptoms and structural progression of osteoarthritis; one study assessed the size of these lesions, in addition to pain, after intraarticular corticosteroid or saline injection (33). Patients had an magnetic resonance imaging (MRI) assessment of the knee before, at 14 weeks, and again at 26 weeks post-injection. At 14 weeks, there was a decrease in the size of lesions in the study group and an increase in the size of lesions of the saline group. At the 26-week mark, though, the between-group difference decreased (33). Although there have been demonstrable benefits of corticosteroid injections, particularly in short-term pain reduction, there is limited data showing benefit on quality of life (20), joint stiffness (34), or quadriceps strength (35).

Knee osteoarthritis patients commonly undergo physical therapy or follow a regimented exercise program before or concurrently with intraarticular corticosteroid injections. A study comparing outcomes of physical therapy versus glucocorticoid injections for knee osteoarthritis revealed that at one year, patients who underwent physical therapy had less pain and functional disability than those who received a corticosteroid injection (36). To assess whether the injections could supplement the nonpharmacologic treatment with additional benefits, 5 studies (33,37-40) were conducted on the same population of 100 patients undergoing a 12-week exercise program. Half of the patients received a placebo injection, while the others received an intraarticular corticosteroid injection; the patients started their exercise programs 2 weeks post-injection. The studies assessed Knee Injury and Osteoarthritis Outcome Score for pain and function, inflammation (IL-6 levels, MRI effusion synovitis score, ultrasound synovial size, ultrasound Doppler activity of synovial membrane, number), number of baker's cysts, pressure-pain sensitivity (using cuff pressure algometry on the calf), and bone marrow lesion size. Patients were assessed before starting the program (week 2), after completing the program (week 14), and at a follow up (week 26). Researchers found benefits to the steroids at week 14 in bone marrow lesion size and synovium thickness, but by week 26 there was no significant difference between the treatment arms in any of the outcomes (33,37-40).

In assessing the differences between steroid type, dose, and volume, there is data from several publications. In regard to the effectiveness of different types of steroids, methylprednisolone, triamcinolone hexacetonide, triamcinolone acetonide, betamethasone, and a novel formulation of triamcinolone have been examined. Head to head comparisons of methylprednisolone and triamcinolone generally conclude that they are of similar effectiveness, though methylprednisolone has sometimes been reported to have slightly more benefit. One study showed that smaller doses of triamcinolone hexacetonide were more effective at 3 weeks, but showed no difference to larger doses of methylprednisolone by 8 weeks; another showed no significant differences between the steroids through 24 weeks (20,41). Yavuz et al (42) reported, though, that patients who received methylprednisolone reported slightly better pain scores than patients who received triamcinolone acetonide or betamethasone through 6 weeks. Several studies have shown that there is a beneficial effect with betamethasone, but that it is not as long-lasting as that of methylprednisolone or triamcinolone (20,30). When comparing formulations of triamcinolone, one study found that hexacetonide had better pain reduction at 12 weeks compared to acetonide, and when acetonide was compared to the novel, extended-release formulation there was no difference at 12 weeks (20,43).

Data comparing the dosage of steroids is a bit more limited. Varied doses of triamcinolone acetonide or dexamethasone palmitate did not reveal a significant difference in pain relief (20,44,45). Head to head dose comparisons of methylprednisolone have not been completed in humans, though there has been demonstrable effectiveness in 40 mg and 60 mg doses (smaller doses in animals have demonstrated reduced benefit). However, there can be extrapolated data from the steroid type data because the mixed results comparing methylprednisolone and triamcinolone also had varying doses. Unfortunately, there is no data that focuses on the volume of steroid injected, and no volume has been evidently superior, but studies have used volumes ranging from 1 mL to 11 mL (20).

Though most studies compare corticosteroid injections to placebo injections, there are some that compare it to other therapeutic options, most commonly hyaluronic acid injections. In the studies that assessed the comparison of corticosteroid and hyaluronic acid injections, patients who received corticosteroids often had more immediate benefits, but over time the benefit of the 2 treatment arms equilibrates and ultimately hyaluronic acid often provides longer term relief of symptoms. Additionally, neither demonstrated an impact on disease severity (30,46,47). One review compared the effects of acetaminophen, nonsteroidal anti-inflammatory drugs (several types), oral placebo, and hyaluronic acid, corticosteroid, and placebo intraarticular injections on pain and function (34). The analysis revealed that acetaminophen was least efficacious when it came to pain relief and that corticosteroid injections outperformed oral interventions. Regarding function, corticosteroid injections were not significantly superior to oral placebo (34).

Several studies called for increased evaluation of the long-term effects of ICS on patients. Though data are still limited, a few studies have investigated these impacts. Outcomes assessed in these studies focus on sustained pain relief, function, joint space narrowing, and cartilage loss. The studies evaluate outcomes from 1 to 4 years out, with variation in whether patients

received one or multiple injections. In one review, the outcomes were so mixed that the authors were unable to make a final assessment, instead calling for more randomized controlled trials to better evaluate the effects (48). A retrospective study reviewed over 400 patients who received injections (77.2% received intraarticular corticosteroids and 18.9% received subsequent injections of corticosteroids or hyaluronic acid), and the results supported previous claims of short-term relief for these patients without sustained benefit. In fact, patients who received the subsequent corticosteroids experienced worsening pain, stiffness, and function over the recorded period (49). There were also randomized controlled trials that intentionally gave patients standing ICS (methylprednisolone or triamcinolone acetonide) every 12 weeks over a period of 2 years. Only one of the 3 studies found clinically significant benefit in pain relief (32), while the others saw no benefit to the injections (44,50). In assessing the joint, there was a statistically insignificant reduction in joint space in the corticosteroid group compared to saline (32) and a significant decrease in cartilage volume (per MRI assessment) in patients receiving the steroids (50). Furthermore, corticosteroid injections have been associated with increased risk of knee arthroplasty in patients with or at risk of developing symptomatic osteoarthritis of the knee. Utilizing data from the Osteoarthritis Initiative, Wijn et al (51) found that 31.3% of the 796 patients who received corticosteroid injections and 5.0% of the 3,026 who did not receive the injections had knee arthroplasty; it was calculated that each injection increased the absolute risk of arthroplasty by 9.4% at 9 years' follow-up compared to those who did not receive injections. Additionally, evidence has been found suggesting that corticosteroid treatment (specifically dexamethasone) can induce senescence in tenocytes, causing long-term degenerative damage in tendon tissue (52).

As a result of the varied data on the effectiveness of intraarticular corticosteroid injections, there has been investigation into whether there are other factors that would affect patient response to intervention. Researchers assessed the visual analog scale (VAS), distance walked one minute, health assessment questionnaire, range of motion, duration of stiffness (morning and post-activity), tenderness, local heat (present or absent), synovial thickening (present or absent), and effusion (graded). One group found no difference (35), while another found an increased benefit in patients who had a joint effusion that was successfully aspirated (53).

A review of the safety of corticosteroid injections reported no major adverse events, though there was a call for physicians to share more of the complications in order to address and prevent them in the future (54). Despite no major events being recorded, one observational study of 20 patients found that 60% of bilateral corticosteroid knee injections resulted in transient (1 – 8 weeks) episodes of secondary adrenal insufficiency (55). Additionally, a review noted the incidence of joint infections to be one out of 14,000 to 77,000 procedures and that transient hyperglycemia can occur in patients with diabetes mellitus (56).

Based on these outcomes, the American Academy of Orthopedic Surgeons concluded that there is inconclusive evidence for this modality (26). As of 2019, the organizations' guidelines do not have a strong recommendation for or against ICS of the knee; it is advised that practitioners be alert to new, clarifying evidence regarding these injections and that patient preference should have a large influence on treatment selection (26). While acknowledging only a short-term benefit (1 to 3 weeks), the American College of Rheumatology recommends that ICS of the knee be used in patients whose symptoms are not adequately managed by acetaminophen and be administered no more than every 3 months in knee osteoarthritis (13). Additionally, the updated Cochrane Review strongly stated that "it remains unclear whether there are clinically important benefits 1 to 6 weeks after corticosteroid injection" as a result of low-quality trials, small-study effects, and heterogeneity. The author went on to say that ICS "should be considered experimental in knee osteoarthritis and not be routinely used" (30).

Injection of Other Joints

Data assessing the utility of ICS in the shoulder is robust in tendinopathies but is limited in patients with glenohumeral osteoarthritis. One retrospective study compared ICS to hyaluronic acid injections in such patients who received treatment and were then reassessed at 1, 3, and 6 months. The pain (VAS) in patients receiving corticosteroid injections decreased at each of the follow-ups compared to the initial evaluation, but with less of an effect than hyaluronic acid and with decreased efficacy after one month. Additionally, there was only a significant improvement in the disability of the shoulder at the one month follow-up (57). Furthermore, the American Academy of Orthopedic Surgeons was unable to find any studies of sufficient quality to use in their guidelines for the treatment of

glenohumeral osteoarthritis and therefore deemed it an inconclusive recommendation (58).

Hand osteoarthritis also has limited data, but one study observed 60 patients (96.67% women) receiving an injection of corticosteroids or lidocaine into the most painful interphalangeal joint. At the 12-week mark, VAS scores revealed that pain on movement and joint swelling was significantly better in the corticosteroid group than in the control, but there was no difference between groups in pain at rest (59). The American College of Rheumatology does not support the use of ICS in hand osteoarthritis (13).

Within the foot and ankle, one study investigated 18 patients (36 foot and ankle joints) who received ICS. There was a statistically significant Foot and Ankle Outcome Score improvement up to 6 months post-injection. Also, it was noted that a patient's response at 2 months might provide insight into how the patient will respond at one year (60).

Adverse Effects

Corticosteroids have a wide array of side effects, but the focus here will be on complications associated with injections. These effects are related to immediate pharmacological actions of corticosteroids, as well as their systemic effects. Several of these side effects are associated with injection sites, injection frequency, or injection used, and therefore can be minimized.

Minor Adverse Effects

Minor pharmacological effects include elevated serum glucose (particularly in patients with diabetes), skin rash including erythema of the face/torso, post-injection flare, reduction in immunity, increased pain, and increased propensity to infection.

A 50-year review calculated an incidence from 0% to 81% for minor adverse events (skin rash, flushing, increased pain, steroid flare) and 0% to 5.8% for major events (rupture, infection, atrophy, calcification) (61). Several studies have investigated how this may mechanistically occur, and most have concluded that steroids affect the collagen directly. In vitro studies and animal models have supported this, but subcultures (which lead to cell culture artifacts) and high levels of dexamethasone were used. Scutt et al (62) used physiologic and pharmacologic dexamethasone levels on primary cells from rat tail tendon digests, as well as fibroblastic colony-forming units (to test the progenitor cell population) to create a more physiologic environment; the researchers concluded that there is a concentration-dependent effect directly through inhibition of tenocyte proliferation, as well as indirectly by modulating recruitment of progenitor cells.

Although it has not been directly studied, the endocrine disruption from a single intraarticular steroid injection suggests similar systemic effects on immune response. As previously mentioned, corticosteroids have anti-inflammatory effects; they reduce pain related to inflammation by down-regulation of immune function as well as reduction of inflammatory cells and mediators (lymphocytes, macrophages, and mast cells) (63,64). The use of systemic corticosteroids can adversely affect the innate (immediate) immune response by impairing the ability of neutrophils to migrate to infection sites as well as macrophage and monocyte function (65). The adaptive immune response (leads to immunological memory) is also negatively affected by corticosteroids, as the capability of plasma cells to produce immunoglobulins IgG and IgA is reduced by 10% to 20% after exposure (66). Injection therapy plausibly has similar effects to the oral administration effects described in the literature.

Considering these adverse immune influences of corticosteroids, influenza infection is of increased concern for those prescribed or injected with corticosteroids, with specific concern during the current COVID-19 pandemic. Meta-analysis of orally-administered corticosteroid versus placebo demonstrates an increased risk of influenza infection within the steroid group. One study found a dose-dependent relationship for infection risk, showing a relative risk of 1.5 with low doses of steroids and a relative risk greater than 8 with doses above 40 mg/day (67). In another study, rheumatoid arthritis patients taking oral prednisone had relative risks ranging from 1.4 (< 5 mg/day dose) to 2.3 (> 10 mg/day dose) for hospitalization due to pneumonia compared to rheumatoid arthritis patients not taking oral prednisone (68). Although data for single-dose exposure to corticosteroids is limited, early evidence is provided in a report on an observational cohort from the Mayo Clinic. Over 5 influenza seasons, an increased incidence of influenza infection was associated with steroid injection compared to no injection (69). There are currently no studies specifically examining the relationship between corticosteroid injections and COVID-19, however, the findings presented here raise concern for a potential relationship (70).

Skin hypopigmentation and subcutaneous fat atrophy can occur after injection into any soft tissue and are known side effects of corticosteroid injections. Skin

hypopigmentation has been reported to occur in 1.3% to 4% of patients who underwent local corticosteroid injection; this condition typically occurs 1 to 4 months after injection and is most noticeable in dark-skinned patients. The exact mechanism of hypopigmentation is unclear, though steroids or biologically inactive components of steroids have been known to be involved (especially with triamcinolone) (60,61). Additionally, dermal complications are often explained by mechanical effects caused by edema, changes in ground substances, or vasoconstriction (61). Subcutaneous fat atrophy typically lasts for 6 to 12 months after corticosteroid injections; this condition is generally reversible and resolved within one year (71). The risk of both skin hypopigmentation and subcutaneous fat atrophy can be reduced if steroids with suitable solubility and potency are used. Steroids with low solubility, such as triamcinolone acetonide, are preferred for injections into the joints of deep structures (knee, elbow, and shoulder); steroids with high solubility, such as betamethasone sodium and dexamethasone, are preferred for injections into soft tissues (bursa, tendon sheath, metacarpophalangeal joint, proximal phalangeal joint, and carpal tunnel) (71). Generally, it is believed steroids with shorter effectiveness time cause fewer complications; however, this implies the need for injections more often, creating the potential for additional complications.

Moderate to Severe Adverse Effects

Multiple adverse effects related to corticosteroid administration include long-lasting pharmacological actions, infection, nerve damage, Charcot arthropathy, osteonecrosis, steroid arthropathy, tendon rupture, tissue arthropathy, fat necrosis, calcification, joint instability, and, finally, most important aspect of the adverse events is the hypothalamic-pituitary-adrenal axis suppression.

Joint instability is associated with the administration of more than 2 injections per year, but in a 10-year large series the incidence was < 1%. In soft tissue, collagenous damage (ligament or tendon rupture, especially in Achilles injections) and calcification have a greater incidence with fluorinated corticosteroids—these are no longer recommended for use. Rupture is also associated with an injection directly into the tendon as well as excessive use in one area (72); one case showed rupture at 29 injections, while another showed a bowing deformity at 10 injections (73).

Among the risks associated with corticosteroid injections is avascular necrosis, also known as osteonecrosis. Avascular necrosis is the death of bone tissue caused by a lack of blood supply and typically manifests with tiny breaks and an eventual collapse of the bone, occurring most commonly in the hip, then the knee and shoulder. A decrease in blood flow to the femoral head can occur through vascular interruption by trauma (fracture or dislocation), extravascular compression (by lipocyte hypertrophy and marrow fat deposition), and thrombotic occlusion (by intravascular thrombi or embolic fat); traumatic interruption is a well understood mechanism, but the pathogenesis of nontraumatic interruption is not entirely known (74). Corticosteroids are the most common cause of nontraumatic avascular necrosis, accounting for 10% to 30% of all cases (75), and are an especially notable risk factor at high doses (74,76-82). In a 2007 animal model study, groups of rats were treated with either sterile human serum and methylprednisolone, only methylprednisolone, or saline; researchers found areas of osteonecrosis, among other complications, in the first group and cellular differentiation of bone marrow in the second group. From these findings, researchers concluded that steroid administration, though not the main cause of the condition, increases the risk of avascular necrosis of the femoral head (78). Another study measured regional blood flow of bone in rabbits injected with either saline or methylprednisolone on varying treatment schedules (blood flow measured in perfusion units, PU). After injections of normal saline, no statistical difference was found in blood flow between the right and left hips (39.26 ± 5.64 PU and 38.58 ± 4.35 PU, respectively). In another group, a weekly injection of methylprednisolone for 6 weeks showed a decrease in blood flow of the femoral head (24.74 ± 3.13 PU) and a further reduction was shown by 12 weeks of treatment (15.93 ± 2.33 PU). For further evidence, methylprednisolone was administered to another group weekly for 6 weeks, reducing blood flow to 31.63 +/- 4.79 PU, then treatment was discontinued for 3 weeks and blood flow demonstrated an increase to 34.6 +/- 1.34 PU. For the last group, blood flow decreased in response to 6 weeks of steroid treatment (25.89 +/- 4.01 PU), then increased after treatment was stopped for 6 weeks (29.86 +/- 2.59 PU) (21). Of patients treated with corticosteroids, avascular necrosis occurs in 5% to 25%, depending on the report (75). Most studies have suggested that high doses of corticosteroids present more risk than cumulative dose or duration of therapy, though quantifiable dose thresholds are difficult to identify. Corticosteroid-associated avascular

necrosis has an incidence of approximately 10,000 to 20,000 cases per year in the US and accounts for 10% of all arthroplasties performed annually (74,75).

Though the mechanism of steroid use and avascular necrosis is incompletely understood, many studies have identified potential pathways. In patients and experimental animals with corticosteroid-associated avascular necrosis, hypertrophy and proliferation of adipocytes as well as abnormal lipid metabolism have been observed (75). Lipid deposition in the extravascular marrow space and within osteocytes, along with adipocyte hypertrophy, after corticosteroid administration has been demonstrated to elevate the intraosseous extravascular pressure and diminish blood flow (a similar effect is seen in avascular necrosis of Gaucher's disease) (83). Corticosteroids can also cause an increase of the synthesis of vasoactive peptides and peripheral vascular resistance, resulting in elevated intraosseous pressure. More direct effects on bone cells that contribute to avascular necrosis have also been observed after corticosteroid use, including dysregulation of bone formation and resorption balance, which contribute to bone loss in the subchondral trabeculae and subchondral fracture (74). Various diseases have been specifically observed for corticosteroid-associated avascular necrosis, including systemic lupus erythematosus, rheumatoid arthritis, asthma, inflammatory bowel diseases, and organ transplantation (74). A study on patients with systemic lupus erythematosus was conducted to determine risk factors for avascular necrosis; results revealed that patients with cumulative corticosteroid dose above 20 g and immunosuppressant use had a 15.44-fold increased risk for avascular necrosis compared with patients without these risk factors (76).

Another treatment combination that has been studied is the use of steroids and local anesthetic agents. Farkas et al (84) looked into this combination and the effect on chondrocytes by comparing the cartilage toxicity of steroid treatment alone, of local anesthetics alone, and of the treatment combination of steroids and local anesthetics. Results revealed that all 3 caused the death of cartilage cells, but when the 2 medicines were combined (glucocorticoids plus local anesthetic), the death of chondrocytes was amplified to a greater degree than when the drugs were used separately. Additionally, there was a time-dependent decrease in cartilage cell viability after exposure (84).

The published literature shows ICS to have virtually identical systemic endocrine effects to those of epidural corticosteroid injections. Serum cortisol and the hypothalamic-pituitary-adrenal axis have been shown to be significantly suppressed for 1 to 4 weeks after a single intraarticular injection, and suppression has been seen for 1 to 2 weeks following a relatively low dose (20 mg triamcinolone) intraarticular injection (85,86). In addition to the observed suppression, an intraarticular injection resulted in an increase in blood glucose levels within a few days in controlled diabetic patients with knee osteoarthritis (85).

Another effect on the endocrine system that providers must consider is glucose levels, particularly in diabetic patients. Though there is a consensus that intraarticular injections increase patient glucose levels, the extent and significance is still not certain. In a review of over 500 articles (ultimately only 72 patients of mostly knee and shoulder injections included), the highest glucose level post-intraarticular steroid injection recorded was 500 mg/dL (87). This is in contrast to a single study reviewing hand corticosteroid injections in patients with diabetes mellitus. This study revealed statistically significant, but not clinically significant, increases in glucose level before and after injection (88). In addition to elevated glucose levels, one study found that patients with noninsulin dependent, type II diabetes mellitus have an increased insulin resistance after receiving an injection (89). The duration of these changes was recorded for as little as one day, and as many as 7 days (88-95), with a peak ranging from 21 to 72 hours (87,91,95). A majority of studies identify insulin dependence (i.e., type I diabetes mellitus, or insulin-dependent type II diabetes mellitus) as the greatest predictor for having more robust and a longer duration of symptoms (88,92,93). There was one study of hand injections which demonstrated a dose dependent response (95), but this was not consistent through all other studies (87). An outlier to the previously mentioned findings is a study by Twu et al (90), which determined that only knee corticosteroid injections have significant influence on glucose levels (wrist, hand, and shoulder injections did not), and that A1C rather than insulin dependence is the greatest predictor for degree of effect.

In more recent years, there has been growing concern that ICS cause damage to the joint cartilage, which is particularly concerning in patients with osteoarthritis. Hartman et al (96) found that, on a molecular level, endogenous glucocorticoid supports cartilage and bony integrity, however, the exogenous type impairs cartilaginous bone growth and causes

osteoporosis. Chijimatsu et al (97), through in vitro studies, found a dose-dependent effect when using dexamethasone. Yang et al (98) found a similar dose-dependent response, but added that, mechanistically, the steroids suppress the synthesis of cartilage matrix components and affect the NAD+ and NADH levels. They also found that melatonin may be protective against this effect through its impacts on NAD+ and NADH (98). Corticosteroids have been found to specifically decrease synthesis of type I collagen and glycosaminoglycan and increase protein catabolism, thus affecting the biomechanical properties of tendons and slowing the healing process. Additionally, the use of injections may predispose the tendons to weakening; therefore, the use of corticosteroid injections for chronic conditions (such as chronic tendinosis) is considered questionable (63,64).

Conclusions

Corticosteroids have been used to treat various musculoskeletal conditions since the discovery of synthetic cortisone in 1950. Since that time, there has been a rapidly expanding use of this medication for a variety of conditions including those that involve various joints, such as osteoarthritis. The current evidence would suggest that the use of corticosteroids provides limited and short-term benefit for reducing pain, and there is limited evidence that this medication can improve functioning. These benefits generally last several weeks without long-term effectiveness. In addition to their limited short-term effectiveness, corticosteroids are associated with multiple potential adverse events; these issues include toxic effects to articular cartilage and numerous systemic side effects, such as a reduction in immune function. Observational evidence has linked corticosteroid use with an increased risk of infection, including viral infections, which is of special concern with regard to the current COVID-19 pandemic. Therefore, clinicians should limit the use of this medication to conditions with a clear inflammatory component associated with acute pain which require immediate reduction of inflammatory mediators to facilitate recovery.

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