DRUG TREATMENT OF SOFT TISSUE INJURIES EFFICACY AND TISSUE EFFECTS

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INTRODUCTION

Acute and chronic soft tissue injuries occur far more commonly than fractures. Accidents, physical labor, and sports frequently cause sprains, strains, contusions, and overuse syndromes of tendons, muscles, musculotendonous junctions, ligaments, and synovial joints. Although the soft tissue injuries that result from demanding labor and sports receive the most attention, the same types of problems can result from participation in recreation and fitness programs, or even more modest physical activity.

Few soft tissue injuries resulting from minor accidents, sports, or physical labor require surgical intervention. Ideally, partial suppression of inflammation caused by injury reduces secondary tissue damage due to release of degradative enzymes and other events during inflammation. Suppression might also limit disuse changes in the tissues, allow earlier rehabilitation by decreasing pain and swelling, and accelerate healing by shortening the duration of acute inflammation. Therefore, when patients seek treatment for the pain and impaired function of soft tissue injuries, physicians commonly prescribe modification of activity and anti-inflammatory medications; primarily oral non-steroidal anti-inflammatory drugs (NSAID's) and injectable corticosteroids. Physicians use these drugs with the intent of decreasing pain and promoting recovery[1,21,34,49]. Some physicians also use short courses of oral corticosteroids for the same reasons[13,31]. Besides these medically accepted anti-inflammatory medications, patients may choose other drugs to treat their injuries. These medically unaccepted treatments of soft tissue injuries include anabolic steroids and dimethyl sulfoxide (DMSO)[2,6,37,38,45,50,59,73,85,90].

This article reviews the efficacy of medications commonly used to treat soft tissue injuries and the effects of these drugs on the tissues. The first section surveys the drugs commonly used in attempts to decrease pain and promote recovery from injury. The next section reviews the effects of these drugs in soft tissue injuries, and the last section discusses the specific effects of these drugs on dense fibrous tissues and cartilage.

DRUGS USED TO TREAT SOFT TISSUE INJURIES

Non-steroidal Anti-inflammatory Drugs

The group of commonly used NSAID's includes aspirin, diflunisal, fenoprofen calcium, ibuprofen, indomethacin, naproxen, piroxicam, phenylbutazone, sulindac, and tolmetin sodium. These chemically heterogeneous drugs have important differences in their activities, but they share certain clinical and tissue effects[1,21,89]. They all have some analgesic, antipyretic, and anti-inflammatory activity. They also share side effects such as variable potential for gastric or intestinal ulceration and interference with platelet function. They all inhibit the synthesis and release of prostaglandins. Damaged cells release prostaglandins and the available evidence shows that prostaglandins act as mediators of inflammation. Presumably NSAID's suppress inflammation primarily by inhibition of prostaglandin synthesis, although they may also affect inflammation by other mechanisms.

Corticosteroids

Corticosteroids used for their anti-inflammatory activity include cortisone, hydrocortisone, prednisone, methylprednisolone, triamcinalone, and dexamethasone. They suppress or prevent the initial events in inflammation by inhibiting capillary dilation, migration of inflammatory cells, and tissue edema. Once the inflammatory process starts they inhibit capillary and fibroblast proliferation and collagen synthesis. These later effects can compromise healing[9,13,22,39,88].

These medications also influence metabolism, fluid and electrolyte balance, and the function of cells in multiple organs and organ systems including the kidney, liver, skeletal muscle, bone, cartilage, cardiovascular system, immune system, and nervous system[13]. Individual drugs vary considerably in their spectrum of activity. For example, at equivalent dose levels, triamcinolone has five times the anti-inflammatory activity of hydrocortisone, and dexamethasone has twenty-five times the anti-inflammatory activity of hydrocortisone. On the other hand, hydrocortisone causes sodium retention while triamcinalone and dexamethasone have little or no effect on sodium retention.

Along with the intended therapeutic results, administration of corticosteroids can cause tissue damage and disturb the function of a variety of tissues and organ systems. Despite multiple reports of the deleterious consequences of oral or parenteral corticosteroids[9,13,50], the relationships between corticosteroid dose levels and specific complications remain unclear. A safe dose of corticosteroids has not been clearly established.[5] Short term moderate or low dose oral corticosteroid therapy has not been shown to cause significant complications in normal people,

but multiple case reports describe bone necrosis associated with short term high dose corticosteroid therapy[5,84]. Reported complications of prolonged or repeated use of oral corticosteroids include disturbances of fluid and electrolyte balance, glucose metabolism, hypertension, increased susceptibility to infections, impaired wound healing, bone necrosis, tendon ruptures, gastrointestinal ulceration, behavioral disturbances, osteoporosis, myopathy, and in children, inhibition of growth[9,13,39].

Few systemic complications of local corticosteroid injections have been described[20,48,49]; one author reported a patient who developed bone necrosis following multiple corticosteroid injections[77]. Studies discussing the problems associated with corticosteroid injections show that subcutaneous fat necrosis and loss of skin pigmentation are the most common adverse effects; tendon ruptures and accelerated joint destruction have occurred less frequently[20,48,49].

Anabolic Steroids

Examples of anabolic steroids include methyltestosterone, testosterone propionate, methandrostenolone, oxandrolone, and stanozolol. They all have androgenic and anabolic activity, but they vary in the ratio of anabolic to androgenic activity. For example, testosterone propionate has an anabolic-androgenic ratio of 1:1, but stanozolol has a ratio of 100:1. These drugs have two generally accepted medical uses: treatment of selected types of anemia and treatment of hypogondal males[37,38]. Although the predominant activities of these medications are anabolic and androgenic, like other steroids, they influence cell function in multiple tissues and organ systems including muscle, liver, reproductive organs, the immune system, the central nervous system, and the hematopoetic system.

Some athletes use oral and injectable anabolic steroids with the intent of improving performance through gains in strength, ability to endure increased training, and accelerated recovery from soft tissue injury[6,37,38,46]. Despite extensive anecdotal evidence[6], the efficacy of anabolic steroids for these purposes remains questionable. Published results of anabolic steroid use by athletes show that these drugs do not predictably improve physical performance or aerobic capacity, and they have inconsistent effects on strength[37,38,46]. They may help increase strength, as measured by a single repetition maximum weight lift. This increase in power is seen in athletes who have been training intensively in a weight lifting program before the start of steroid use, and who also continue intensive training and maintain a high protein diet[37,38]. With other measures of strength, and in athletes that do not meet these criteria, anabolic steroids have not been shown to predictably increase strength or improve performance in specific sports.

Complications of anabolic steroid use occur frequently. More than 30% of athletes taking anabolic steroids reported subjective side effects including changes in libido, aggressiveness, and muscle spasm[37,38]. Use of these drugs also causes abnormalities of liver function tests, decreased serum testosterone levels, and decreased spermatogenisis. In addition, benign and malignant liver tumors have been reported in association with anabolic steroid use[37,38].

Dimethyl Sulfoxide

The physical and chemical characteristics of DMSO, a clear colorless liquid, make it an exceptional solvent, better than water for many substances. It lowers the freezing point of fluids and protects cells against damage due to freezing, and therefore has an important role in preserving tissues and cells like erthrocytes, platelets, and bone marrow elements[73,85]. When applied topically, it easily penetrates the skin and appears in the blood within minutes. It probably has local anesthetic activity and may have a central analgesic effect[85]. In some experiments it appears to have anti-inflammatory activity and several studies suggest that it may reduce collagen synthesis or enhance collagen degradation[85]. Currently accepted uses include preservation of cells and treatment of intersitial cystitis of the bladder, gastrointestinal amyloidosis, and dermatologic lesions of scleroderma[73].

EFFECTS OF DRUGS IN SOFT TISSUE INJURIES

Non-steroidal Anti-inflammatory Drugs

NSAID's have established roles in the treatment of chronic inflammatory diseases involving the musculoskeletal system, including rheumatoid arthritis and other rheumatologic disorders. They also form the primary medical therapy for osteoarthritis. The efficacy of NSAID's in providing symptomatic improvement and their tissue effects have been examined in patients with these chronic conditions and in animal experiments designed to assess the effects of repeated use of these medications on normal tissues.

Despite their widespread use for treatment of acute soft tissue injuries such as ligament and joint capsule sprains, and chronic injuries such as patellar or achilles tendonitis, the efficacy of NSAID's has not been clearly demonstrated[1,21,89]. Non-steroidal anti-inflammatory drugs decrease acute soft tissue inflammation, and clinical experience suggests that they decrease the pain associated with tissue injury and joint stiffness[1,21,33,34]. There is less evidence that NSAID's can promote restoration of normal tissue function following injury. A study of ligament repair in rats showed that piroxicam increased the strength of

healing rat ligaments fourteen days after injury if the drug was administered for the first six days after injury[32]. It did not affect the ultimate strength of healed ligaments or the strength of normal ligaments. An experimental study suggested that a NSAID promoted return of function following muscle strain[3], but experimental and clinical studies have not clearly shown that NSAID's promote a more rapid return to full function or improve performance following injury[89].

Corticosteroids

The anti-inflammatory potency of corticosteroids far exceeds that of the available non-steroidal medications, but the frequency of serious complications is also much higher. Like the NSAID's, corticosteroids have a generally accepted role in the treatment of chronic inflammatory diseases of the musculoskeletal system including rheumatoid arthritis. The role of these medications in the treatment of acute and chronic soft tissue injuries is less clear.

Corticosteroid Injections

Despite the limited documented evidence of efficacy in treatment of soft tissue injuries, many physicians use corticosteroid injections based on clinical experience[20,49,50]. One investigator reported that the symptoms of bursitis and tendonitis responded more frequently to corticosteroid injections than other conditions, including knee synovitis associated intra-articular derrangements and acromioclavicular joint arthiritis. However, many patients had symptoms return following injection[49]. Experimental studies show that corticosteroids decrease scar tissue adhesions following tendon injuries[41] and decrease joint stiffness following fractures[36]. They have not shown that corticosteroids accelerate healing or return to function[49].

Recent reviews of corticosteroid injections for treatment of acute and chronic sports injuries stress that injections should be used with caution[48,49]. The author advised physicians to consider corticosteroid injection only after other non-surgical treatments have failed. Injections are most efficacious when the physician can identify a discrete, palpable source of the patient's symptoms. It is recommended that no more than three injections spaced weeks apart should be given. A second or third injection should be given only if the first injection decreased symptoms [48,49]. Following injection, the patient should have a period of rest or protection from further injury. Corticosteroid injections should not be used immediately after acute tendon, ligament, or joint injury; immediately before competition; or in the presence of infection[48,49]. Corticosteroids should not be injected into tendons or ligaments.

Oral Corticosteroids

Although oral corticosteroids have potent anti-inflammatory effects, few physicians use them for the treatment of soft tissue injuries[13]. Lack of studies on the use of these drugs for treatment of soft tissue injuries in the last ten years[13,50] makes it difficult to assess their efficacy in improving function or accelerating return to activity following injury. Because of the difficulty in documenting the efficacy of oral corticosteroids and their potential complications, some authors recommend against use of these medications for the routine treatment of soft tissue injuries[13,50].

Anabolic Steroids

Among some groups of athletes, anabolic steroids have a reputation of expediting recovery from injury[6,50]; however, available objective evidence does not confirm this effect[37,38,46]. No reported studies have shown accelerated healing of ligament, tendon, or joint injuries due to anabolic steroids[37,38]; in fact, several reports suggest that these drugs may increase the probability of certain injuries[37,45,59,90].

Dimethyl Sulfoxide

Some patients report excellent results of topical DMSO treatment of musculoskeletal soft tissue injuries, but attempts to prove the efficacy of this treatment in controlled trials have produced conflicting results[18,19,56,73,74,78,79,85]. Application of 60% to 95% DMSO reportedly relieved the symptoms of acute bursitis within thirty minutes in about 90% of patients[78,79]. A study of 80% DMSO treatment of acute sprains, strains, bursitis and tendonitis found significantly better results with DMSO than with placebo[18,29], but another study found thirteen treatment failures in twenty patients with acute bursitis or tendonitis[56]. A double blind trial of DMSO treatment of rotator cuff tendonitis and tennis elbow did not find any significant benefit of the drug[74].

EFFECTS OF ANTI-INFLAMMATORY DRUGS ON DENSE FIBROUS TISSUES

Nonsteroidal Anti-inflammatory Drugs

Despite the extensive use of NSAID's, no evidence of damage to normal dense fibrous tissue has been reported[32]. The anti-inflammatory activity of NSAID's may have an effect on the early stages of dense fibrous tissue repair; but clinically significant inhibition of healing has not been documented. One study showed that they may temporarily increase the strength of healing dense fibrous tissues[32].

Corticosteroids

In contrast to the NSAID's, corticosteroids have been reported to cause harmful effects in normal and injured

dense fibrous tissues[49,64]. They alter the metabolism of normal tissues and multiple authors have reported spontaneous tendon and plantar fascia ruptures following corticosteroid injection or systemic use[10,20,30,35,40,44,47,51,58,80]. It is controversial whether inflammation or injury weakened the tissues before steroid use in these patients. However, animal experiments show that steroids inhibit matrix synthesis by normal mesenchymal cells[4]. Clinical experience also shows that multiple steroid injections may cause tissue atrophy[49].

The mechanism of apparent spontaneous rupture of tendons following corticosteroid use remains uncertain. Normal composition, structure, and mechanical properties of these tissues depend on matrix turnover. Conceivably, corticosteroids suppress synthesis of the matrix macromolecules, thereby preventing replacement of degraded matrix due to normal turnover. With time, this negative balance would weaken the tissue. It is also possible that corticosteroid injection might directly disrupt matrix organization[42,86]. Damage associated with steroid injection may be more severe than that associated with saline injection[86]. Some authors have found hyaline material in the region of corticosteroid injection into dense fibrous tissue, suggesting necrosis following injection[7,42,86].

Studies that examined the strength of normal tendons after steroid injections have yielded variable results. Some of the inconsistency may result from differences in doses of corticosteroids, location of the injection (injection into the tissues surrounding the tendon versus injection into the tendon), time of testing after injection, and methods of measuring tendon strength. Two groups of investigators found that corticosteroid injections did not weaken normal rabbit tendons[52,57,75]. However, repeated intra-articular injections of large doses of corticosteroids decreased the strength and stiffness of monkey anterior cruciate ligament bone-ligament-bone units[64]. Two other studies have shown decreases in tendon strength following injections directly into the tendon substance[42,86]. In one study, the ultimate strength of normal rabbit Achilles tendon decreased 35% within forty-eight hours after intra-tendinous injection of corticosteroid.[42]. Microscopic examination of the injected tendons showed disruption of the normal collagen fibril arrangement and clefts within the matrix. Two weeks after injection the failure strength of the injected tendons had improved to near normal. An amorphous eosinophilic staining material had appeared within the substance of the matrix, and the collagen fibril arrangement appeared near normal. These results showed that injection of corticosteroids directly into dense fibrous tissue weakens the tissue, but following a single injection the cells can restore the matrix toward normal. Because of the potential increased risk of tendon rupture, several authors have advised physicians to use extreme caution in selecting corticosteroid injections for treatment of tenosynovitis, or to avoid using this treatment altogether[49,50,83,86].

Corticosteroids also alter the healing of dense fibrous tissues. Steroid mediated inhibition of fibroblast proliferation and synthesis of new matrix has the benefit of decreasing adhesions between injured dense fibrous tissues and the surrounding tissues[43,91]; however, it delays development of wound strength[39,41]. In experimental studies corticosteroid injections of transected tendons decreased tendon weight, load to failure, and energy to failure[41,91]. Presumably, these consequences of corticosteroid injections result from inhibition of cell synthetic function. They may prolong healing and increase the probability of complications such as failure of healing and wound disruption[9,39,49,88].

Anabolic Steroids

Anabolic steroids may also weaken normal dense fibrous tissues. Several reports describe tendon ruptures or tears associated with anabolic steroid use[37,45]. Experimental studies also suggest that these drugs damage dense fibrous tissues[59,90]. Administration of an anabolic steroid to mice subjected to an endurance training program caused degenerative changes in musculo-tendonous junctions including increased variability in collagen fibril diameter, organization, disruption of collagen fibrils, and calcification[59]. A study of rat tendons showed that exercise and anabolic steroids caused tendons to reach breaking strains earlier and supported the argument that anabolic steroids may predispose dense fibrous tissues to injury[90].

Dimethyl Sulfoxide

Like corticosteroids and anabolic steroids, DMSO may weaken dense fibrous tissues. In tissue cultures it inhibits fibroblast proliferation[15] and decreases collagen synthesis in at least one cell line[8]. If the drug has the same consequences in vivo, it could increase the probability of tendon, ligament, and joint injury. In one experimental study the investigators washed the skin over mice Achilles tendons with a 70% solution of DMSO and then measured the strength of the achilles tendons[2]. They found a variable effect on the force required to separate the tendons. In the first week of treatment it decreased 20.2%; however, over the next two weeks it increased and then decreased again. The investigators concluded that the decreased separation force due to DMSO treatment made the tendons more susceptible to injury[2].

EFFECTS OF ANTI-INFLAMMATORY DRUGS ON CARTILAGE

Nonsteroidal Anti-inflammatory Drugs

Selected NSAID's alter the synthetic activity of normal chondrocytes, and thereby change the composition and possibly the mechanical properties of the cartilage matrix. A series of studies shows that prolonged administration of salicylates and several other NSAID's suppresses proteoglycan synthesis in normal cartilage and sometimes alters the organization of the cartilage matrix by interfering with proteoglycan aggregate formation[16,17,67-69,71,72]. However, one study found that a different NSAID decreased cartilage proteoglycan turnover and increased the stiffness of normal cartilage[76].

The clinical significance of the effects of NSAID's on normal cartilage in vivo remains uncertain, but a significant decrease in cartilage proteoglycan concentration decreases cartilage stiffness and increases cartilage permeability[23,26,27,62,63]. These changes might theoretically make the tissue more vulnerable to injury[22], but none of the reported studies show that NSAID's cause progressive degeneration of normal cartilage.

NSAID's also affect chondrocyte function in injured or degenerating cartilage[16,17,66,70,72]; several investigations have shown that aspirin suppresses proteoglycan synthesis more severely in osteoarthritic cartilage than in normal cartilage[70,72]. Prolonged oral administration of aspirin aggravated the degeneration of canine articular cartilage caused by immobilization[66] and exacerbated the degeneration of articular cartilage in unstable joints[70]. In dogs with knee instability due to transection of the anterior cruciate ligament, prolonged administration of aspirin decreased articular cartilage thickness, cartilage proteoglycan content, and proteoglycan synthesis compared with the unstable knees of dogs that did not receive aspirin[70]. Although these studies show that NSAID's, and in particular aspirin, alter chondrocyte synthetic function, the clinical significance of these observations has not been demonstrated.

Corticosteroids

Multiple experimental studies show that repeated intra-articular injections of corticosteroids cause progressive deterioration of normal articular cartilage, and that increasing amounts of corticosteroids increase the severity of cartilage damage[11,53,54,61]. Following intra-articular corticosteroid injections, chondrocyte synthesis of collagen and proteoglycans rapidly and profoundly decreases [11,53,54,65]. Then, matrix proteoglycan concentration drops, decreasing cartilage stiffness and increasing permeability[63]. Acute or repetitive loading of the damaged articular cartilage may cause mechanical disruption of the weakened matrix and cause progressive loss of the articular cartilage[11,12,22,25].

Systemic corticosteroid administration also depresses chondrocyte synthetic activity[55]. In otherwise normal joints, if the articular cartilage damage due to corticosteroids leaves the tissue physically intact with enough viable chondrocytes, the cells will attempt to repair the damage. Following cessation of intra-articular steroid injections, chondrocytes increase their rate of proteoglycan and collagen synthesis up to 900%[12]. The increase results from accelerated activity by existing cells and an apparent increase in the number of cells due to cell proliferation. Under favorable circumstances, the increased matrix synthesis will return the matrix proteoglycan concentration toward normal[12].

Corticosteroid injection of synovial joints damaged by rheumatoid or osteoarthritis often gives patients rapid relief of pain[29]. In advanced joint disease, where synovial inflammation contributes to the patient's symptoms and to the progression of the disease, suppression of inflammation by corticosteroids may help maintain joint function. Unfortunately, other effects of the corticosteroids may more than offset these potential benefits. Corticosteroid injections presumably suppress chondrocyte synthetic activity in injured or degenerated cartilage at least as effectively as they do in normal cartilage. Suppression of chondrocyte synthetic activity may prevent the cells from repairing matrix defects due to injury or disease and thereby hasten the deterioration of the articular cartilage. Multiple clinical reports describe rapid joint disintegration in patients with rheumatoid arthritis and osteoarthritis following intra-articular steroid injections[14,28,60,81-83,92]. Although the steroid induced inhibition of chondrocyte synthetic activity may have accelerated the joint destruction in these patients, decreased pain may have also had a role. Relief of pain following the injections allows the patients to increase their activity, and the increased loading may contribute to loss of the damaged articular cartilage[28]. The apparent frequency of this problem and the results of the clinical and experimental studies have led some physicians to recommend stopping the practice of multiple joint injections with corticosteroids, and that there should be strong justification for single joint injections[83].

Conclusions

Drug treatment of acute and chronic soft tissue injuries is a common practice. Physicians frequently recommend NSAID's or local corticosteroid injections to decrease pain, and in some instances accelerate restoration of function. Oral corticosteroids have also been used, and some patients elect to use drugs like anabolic steroids or dimethyl sulfoxide. Yet the efficacy and effects of many of these drugs in the treatment of soft tissue injuries have

not been clearly established.

Non-steroidal anti-inflammatory drugs suppress inflammation and provide analgesia, but their capacity to minimize tissue damage and accelerate return to normal function after injury have not been clearly proven. Although some NSAID's alter chondrocyte synthetic function, the clinical significance of these observations has not been demonstrated. No evidence of damage to normal dense fibrous tissues caused by these drugs has been reported. Thus, when treatment of an injury requires analgesia and supression of inflammation, short duration treatment with NSAID's may be helpful and is not likely to cause significant complications. If there is no need for an anti-inflammatory effect, acetaminophen offers a reasonable alternative.

Corticosteroids have much greater anti-inflammatory potency than NSAID's, but they also have not been shown to accelerate restoration of function. Most importantly, their use is associated with more serious complications. Several reports describe tendon ruptures following use of oral corticosteroids and corticosteroid injections for treatment of tenosynovitis. Multiple studies show that repeated intra-articular injections of corticosteroids are associated with progressive deterioration of articular cartilage. Therefore, corticosteroid injections of tendons or ligaments should be avoided and repeated corticosteroid injection of the same site should be performed with caution. In most patients corticosteroid injections should be used only after other non-surgical treatments have failed or can reasonably be expected to fail based on previous clinical experience, and when the physician can identify a discrete localized source of the patient's symptoms. Following injection, the patient's activity should be restricted. Because of the lack of controlled studies showing the efficacy of oral corticosteroids, as well as their potential complications, physicians should not recommend these medications for the routine treatment of soft tissue injuries. If oral corticosteroids are used, doses should be carefully monitored. No reported studies have shown accelerated healing of ligament, tendon or joint injuries due to anabolic steroids; several reports suggest that these drugs may increase the probability of certain injuries as well as cause other complications. Therefore, physicians should discourage use of these drugs.

Some patients report good results of topical DMSO for treatment of soft tissue injuries, but attempts to prove the efficacy of this approach in controlled trials has produced conflicting results.

A clear need exists for more and better clinical and experimental studies of the efficacy and tissue effects of drug treatment of soft tissue injuries. Currently, physicians must base drug treatment of soft tissue injuries on clinical experience, knowledge of selected experimental and clinical studies, as well as understanding of the general analgesic and anti-inflammatory activities of these commonly used medications.

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