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A Risk-Benefit Assessment of Intra-Articular Corticosteroids in Rheumatic Disorders

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Abstract

The appeal of intra-articular corticosteroid therapy has increased with the growing emphasis on early disease control in rheumatoid disease. The impact on the patient's pain and stiffness is impressive and prompt. This may encourage patient compliance with longer term therapies given to slow the course of the disease. The release of corticosteroid into the circulation also provides some generalised improvement. This can prove helpful during the management of flares of inflammatory disease.

There is less evidence to support the use of intra-articular corticosteroids in other inflammatory arthritides, but experience suggests that the benefits are similar. In osteoarthritis the benefits are less certain, but intra-articular therapy may prove important in patients who cannot undergo salvage operative procedures because of intercurrent illness.

The benefits of intra-articular corticosteroids may be enhanced by rest after the injection, or by the additional administration of agents such as radio-colloids, rifampicin (rifampin), or osmic acid. Most controlled trial data have been published on knee injections, but other joints can be useful targets for local therapy.

The risks are mainly related to the discomfort of the procedure, localised pain post-injection and flushing, but most feared is septic arthritis which probably occurs in about 1 in 10 000 injections. Careful aseptic technique is the best protection. Tissue atrophy at the injection site, abnormal uterine bleeding, hypertension and hyperglycaemia rarely cause problems. Osteonecrosis might be as much a problem with uncontrolled painful arthritis as with a joint rendered less symptomatic by corticosteroid injections.

Intra-articular corticosteroids form an important part of the management of inflammatory joint disease and might be considered where an inflammatory element occurs in osteoarthritis. They may be used at any stage in the arthritic process, but should be seen as an adjunct to other forms of symptom relief. In patients needing multiple joint injections, systemic therapy should be reviewed to see if better disease control could reduce the need for invasive therapy.

The intra-articular injection of corticosteroids gained an important role in the management of inflammatory arthritis at an early stage in the therapeutic use of these drugs. Despite changing fashions in the use of other symptom-relieving therapies, joint injection remains an important part of management of pain and stiffness throughout the evolution of inflammatory joint disease. Intra-articular corticosteroids may even help advanced destructive arthritis where symptoms arise from mechanically derived synovitis from joint debris rather than an immunological process. This article evaluates the benefits and risks of intra-articular corticosteroids, initially in rheumatoid arthritis, but also in other joint diseases; it also evaluates the available information on the possible mechanisms of action, and examines special problems that might arise in the use of joint injection. Finally, it explores possible means of improving the risk-benefit ratio of intra-articular injections.

1. History and Development

It was in 1948 that Hench and colleagues first spectacularly demonstrated the benefits of corticosteroid therapy in rheumatoid patients.[1] The cine film of an immobile patient managing to leap up and down the practice steps in the physiotherapy department after treatment must have astonished the audience of the day. However, systemic corticosteroid therapy rapidly lost popularity as the adverse effects appeared and anecdotal reports suggested that increasing doses were needed to relieve pain as the disease progressed in some patients.

Intra-articular corticosteroids evolved[2] to obviate the need for systemic corticosteroids by means of slow-release crystalline preparations that allow local anti-inflammatory effects. Early reports suggested benefit lasting up to 21 days,[3] but may underestimate the improvement seen in an era of disease suppression by systemic therapy. The widespread use of disease-modifying drugs may have reduced the use of intra-articular treatment, as described in a North American cohort study.[4]

2. Mechanism of Action

The inflammatory arthritides are the principal conditions treated by intra-articular corticosteroids. The duration of action is protracted; in our hands the median duration of improvement after injection of the rheumatoid knee with triamcinolone hexacetonide is 13.5 weeks.[5] A satisfactory explanation of the benefits must account for the prolonged relief of pain when the pharmacokinetics[3] suggest that the vast majority of injected corticosteroid is eliminated within a month. It seems likely that a change in the inflammatory process occurs and persists long after the corticosteroid has left the joint. The structure of the corticosteroid is not all-important, as shown by the more prolonged effect of triamcinolone hexacetonide 20mg compared with triamcinolone acetonide 40mg.[5]

Triamcinolone hexacetonide has been shown to inhibit the expression of genes for collagenase, human leucocyte antigen (HLA)–DR, tissue inhibitor of metalloproteinases, and complement components C2 and C3 in 3 rheumatoid patients following knee injection.[6] Similarly, in experimental osteoarthritis in dogs abnormal neutral proteoglycanase activity was blocked by systemic prednisone therapy.[7]

A confident understanding of such molecular mechanisms might help in the design of better release systems for corticosteroids and possibly permit a more even and prolonged therapeutic effect. Tackling the issue alone by slowing the release of corticosteroid,[8-10] for example by decreasing the solubility of the preparation, has not always proved successful (e.g. rimexolone, which is exceptionally slowly released, but no more effective than triamcinolone).[11,12]

3. Use of Intra-Articular Corticosteroids in Rheumatoid Arthritis

3.1 Choice of Injectable Corticosteroid

The modern preparations of methylprednisolone and triamcinolone appear to maximise the anti-inflammatory effects,[13] and duration of benefit is reported for several months (our published[5] and unpublished observations). In some cases, the release of corticosteroid from the joint can prove an asset in helping settle a generalised flare of inflammatory arthritis, though previous literature[14] has emphasised the capacity of depot preparations to be retained intra-articularly. In our hands, the response to a soluble hydrocortisone succinate preparation was very brief and unsatisfactory.[5]

3.2 Aspiration Before Injection

Aspiration before injection is of doubtful importance. In patients with tense effusions it is appropriate to hasten symptom relief, but observation suggests that aspiration is seldom complete.

Folds of synovium or rice bodies may occlude the aspirating needle or an effusion may occasionally be loculated. Our work could not associate an improved response with greater volumes of fluid when aspiration to dryness preceded joint injection.[5]

3.3 Post-Injection Rest

A controlled study of 24 hours rest after injection of the rheumatoid knee suggested enhanced benefits lasting up to 6 months.[15] Previous work describes similar benefits, but recommends substantially longer restrictions.[14,16] A further trial on rest in smaller patient numbers failed to show any benefit of rest, although the assessments associated with the negative conclusion were different.[17]

3.4 Accuracy of Joint Injections

In our experience, the easier the joint is to penetrate the more reliable is the response to injection. Hence, accessible larger joints do best. Even in experienced hands, however, the synovial cavity of a variety of joints was not necessarily punctured[18,19] and, in a study of patients with isolated shoulder pain of subacromial or glenohumeral origin, the accuracy of corticosteroid placement (less than 50% was located optimally) was also reported to affect clinical outcome.[20] However, the response may still prove satisfactory, as the corticosteroid may diffuse into or may be sited at the point of the inflammatory tissue. In a therapy associated with a significant placebo response,[12] it is not surprising that outcome can prove difficult to predict.

The easiest joint to inject is the knee,[18] and the published data have examined response to therapy in greatest detail in this joint. Unfortunately, much of the early work does not clearly define the means of assessing response, but gives interesting information on surprisingly brief responses in a wide variety of joints.[2] Caldwell, in a review of intra-articular corticosteroids,[21] describes response rates of at least 90% in rheumatoid knees, elbows, proximal interphalangeal and metacarpophalangeal joints after 1 or more injections; hip and temporomandibular joint injections proved less successful.

3.5 Recommendations for Specific Joints

3.5.1 The Knee

The rheumatoid knee can be approached medially or laterally. In a patient with a fixed flexion deformity from swollen synovium, inferomedial or inferolateral (below the patella) approaches may be preferable.

The response to therapy can be assessed by a pain score. Our own studies[5,13,22] have used a sequential self-completion chart allowing a 5-point score for pain (no pain, mild, moderate, severe, or very severe pain) on a weekly basis. We used an area under the curve method to assess 'total knee pain' during the period of follow-up, but also found it useful to assess the number of weeks pain-free following injection and the time that elapsed before the pain reached the pre-injection pain level (tables I and II).

Triamcinolone hexacetonide 20mg proved superior to triamcinolone acetonide 40mg in our rheumatoid patients, but we have not been able to show any difference between the former injection and depot methylprednisolone 80mg.

Previous open synovectomy often renders penetration to the joint cavity more difficult and painful.

Popliteal (Baker's) cysts are usually tense and uncomfortable. Patients often hold the knee bent, which predisposes to the development of fixed flexion deformities. When cysts rupture they present as a painful swollen calf clinically difficult to distinguish from a deep venous thrombosis. The tension in the popliteal fossa may also give rise to venous stasis secondary to popliteal swelling[25] and examination by ultrasonography may diagnose both a cyst and thrombus. On the basis that cysts are a product of knee synovitis, treatment of the cyst is inappropriate but rest and injection of the knee will halt progression in most cases. Thereafter the underlying condition causing the synovitis can be treated.

Occasionally, excision of a symptomatic popliteal cyst is needed, particularly if encysted fluid has tracked down to the calf and does not resorb after knee injection.

Table I. Benefits of injection to the rheumatoid knee. Data from Blyth et al.[5] and our unpublished observations

Agent	Residual knee pain (median AUC score)	Pain-free at 2 wk (%)	Median time until pain returned to pretreatment score (wk)
Triamcinolone acetonide 40mg	12	27	10
Triamcinolone hexacetonide 20mg	10	35	>12
Hydrocortisone succinate 100mg	28	0	1.5

AUC = area under the curve of self-assessed pain versus time.

3.5.2 The Shoulder

Synovial structures that may be involved are located at the glenohumeral joint, the acromioclavicular joint, the subacromial space, or along the long head of biceps. It is possible in some patients to demonstrate the origin of pain by injecting local anaesthetic to each area in turn and repeating examination after the anaesthetic has had time to work.[26] Alternatively, the shoulder may be examined for particular clinical signs (e.g. a lateral painful arc suggestive of subacromial problems, a high painful arc of acromioclavicular involvement, or restricted rotation in glenohumeral disease). Local anaesthetic testing is laborious and, possibly because of communication between different synovial structures or because of diffusion of therapy after injection, in a series of 90 rheumatoid shoulders we treated[27] there was no difference in response whether anterior glenohumeral or glenohumeral subacromial and acromioclavicular injection was undertaken. Patients however found the anterior injection a less painful procedure. The glenohumeral joint may also be approached posteriorly.[28] In patients who fail to respond to a glenohumeral injection we usually offer subacromial corticosteroid.[26] The acromioclavicular, sternoclavicular, and thoracoscapular articulations also form part of the shoulder girdle, but all are difficult to penetrate. In rheumatoid disease, thoracoscapular pain and crepitus are usually self limiting.

3.5.3 The Ankle and Subtalar Joints

These joints often communicate posteriorly to create a common synovial cavity in rheumatoid arthritis and presumably in other inflammatory arthritides.[29]

Bursitis anterior to the Achilles may be the source of the pain, in which case swelling is visible. Injection of bursitis may prove beneficial but injection of a tender Achilles tendon must be avoided for fear of rupture.[30]

Heel pain in the absence of a tender spot on palpation may be caused by an inflamed subtalar joint rather than plantar fasciitis. In either case a viscoelastic heel pad may be therapeutic without resorting to invasive corticosteroid injection.

Table II. Comparison of benefits of injection with triamcinolone acetonide 40mg in different rheumatoid joints[5,23,24]

Joint	Residual joint pain (median AUC score)	Pain-free at 2 wk (%)	Median time until pain reached pretreatment score (wk)
Knee	12	27	10
Glenhumeral	22	36	12
Ankle	15	25	NA

AUC = area under the curve of self-assessed pain versus time; **NA** = not assessed.

3.5.4 Elbows

Synovitis is usually most readily palpated posterolaterally, and this is therefore the favoured approach. Lateral injections may be technically easier in patients who have undergone excision of the radial head.

3.5.5 Wrists

The joint cavity may be difficult to penetrate and we favour a dorsal approach. Most patients will already have wrist supports and we advise their use for 24 hours following injection.

3.5.6 Small Joints of the Hands and Feet

These are sited at potentially dirty areas, particularly near the interdigital clefts of the toes. The narrow bore of fine (25 gauge) needles does not seem to restrict access of crystalline corticosteroid to the joint. The use of a local anaesthetic cream applied to the skin 30 to 60 minutes before injection may make the procedure pain-free.

Particularly in rheumatoid arthritis, it is important to consider that the origin of pain may be tendon sheath synovitis or bursitis or even rheumatoid nodules, all of which may be responsive to corticosteroid injection.

3.5.7 Temporomandibular Joints

These again are usually the site of short-lived inflammatory disease. Possibly the fibrocartilage between the articulating surfaces of the hyaline cartilage, or the laxity of the joint ensures that episodes of arthritis in temperomandibular joints are self-limiting. The proximity of the facial nerve has discouraged joint injections, but they might be considered if limitation of movement and pain start

to interfere with nutrition.[31] Temporomandibular pain may have an alternative cause and is often treated by bite-relieving splints.

3.5.8 Spinal Joints

Rheumatoid disease often gives rise to pannus around the cranio-cervical junction and the odontoid peg of the second cervical vertebra. Any additional ligamentous laxity in this area might precipitate cervical myelopathy. Furthermore, the inflammatory tissue is probably concentrated anteriorly so that access would require computed tomography guidance for injection via a transoral route. Injection in this area should be reserved for the inoperable patient with intractable pain.

3.5.9 Hips

Again, the hip joint is deep and the joint line never palpable. Methods are described for hip joint injection via an anterior approach but the femoral nerve, artery and vein seem a major discouragement.[32] A lateral approach can be undertaken but for a reliably sited injection radiological guidance is advised.

4. Intra-Articular Corticosteroids in Other Arthropathies

Table III provides a summary of the conditions in which joint injection may prove helpful (table III).

Table III. Conditions in which joint injection with corticosteroids may prove helpful

Rheumatoid arthritis
Psoriatic arthritis
Crystal arthropathies – especially acute gout or pseudogout
Ankylosing spondylitis with peripheral joint involvement
Osteoarthritis
Juvenile chronic arthritis
Adhesive capsulitis of the shoulder
Synovitis associated with polymyalgia rheumatica
Reactive arthritis
Sarcoid/granulomatous joint disease

4.1 Osteoarthritis

Joint injection in osteoarthritis is less helpful than in inflammatory arthritides.[33] Controlled trials in osteoarthritic knees have failed to show improvement greater than that seen in a placebo group beyond 3 weeks. Benefits may be more prolonged after injections of the thumb carpometacarpal joint.[34] The American College of Rheumatology have suggested that injection can be a useful therapy in the presence of inflammatory features such as a joint effusion.[35] Unfortunately our audit of joint injections suggests that clinical examination is not 100% reliable in predicting the presence or absence of joint fluid and we believe that intra-articular corticosteroid is a reasonable treatment to try, but it should not be repeated too frequently or in the absence of pain relief. Balch et al.[36] managed painful osteoarthritic knees by injections repeated at most every 4 weeks. Others have failed to identify factors that predict response of osteoarthritic knees to injection.[37,38]

In our local orthopaedic unit, 50% of osteoarthritic knees that come to replacement are associated with chondrocalcinosis. This raises the possibility that severe knee osteoarthritis has an inflammatory component and we wonder if patients who are awaiting knee replacement should be offered injection in the hope of reducing symptoms during the waiting period, (despite the previous studies that have failed to associate response with the presence of crystals or inflammatory cells in aspirated fluid).[39,40]

4.2 Crystal Arthritis

Most cases of crystal arthritis are self-limiting and can be managed by oral therapy. Some patients with severe or prolonged episodes may tolerate anti-inflammatory agents less well, especially cardiac patients with decompensation or borderline renal function, and be intolerant of colchicine. Aspiration and injection of the affected joint may then shorten a severe episode[2,41] or assist in disease control in chronic pyrophosphate arthropathy.

The role of intra-articular corticosteroids in apatite-associated large joint lysis or cholesterol crystal synovitis is less clear. We have experience of a patient with advanced destructive change in a shoulder which proved more painful after the aspi-

ration of 560ml of cholesterol crystal-laden fluid which probably kept the grossly eroded joint surfaces apart.

4.3 Seronegative Spondarthritides

Inflamed peripheral joints respond in much the same way as rheumatoid joints.

The nonplanar nature of sacroiliac joints and the difficulty in locating the joint cavity makes injection unreliable, but successes are reported particularly when joint puncture was assisted by fluoroscopic control.[42]

4.4 Polymyalgia Rheumatica

Synovitis of large joints occasionally proves a limiting factor in reduction of oral corticosteroid dosages. At that point, intra-articular therapy should be considered.

4.5 Chronic Low Back Pain

Although facet joint injections are recommended by some, a controlled trial of methylprednisolone acetate 20mg administered under fluoroscopic control proved negative.[43]

4.6 Juvenile Chronic Arthritis

Intra-articular injections are particularly valuable in oligoarticular disease for relief of pain and swelling, increase in range of motion, correction of flexion deformity, and prevention of periarticular muscular atrophy or growth disturbances. A recent paper provides magnetic resonance imaging data to support the observed clinical improvements.[44]

4.7 The Painful Shoulder

A recent systematic review suggested improved movement following subacromial corticosteroid injection, but failed to show benefit from intra-articular injection.[45] It may be that lack of uniformity in definition of shoulder problems has led to difficulties in assessing response to therapy.[46]

5. Risks of Intra-Articular Corticosteroid Injection

A leaflet explaining the risks and benefits may help patients decide if they wish to have a joint injection. Our leaflet covers infection, flushing, post injection pain, allergy, and possible bone damage after frequent injections.

5.1 Flushing

1 in 6 of our patients complain of flushing, though others find it less frequently.[21,31] It is most prominent in the face and is compared to postmenopausal flushing in patients who have experienced both.

Patrick and Doherty[47] believe that flushing is less frequent with certain injections, but this did not prove so when we compared them in 200 patients receiving triamcinolone acetonide or hexacetonide to the rheumatoid shoulder.[23] Occasionally the vasodilation is sufficient to cause lightheadedness and patients should be warned to rest if necessary. If uncertainty arises, this innocent problem can be distinguished from sepsis by checking the temperature, acute phase reactants (which usually fall after joint injection for inflammatory arthritis), and the peripheral blood white cell count. Usually flushing resolves within 3 or 4 days; some patients are pleased to have more than usual colour in their cheeks.

5.2 Flare of Pain

Patients should be warned that any procedure involving needle puncture may result in a bruised feeling. Chemical synovitis in response to injected crystalline material[48] is also recognised and can be associated with warmth, swelling, and effusion, usually within a few hours of the procedure.[49,50]

Aspiration should be performed to exclude infection. Our data agree with previously published work in that approximately 1 in 6 will experience a post-injection flare, although the rate was substantially increased by co-injection with rifampicin (rifampin). Resolution will occur over a few days with aspiration, analgesics and splintage as

needed. In a randomised comparison of subcutaneous lidocaine (lignocaine), subcutaneous plus intra-articular lidocaine, topical ethyl chloride spray or no local anaesthetic at the time of injection we were unable to detect any difference in immediate or 24-hour post-injection pain using a visual analogue pain scale. Nevertheless, unless one can be certain of easy access, it seems kind to use local anaesthetic down to the joint cavity. If there is any reason to undertake synovial fluid microscopy, local anaesthetic should not be mixed with corticosteroid, which is birefringent.

5.3 Septic Arthritis

This is the most feared complication of intra-articular injections. Hollander's early work reported a risk of 1 in 14 000 procedures.[8] In unselected case series of septic arthritis, injection is a rare antecedent. In Sweden a careful review of septic arthritis confirmed that arthrocentesis before sepsis was not common, but suggested that the more incapacitated rheumatoid patients and those receiving cytotoxic drugs were at greater risk.[51] Patients should know that sepsis in a joint could have serious long-term consequences and requires more intensive antibacterial therapy than most bacterial infections.

Appropriate precautions include the use of an aseptic no-touch technique, alcohol-based antiseptics, and careful thorough hand-washing.[52] The American College of Rheumatology guidelines suggest that conversation during the procedure is inappropriate because of airborne bacteria, but we believe that relaxation of the patient facilitates minimal movement of the needle. Skin micro-organisms are probably important in infection, and patients with proliferative skin lesions, such as psoriasis, should be injected through areas of unaffected skin. Corticosteroids may reduce the joint's defences against transient bacteraemia, so distant infections should be treated before joint injection is undertaken.

5.4 Osteonecrosis

There are reports[53-56] of joint damage possibly relating to the catabolic effects of anti-inflammatory corticosteroids. Equally, there are patients with inflammatory arthritis who develop radiological appearances of avascular necrosis without having received joint injections, and there are reports of patients managed long term by frequent injections without ill effect.[36,41] In a small cohort of 13 patients receiving 4 or more injections to the same joint in the space of a year, arthroplasty was not significantly more common on the heavily injected side after an average follow-up of 7.4 years.[57] In experimental osteoarthritis, intra-articular triamcinolone hexacetonide given before the onset of disease reduced the pathological changes[58-60] and biochemical work has demonstrated reductions in the cartilage proteolytic enzyme stromelysin, reduced interleukin-1β levels[60] and reduced metalloproteinase synthesis in human osteoarthritic cartilage exposed to corticosteroids.[61] Some experimental work has suggested loss of cartilage proteoglycans after intra-articular corticosteroids,[62] but with uncertainty about a definite clinical association we use an interval of 3 months between injections as the norm for any particular joint, provided that the patient is convinced of the benefit.

Usually as arthritis progresses the response declines and surgical solutions are sought as an alternative.

5.5 Tissue Atrophy

Osteonecrosis may be a form of atrophy comparable to that seen with dermatologically applied corticosteroids. Similarly, atrophy is occasionally seen around the site of a joint injection presumably because of leakage along the needle track to subcutaneous tissue.[63] Although this has been reported to be painful, it is most often appreciated at a late date and is generally only cosmetically important. Fluorinated corticosteroids may be more frequently responsible. Ligamentous laxity may

also occur as a result of the atrophic effects of corticosteroids.

5.6 Abnormal Uterine Bleeding

This is presumably a corticosteroid effect but is generally transient.[64] Further investigation is indicated in any case lasting beyond 1 menstrual cycle.

5.7 Pancreatitis

This has been attributed to both injectable corticosteroids[31] and nonsteroidal anti-inflammatory drugs. As it is a sudden illness, often of unknown cause, it is usually difficult to be certain about a drug-induced origin.

5.8 Psychosis

We have experienced 1 rheumatoid patient who was treated for a flare by 3 joint injections in as many days. His previously manageable psychosis destabilised and he required in-patient psychiatric care.

5.9 Hypertension

Rises in blood pressure occur occasionally, but are unlikely to be sustained provided that background control is adequate.

5.10 Fluid Retention

Care is needed in the presence of severe cardiac disease in case decompensation occurs; this is most likely to present as breathlessness or chest pain.

5.11 Other Adverse Effects of Corticosteroids

Uncontrolled severe rheumatoid arthritis is associated with osteoporosis even at early stages. Intra-articular corticosteroids almost certainly contribute to drug-induced osteoporosis, but when administered may improve mobility and permit favourable regular exercise.[65] Measurements of osteocalcin after joint injections might suggest that a drug effect exists,[65] but there are no data on bone density.

Asymptomatic periarticular calcification has been described, especially in finger joints, after injection.[66]

The data sheets of injectable corticosteroids inevitably mention all the effects of systemic corticosteroids, but the classical Cushingoid state seen after long-term oral corticosteroid therapy is not seen in patients receiving 3 or 4 joint injections per year. The intermittent nature of such treatment has led to infrequent reports of adrenocortical suppression.[65-70] In patients who need regular joint injections, other therapeutic approaches should be considered. For instance, it may be that treatment is provided to a modest number of joints by injection when polyarthritis warrants second-line drugs to control inflammation.

6. Special Cases

6.1 Pregnancy

All would prefer not to use drug therapy during pregnancy. In the presence of synovitis aspiration, bed rest and splintage may be enough to settle a flare and intra-articular corticosteroids should be avoided if possible. The animal work associating triamcinolone acetonide used in early pregnancy with cleft palate has never been seen in humans,[71] and intra-articular corticosteroids are often a favoured and effective means of controlling inflammatory joint disease in pregnancy.

6.2 Lactation

Theoretically, corticosteroids secreted through breast milk may have effects on the child. After triamcinolone hexacetonide 20mg is injected into the rheumatoid knee, plasma concentrations are measurable in the recipient for about a month. Any effects on the child are likely to be trivial unless the mother is already taking additional oral corticosteroid therapy.

6.3 Diabetes Mellitus

Blood glucose control may deteriorate for a few days after a depot corticosteroid injection and a

Table IV. Broad diagnostic groups who may be suitable for joint injection

Monoarthritis – where infection as an underlying cause has been excluded
Polyarthritis – where 1 joint shows outstanding synovitis (not due to infection)
Polyarthritis – where 1 joint has dominant symptoms that have previously been relieved by intra-articular injection

temporary adjustment to hypoglycaemic therapy may prove necessary.[31]

6.4 Anticoagulant Therapy

Joint injections are associated with a low risk in patients taking warfarin, providing the most recent international normalised ratio (INR) is <4.5.[72] No data are available for patients receiving heparin.

7. Conclusions and Recommendations

Injection of inflamed joints with intra-articular corticosteroids can provide excellent symptom relief in carefully selected patients (table IV). In all cases risks must be minimised (table V) and benefits maximised. The following points must be considered.

(i) The joint responsible for major symptoms must not be infected. If there is any doubt, joint aspirate culture results should be checked before injection. Routine culture of aspirated fluid may not be cost-effective in some healthcare systems.[73]

(ii) The overall treatment of inflammatory arthritis should provide optimal disease control, or adjustments should be made so that control will improve and if possible avoid the need for repeated injections. Sometimes joint injections can prove a useful means of symptom control while awaiting the response to second-line therapy in rheumatoid disease.

(iii) The likelihood of benefit in the absence of significant adverse effects is high. Intra-articular corticosteroid therapy can prove a good way of gaining the patient's confidence when other therapies have proved either ineffective or toxic. Compared to other short-acting therapies in rheumatoid disease, intra-articular corticosteroids have a favourable risk-benefit ratio.

(iv) Experienced practitioners are likely to achieve better results by reducing pain caused by the procedure and by more precise delivery of the injected agents. This also makes atrophic problems, particularly associated with triamcinolone hexacetonide, less likely.

(v) Triamcinolone hexacetonide is most likely to provide long-lasting relief when injected into the rheumatoid knee.

(vi) Patients who fail to gain the expected benefit might be considered for 24 hours bed rest and possibly splintage after injection. Alternatively, intra-articular rifampicin, osmic acid, methotrexate, or radioisotopes might be added (table VI).

Table V. Maximising the safety of a joint injection

Ensure there is no active infection elsewhere (e.g. chest or urinary tract)
If distant infection is present, treat it first with antibacterials appropriate to bacteriology results, or where not possible, ensure a definite clinical response has occurred
In patients with valvular heart disease, consider antibacterial prophylaxis. The risk of endocarditis is small and most patients will already know if serious adverse reaction to antibacterials is likely to develop
The best site for injection is the most readily palpable joint line or cystic space which is not close to nerves or major vessels
Always use a no-touch technique
Antiseptic agents need adequate time to have an effect
Never inject against resistance: the joint cavity may not have been entered
If aspirate is obtained and suggests an inflammatory process, it should be sent for culture
If fluid is purulent, defer injection until routine culture and microscopy are known to be negative
When using injectable local anaesthetic, the same needle can be used to penetrate the joint cavity and hence diminish the number of skin punctures
Always avoid joint injections when there is: septic arthritis periarticular cellulitis, skin ulcers, or osteomyelitis uncontrollable bleeding diatheses known hypersensitivity to the proposed injection
Consider all alternatives before injection when there is: a history of previous ineffective injection the presence of adjacent skin lesions haemarthrosis joint instability brittle diabetes mellitus

Table VI. Additional measures that may enhance the benefits of joint injection with corticosteroid

Rest for 24 hours after the injection (possibly with splintage)[14,15]a
Additional injection with:
rifampicin (rifampin)[22]a
radio colloids,[75,76]a e.g. ^{90}Yttrium, ^{186}Rhenium, ^{169}Erbium
osmium tetroxide[77]a
methotrexate (psoriatic arthritis)[22,78,79]b
hyaluronic acid polymers (osteoarthritis)[80]c
superoxide dismutase[81-83]c
Improved overall disease control
Joint lavage[74]d

a Proven added effect in at least 1 controlled trial.

b Reports of clinical/laboratory benefit.

c Benefit shown in the absence of concomitant corticosteroid injection, but case for combination not proven.

d Benefit demonstrated following previous failed corticosteroid injection.

(vii) In patients with osteoarthritis, the use of intra-articular corticosteroid should be considered carefully as the risk-benefit ratio is less favourable. The first injection should be considered a 'trial of therapy'. The physician should remember that injected treatment may be associated with a 50% placebo response rate.

(viii) Patients with diabetes mellitus should be informed that hyperglycaemia may require additional treatment over a few days following injection.

(ix) In patients who normally receive antibacterial prophylaxis for other invasive procedures (e.g. patients with prosthetic heart valves or chronic valvular heart disease), the risk-benefit ratio for antibacterial cover for this procedure should also be considered.

(x) Recent data suggesting a favourable effect of low dosage oral corticosteroid therapy in early rheumatoid arthritis[84] should encourage the aggressive use of intra-articular corticosteroids, which may provide similar benefits.

(xi) There is no absolutely correct method for joint injection,[85] but careful aseptic technique is appropriate and a suitable subject for regular audit. In general the most readily palpable route for injection is the one most likely to cause least pain.

References

1. Hench P, Kendall EC, Slocumb CH, et al. The effects of a hormone of the adrenal cortex and of pituitary adrenocorticotropic hormone on rheumatoid arthritis. Mayo Clin Proc 1949; 24: 181-97
2. Hollander JL, Brown Jr EM, Jessar RA, et al. Hydrocortisone and cortisone injected into arthritic joints: comparative effects of and use of hydrocortisone as a local antiarthritic agent. JAMA 1951; 147: 1629-35
3. Derendorf H, Mollmann H, Gruner A, et al. Pharmacokinetics and pharmacodynamics of glucocorticoid suspensions after intraarticular administration. Clin Pharmacol Ther 1986; 39: 313-7
4. Ward MM, Fries JF. Trends in antirheumatic medication use among patients with rheumatoid arthritis, 1981-1996. J Rheumatol 1998; 25, 408-16
5. Blyth T, Hunter JA, Stirling A. Pain relief in the rheumatoid knee after steroid injection: a single-blind comparison of hydrocortisone succinate, and triamcinolone acetonide or hexacetonide. Br J Rheumatol 1994; 33: 461-3
6. Firestein GS, Paine MM, Littman BH. Gene expression (collagenase, tissue inhibitor of metalloproteinases, complement and HLA-DR) in rheumatoid arthritis and osteoarthritis synovium: quantitative analysis and effect of intraarticular corticosteroids. Arthritis Rheum 1991; 34: 1094-105
7. Pelletier J-P, Martel-Pelletier J. Cartilage degradation by neutral proteoglycanases in experimental osteoarthritis: suppression by steroids. Arthritis Rheum 1985; 28: 1393-401
8. Hollander JL. Intrasynovial corticosteroid therapy in arthritis. Md Med J 1970; 19: 62-6
9. Hollander JL, Jessar RA, Restifo RA, et al. A new intra-articular steroid ester with longer effectiveness [abstract]. Arthritis Rheum 1961; 4: 422
10. Kendall PH. Triamcinolone hexacetonide: a new corticosteroid for intra-articular therapy. Ann Phys Med 1967; 9: 55-8
11. Derendorf H, Mollman HW, Barth J. Comparative pharmacokinetic evaluation of glucocorticoids after intra-articular administration [in German]. Aktuel Rheumatol 1990; 15: 145-53
12. Balfour JA, Benfield P. Rimexolone. Biodrugs 1997; 7:158-63
13. McCarty DJ, Faires JS. A comparison of the duration of local anti-inflammatory effect of several adrenocorticosteroid esters – a bioassay technique. Curr Therapy Res 1963; 5: 284-90
14. McCarty DJ, Harman JG, Grassanovich JL, et al. Treatment of rheumatoid joint inflammation with intrasynovial triamcinolone hexacetonide. J Rheumatol 1995; 22: 1631-5
15. Chakravarty K, Pharaoh PDP, Scott DGI. A randomised controlled study of post injection rest following intra-articular steroid therapy for knee synovitis. Br J Rheumatol 1994; 33: 464-8
16. Neustadt DH. Treatment of rheumatoid joint inflammation with intrasynovial triamcinolone. J Rheumatol 1997; 24: 1349-50
17. Chatham W, Williams G, Moreland L, et al. Intraarticular corticosteroid injections: should we rest the joints? Arthritis Care Res 1989; 2:70-4
18. Sykes HR, Eyes B, Williams E, et al. The accuracy of blind intra-articular injections [abstract]. Br J Rheumatol 1994; 33 Suppl 1.: 132
19. Jones A, Regan M, Ledingham J, et al. Importance of placement of intra-articular steroid injections. BMJ 1993; 307: 1393-40
20. Eustace JA, Brophy DP, Gibney RP, et al. Comparison of the accuracy of steroid placement with clinical outcome in patients with shoulder symptoms. Ann Rheum Dis 1997; 56: 59-63

21. Caldwell JR. Intra-articular corticosteroids: guide to selection and indications for use. Drugs 1996; 52: 507-14
22. Blyth T, Stirling A, Coote J, et al. Injection of the rheumatoid knee: does intra-articular methotrexate or rifampicin add to the benefits of triamcinolone hexacetonide? Br J Rheumatol 1998; 37: 770-2
23. Gordon MM, Blyth T, Hunter JA. A comparison of glenohumeral injections of triamcinolone acetonide (TA) and triamcinolone hexacetonide (TH) in the painful rheumatoid shoulder [abstract]. Br J Rheumatol 1995; 35 Suppl. 1: 78
24. Blyth TH, Irvine S, Paterson AS, et al. A comparison of orthoses [ankle foot orthosis (AFO) or Malleoloc] and steroid injections in the painful rheumatoid ankle. Scand J Rheumatol. 1998; Suppl. 108
25. Belch JJF, McMillan NC, Fogelman I, et al. Combined phlebography and arthrography in patients with painful swollen calf. BMJ 1981; 282: 949
26. Kelly IGK. The source of shoulder pain in rheumatoid arthritis: its implications for surgery. J Shoulder Elbow Surg 1994; 3: 62-5
27. Blyth TH, Hunter JA. Treatment of the rheumatoid shoulder with intra-articular steroid; a comparison of superior and anterior routes of injection [abstract]. Br J Rheumatol 1993; 32 Suppl. 1: 69
28. Dixon ASt J, Graber J. Local injection therapy in rheumatic diseases. Basle: EULAR Publishers, 1989
29. Helliwell P, Woodburn J. Juvenile chronic arthritis: diagnosis and management of tibio-talar and sub-talar disease [letter]. Br J Rheumatol 1998; 37: 579
30. Mahler F, Fritschy D. Partial and complete ruptures of the Achilles tendon and local corticosteroid injections. Br J Sports Med 1992; 26: 7-14
31. Owen DS. Aspiration and injection of joints and soft tissues. In: Kelley WN, Harris ED, Ruddy S, et al., editors. Textbook of rheumatology. 5th ed. Philadelphia: Saunders, 1997: 591-608
32. Plant MJ, Borg AA, Dziedzic K, et al. Radiographic patterns and response to steroid hip injection. Ann Rheum Dis 1997; 56: 476-80
33. Creamer P. Intra-articular corticosteroid injections in osteoarthritis: do they work and if so, how? Ann Rheum Dis 1997; 56: 634-6
34. Dieppe PA. Are intra-articular steroid injections useful for the treatment of the osteoarthitic joint [editorial]? Br J Rheumatol 1991; 30: 199
35. Hochberg MC, Altman RD, Brandt KD, et al. Guidelines for the medical management of osteoarthritis: part II: osteoarthritis of the knee: American College of Rheumatology. Arthritis Rheum 1995; 38: 1541-6
36. Balch HW, Gibson JMC, El-Ghobarey AF, et al. Repeated corticosteroid injections into knee joints. Rheumatol Rehab 1977; 11: 137-40
37. Gaffney K, Ledingham J, Perry JD. Intra-articular triamcinolone hexacetonide in knee osteoarthritis: factors influencing the clinical response. Ann Rheum Dis 1995; 54: 379-81
38. Jones A, Doherty M. Intra-articular corticosteroids are effective in osteoarthritis but there are no clinical predictors of response. Ann Rheum Dis 1996; 11: 829-32
39. Friedman DM, Moore ME. The efficacy of intra-articular steroids in osteoarthritis: a double blind study. J Rheumatol 1980; 7: 850-6
40. Dieppe P, Sathapatayavongs B, Jones H, et al. Intra-articular steroids in osteoarthritis. Rheum Rehab 1980; 19: 212-7
41. Gray RG, Tenenbaum J, Gottlieb NL. Local corticosteroid treatment in rheumatic disorders. Semin Arthritis Rheum 1981; 10: 231-54
42. Maugars Y, Mathis C, Berthelot J-M, et al. Assessment of the efficacy of sacroiliac corticosteroid injections in spondyloarthropathies: a double blind study. Br J Rheumatol 1996; 35: 767-70
43. Carette S, Marcoux S, Truchon R, et al. A controlled trial of corticosteroid injections into facet joints for chronic low back pain. N Engl J Med 1991; 325: 1002-7
44. Huppertz H-I, Tschammler A, Horwitz A, et al. Intra-articular corticosteroids for chronic arthritis in children: efficacy and effects on cartilage and growth. J Paediatr 1995; 127; 317-21
45. Green S, Buchbinder R, Glazier R, et al. Systematic review of randomised controlled trials of interventions for painful shoulder: selection criteria, outcome assessment, and efficacy. BMJ 1998; 316: 354-60
46. Szebenyi B, Dieppe P. Interventions to treat shoulder pain [letter]. BMJ 1998; 316: 1676
47. Patrick M, Doherty M. Facial flushing after intra-articular injection of steroid. BMJ 1987; 295: 1380
48. Kahn CB, Hollander JL, Schumacher HR. Corticosteroid crystals in synovial fluid. JAMA 1970; 211: 807-9
49. McCarty DJ, Hogan JM. Inflammatory reaction after intrasynovial injection of microcrystalline adrenocorticosteroid esters. Arthritis Rheum 1964; 7: 359-67
50. Berger RG, Yount WJ. Immediate 'steroid flare' from intra-articular triamcinolone hexacetonide injection: case report and review of the literature. Arthritis Rheum 1990; 33: 1284-6
51. Ostensson A, Geborek P. Septic arthritis as a non-surgical complication in rheumatoid arthritis: relation to disease severity and therapy. Br J Rheumatol 1991; 30: 35-8
52. Cawley PJ, Morris IM. A study to compare the efficacy of two methods of skin preparation prior to joint injection. Br J Rheumatol 1992; 31: 847-8
53. Alarcon-Segovia D, Ward LE. Charcot-like arthropathy in rheumatoid arthritis: consequence of overuse of a joint repeatedly injected with hydrocortisone. JAMA 1965; 193: 136-8
54. Bentley G, Goodfellow JW. Disorganization of the knees following intra-articular hydrocortisone injections. J Bone Joint Surg 1969; 51B: 498-502
55. Chandler GN, Wright V. Deleterious effect of intra-articular hydrocortisone. Lancet 1985; II: 661-3
56. Laroche M, Arlet J, Mazieres B. Osteonecrosis of the femoral and humeral heads after intra-articular corticosteroid injections. J Rheumatol 1990; 17: 549-51
57. Roberts WN, Babcock EA, Breitbach SA, et al. Corticosteroid injection in rheumatoid arthritis does not increase rate of total joint arthroplasty. J Rheumatol 1996; 23: 1001-4
58. Butler M, Colombo C, Hickman L, et al. A new model of osteoarthritis in rabbits: III: evaluation of anti-osteoarthritic effects of selected drugs administered intraarticularly. Arthritis Rheum 1983; 26: 380-6
59. Williams JM, Brandt KD. Triamcinolone hexacetonide protects against fibrillation and osteophyte formation following chemically induced articular cartilage damage. Arthritis Rheum 1985; 28: 1267-74
60. Pelletier J-P, DiBattista JA, Raynauld JP, et al. The in vivo effects of intraarticular corticosteroid injections on cartilage lesions, stromelysin, interleukin-1, and oncogene protein synthesis in experimental osteoarthritis. J Clin Lab Invest 1995; 72: 578-86
61. Pelletier J-P, Martel-Pelletier J, Cloutier JM, et al. Proteoglycan-degrading acid metalloprotease activity in human

osteoarthritic cartilage, and the effect of intraarticular steroid injections. Arthritis Rheum 1987; 30: 541-8
62. Mankin HF, Conger KA. The acute effects of IA hydrocortisone on articular cartilage in rabbits. J Bone Joint Surg 1966; 48: 1383-8
63. Gottlieb NL, Penneys NS, Brown Jr HE. Periarticular perilymphatic skin atrophy after intra-articular corticosteroid injections. JAMA 1978; 240: 559-60
64. Cunningham GR, Goldzieher JW, de la Pena A, et al. The mechanism of ovulation inhibition by triamcinolone acetonide. J Clin Endocrinol Metab 1978; 46: 8-14
65. Emkey RD, Lindsay R, Lyssy J, et al. The systemic effect of intra-articular administration of corticosteroid on markers of bone formation and bone resorption in patients with rheumatoid arthritis. Arthritis Rheum 1996; 37: 277-82
66. Gerster JC, Fallet GH. Periarticular hydroxyapatite deposition after corticosteroid injections. J Rheumatol 1987; 14: 1156-9
67. Schuster S, Williams IA. Adrenal suppression due to intra-articular steroid therapy. Lancet 1961; II: 171
68. Reid DM, Eastmond C, Rennie JAN. Hypothalamic-pituitary-adrenal suppression after repeated intra-articular injection. Ann Rheum Dis 1986; 45; 87
69. Esselinckx W, Kolanowski J, Ngant de Deuxchaisnes CH. Adrenocortical function and responsiveness to tetracosactrin infusions after intra-articular treatment with triamcinolone acetonide and hydrocortisone acetate. Clin Rheumatol 1982; 1: 176-84
70. Lazarevic MB, Shosey JL, Djordjevic-Denic G, et al. Reduction of cortisol levels after single intra-articular and intramuscular injections. Am J Med 1995; 99: 370-3
71. Committee on Safety of Medicines/Medicines Control Agency. Systemic corticosteroids in pregnancy and lactation. Curr Probl Pharmacovig 1998; 24: 9
72. Thumboo J, O'Duffy JD. A prospective study of the safety of joint and soft tissue aspirations and injections in patients taking warfarin sodium. Arthritis Rheum 1998; 41: 736-9
73. Pal B, Nash EJ, Oppenheim B, et al. Routine synovial fluid culture: is it necessary? Lessons from an audit. Br J Rheumatol 1997; 36: 1116-7
74. Sharma A, Baethge BA, Acebes JC, et al. Arthroscopic lavage treatment in rheumatoid arthritis of the knee. J Rheumatol 1996; 23: 1872-4
75. Gumpel JM, Roles NC. A controlled trial of intra-articular radiocolloids versus surgical synovectomy in persistent synovitis. Lancet 1975; I: 488-9
76. Gumpel JM, Matthews SA, Fisher M. Synoviorthesis with erbium-169: a double-blind controlled comparison of erbium-169 with corticosteroid. Ann Rheum Dis 1979; 38: 341-3
77. Anttinen J, Oka M. Intra-articular triamcinolone hexacetonide and osmic acid in persistent synovitis of the knee. Scand J Rheumatol 1975; 4: 125-8
78. Bird HA, Ring EFJ, Daniel R, et al. Comparison of intra-articular methotrexate with intra-articular triamcinolone hexacetonide. Curr Med Res Opin 1977; 5: 141-6
79. Hall GH, Jones BJM, Head AC. Intra-articular methotrexate. Clinical and laboratory study in rheumatoid and psoriatic arthritis. Ann Rheum Dis 1978; 37: 351-6
80. Wobig M, Dickhut A, Maier R, et al. Viscosupplementation with hylan G-F 20: a 20 week controlled trial of efficacy and safety in the osteoarthritic knee. Clin Ther 1998; 20: 410-23
81. Goebel KM, Storck U, Neurath F. Intra-synovial orgotein therapy in rheumatoid arthritis. Lancet 1981; I: 1015-17
82. Gammer W, Broback LG. Clinical comparison of orgotein and methylprednisolone acetate in the treatment of osteoarthritis of the knee joint. Scand J Rheumatol 1984; 13: 108-12
83. Goebel KM, Storck U. Effect of intra-articular orgotein versus corticosteroid on rheumatoid arthritis of the knees. Am J Med 1983; 74; 124-8
84. Kirwan JR, Arthritis and Rheumatism Council Low Dose Glucocorticoid Study Group. The effect of glucocorticoids on joint destruction in rheumatoid arthritis. N Engl J Med 1995; 333: 142-6
85. Haslock I, MacFarlane D, Speed C. Intra-articular and soft tissue injections: a survey of current practice. Br J Rheumatol 1995; 34: 449-52

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