

Intra-Synovial Corticosteroid Injections in Juvenile Chronic Arthritis-A Review

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Abstract

Locally injected intra-synovial corticosteroids are an important and effective part of treatment for juvenile chronic arthritis (JCA). They work rapidly, effectively and safely. They are most useful for limited joint, tendon sheath or bursal involvement in pauciarticular JCA or the few most active joints in polyarticular or systemic JCA while awaiting the onset of action of disease modifying anti-rheumatic drugs.

This article includes a brief history of intra-synovial steroid use, the mechanisms of action in decreasing inflammation and contraindications, as well as local and systemic complications. Important contraindications include infection, prostheses, arthroscopy, surgical procedures, damaged joints and hypersensitivity. The commonest complication is subcutaneous atrophy while serious complications include infection and damage to the joint and surrounding structures. Proper technique, use of imaging and adequate analgesia or anaesthesia, post injection rest and subsequent mobilisation are important. The efficacy and duration of action of the various steroids available are discussed. Long-acting microcrystalline steroids such as triamcinolone hexacetonide are useful for prolonged remission. Repeated injections can be safe and effective. Failure may be due to incorrect technique, insufficient or short-acting steroid, poor general disease control or intra-synovial septa.

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Introduction

Locally injected intra-synovial corticosteroids are useful to target selected joint, tendon sheath or bursal inflammation in children with pauciarticular or polyarticular juvenile chronic arthritis (JCA). Inflammation is decreased locally and with minimal systemic side effects. It provides rapid and prolonged relief from pain and swelling, thereby allowing improved mobilisation, independence and growth.

History

Intra-synovial corticosteroid treatment started more than 40 years ago. It has been used with increasing frequency in JCA. It produces a quick response and is well tolerated with minimum though potential hazards.¹⁻¹²

Much of the knowledge of intra-articular and peri-articular (tendon sheath, bursal) steroid injection in children with JCA is based on experience in adults with arthritis and from animal models. Few studies have been reported in children.

The natural history of pauciarticular JCA is one of remission and relapses. While some inflamed joints may improve spontaneously, pain and swelling may persist for months in others, leaving permanent deformity and

disability. Children with continued disease activity are at risk for growth anomalies (leg length discrepancy and valgus deformity) as well as muscle atrophy¹³ which can lead to abnormal limb function, abnormal gait and hip development,⁶ and loss of independence. A pain-free joint for 2 to 3 months following a steroid injection is helpful for the development of normal limb function in a young child.

Cortisone was the first corticosteroid used for injection in the 1950s¹⁴ but frequently produced an irritant synovitis. It had minimal anti-inflammatory effect and required systemic absorption and biotransformation to its active metabolite hydrocortisone for anti-inflammatory action.¹⁵ Hydrocortisone acetate was developed one year later and was the first locally active intra-articular steroid, with an anti-inflammatory action limited to days, and a synovial half-life of 60 to 107 minutes.¹⁶

Subsequently other less soluble esters of hydrocortisone and prednisolone were synthesized with more potent and long-lasting effects. Microcrystalline suspensions with decreasing solubility have been marketed. The duration of response after intra-synovial injection is inversely related to solubility in water¹⁴—the more insoluble the steroid, the longer it stays in the joint.

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Thus triamcinolone hexacetonide (TH) which is the least soluble has the longest duration.^{12,17-19}

Indications

Indications for intra-articular steroid use in JCA are summarised in Table I. Local steroid injections are useful especially for active synovitis limited to a few joints or sheaths which have failed to respond to adequate trials of non-steroidal anti-inflammatory drugs (NSAIDs) of at least 2 weeks duration⁷ or when there are adverse effects to NSAIDs (such as nausea, headache and dizziness).⁷ Children with pauciarticular JCA are the best candidates, since few joints are involved and the potential toxicity of drugs such as methotrexate, cyclosporin, chlorambucil, gold and systemic corticosteroids limit their use in these children. Swollen joints, joints with flexion contractures and those with growth disturbances may benefit. In polyarticular JCA intra-articular steroids may also be useful for 1 or 2 troublesome joints while awaiting the onset of action of disease modifying anti-rheumatic drugs (DMARDs) which may take weeks or even months.

Most joints can be injected but large and easily accessible joints (such as knees, ankles and wrists) are the easiest and safest. Multiple joints can be injected simultaneously and repeated if necessary. Inflamed tendon sheaths and bursa also respond to steroid injection.

TABLE I: INDICATIONS FOR INTRA-SYNOVIAL INJECTIONS IN JCA

- Pauciarticular, polyarticular or systemic JCA
- Limited number of injections required such as 1 to 4
- Active inflammation of joints, tendon sheaths, bursae or plantar fascia OR flexion contracture (recent) OR growth disturbances
- In pauciarticular disease, can be definitive treatment for synovitis limited to few joints or after failing an adequate course of NSAIDs
- In polyarticular disease, can be used to target the most troublesome joints/tendon sheaths while awaiting action of disease modifying drugs such as methotrexate

JCA: juvenile chronic arthritis; NSAIDs: non-steroidal anti-inflammatory drugs

Mechanism of Action: Suppression of Synovial Inflammation

Intra-synovial corticosteroids may act in a variety of ways to suppress inflammation locally.²⁰⁻²⁸ Steroids may seal off vessels and suppress angiogenesis.²⁰ They may decrease neutrophil migration into the joint²¹ or decrease secretion of lysosomal enzymes from neutrophils.²² They may inhibit superoxide anion production and suppress T cell dependant function,²³ or decrease production of aggressive mediators by suppressing genes in the synovial membrane that play a role in articular destruction.²⁴ Steroids may work by inhibiting the cyclo-oxyge-

nase pathway of arachidonic acid metabolism thus blocking prostaglandin synthesis²⁵ and probably also inhibit the lipo-oxygenase pathway which generates inflammatory mediators [such as slow reacting substance (SRS) and leukotrienes].²⁶ It has been demonstrated that steroids *in vitro* decrease the formation of collagenase²⁷ and stimulate the production of proteoglycan thus preserving matrix integrity.²⁸ Intra-articular steroid does not work by chemical synoviorthesis⁸ via destruction of hypertrophic synovial membrane. It is not curative.

Technique

Observation of a rheumatologist or orthopaedic surgeon skilfully injecting joints followed by careful practice is the best way to master technique. Success requires good knowledge of anatomy, great care and experience. Aspiration of joint effusion before steroid injection gives improved result²⁹ probably by removing inflammatory mediators and by decreasing pressure within the joint, thus lessening pain, stretching and instability of ligaments as well as damage to joint surfaces. Washout in addition to aspiration gives a slightly better result, but washout alone is not as useful.³⁰ Intra-articular steroid should not be injected at the time of arthroscopy or joint surgery because of the risk of sepsis.³¹⁻³³

Imaging (Before and After Injection)

Magnetic resonance imaging (MRI) with Gd-DTPA (Gadolinium diethylene-triamine-pentaacetic-acid) contrast is useful to identify in detail inflamed tendon sheaths and joints requiring steroid injection (for example in the painful ankle or foot) as well as on follow up to assess improvement.” Ultrasound images though not as detailed as MRI provide a rapid means of differentiating pannus, effusion and popliteal cysts, and may be more readily available than MRI. X-rays show effusion as widening of the joint space but are more useful to visualise bony changes.

Steroid Choice and Amount

In general, the duration of action of intra-synovial steroid is related to its aqueous solubility.¹⁴ Steroids which have been used for intra-articular injection include cortisone, hydrocortisone acetate, dexamethasone, methylprednisolone acetate, betamethasone acetate and phosphate, prednisolone t-butyl acetate, triamcinolone diacetate, triamcinolone acetonide and triamcinolone hexacetonide, methyl 20-dihydroprednisolone and steroids entrapped in liposomes. A list of some intra-articular steroid preparations with the recommended doses for adult rheumatoid knee synovitis and duration of action is found in Table II. A soluble steroid such as hydrocortisone diffuses rapidly out into the bloodstream. Its local effect is less and briefer compared to relatively insoluble microcrystalline suspensions. Triamcinolone hexacetonide (TH) being the

most insoluble has the greatest and longest local effect. However, this is accompanied by a greater risk of crystal synovitis, fat atrophy,³⁴ damage to surrounding tissue or tendons and calcification. For large joints, TH has been demonstrated to have better efficacy clinically and by thermography as well as longer duration of action compared to other steroids.³⁵⁻³⁷ Leakage of steroid into the surrounding tissue is more likely from small joints. Thus TH is best used for large joints such as the knee or ankle while a more soluble steroid like hydrocortisone may be safer for small joints, tendons sheaths and bursae.

Attempts to increase efficacy, prolong duration of local effect and minimise systemic side effects have been made via the incorporation of steroid esters into liposomes.^{38,39} Dingle et al³⁸ showed that steroid entrapped liposomes exert much greater anti-inflammatory effect in experimental rabbit arthritis than comparative doses of a microcrystalline steroid. However, in 6 human patients, improvement was short lived, lasting for only 2 weeks.³⁹ A newer synthesized corticosteroid which is metabolised to an inactive form after systemic absorption, methyl 20-dihydroprednisolone⁴⁰ would theoretically be ideal for local anti-inflammatory activity without suppression of the hypothalamic-pituitary-adrenal axis.

Important considerations which may determine a suitable dose of steroid to be injected into each joint include the size of the joint, its degree of inflammation, the size or body weight of the patient, the potency of the steroid when injected intra-synovially, and its duration of action which depends on aqueous solubility, synovial surface area and synovial vascularity.

Anaesthesia/analgesia/sedation

The child should be kept still to ensure correct placement of needle, maximal aspiration of contents and minimal risk of complications such as steroid leak and

damage to intra-synovial structures. The procedure should be as pain free and atraumatic as possible. A short-acting general anaesthetic (GA) is ideal in younger children, those needing injection to multiple joints, small joints, difficult joints with adhesions, deep joints, joints with possible deranged anatomy from longstanding disease, tendon sheaths and those needing casting for flexion contractures. GA is also useful for those with previous bad reaction to midazolam and when injecting powerful oxidising agents such as osmic acid for chemical synovectomy. Alternatively local anaesthesia with midazolam sedation may be sufficient for older children and those with few large joints needing injection. Midazolam provides amnesia as well as sedation but does not provide pain relief and some children still move when under midazolam alone thereby making injection difficult. Pethidine may provide further sedation and pain relief. A local anaesthetic to the skin such as Emla® (prilocaine 2.5%, lignocaine 2.5%) or lignocaine to skin⁵ applied a half hour earlier takes away the initial sharp pain from needle entry. Steroids can be injected alone into the joint or with intra-articular lignocaine which decreases pain and which also could arise from chemical synovitis.

Post Injection Rest

Post injection rest may enhance the efficacy of intra-articular corticosteroid in reducing inflammation^{41,42} by keeping the steroid in the joint longer and by preventing overuse of damaged joints. The need for additional systemic medication as well as repeated joint injection is thus reduced. Chakravarty et al⁴¹ found that strict inpatient bed rest after knee injection gave a more prolonged duration of clinical response compared to routine outpatient injections in adults with arthritis. Richards⁴² described how post injection rest even for short periods and restricted walking and standing improved pain and swelling. Immobilisation may be provided by simple

TABLE II: INTRA-ARTICULAR CORTICOSTEROID PREPARATIONS: RECOMMENDED DOSES FOR RHEUMATOID KNEE SYNOVITIS AND DURATION OF ACTION

Generic name	Proprietary name	Dose (mg)	Mean duration of response (days)
Hydrocortisone acetate		37.5-100.0	6;40
Dexamethasone acetate	Decadron LA	5	8
Prednisolone acetate	Metacortelone	30	8
Triamcinolone diacetate	Aristocort forte	20-30	8
Methylprednisolone acetate	Depo-Medrol	30-40	
Betamethasone acetate and phosphate	Celestone Soluspan	0.6-5.0	9
Hydrocortisone tertiary butylacetate (TBA)		25.0-37.5	12;30
Prednisolone TBA	Hydeltra-TBA	20-40	15
Triamcinolone acetonide	Kenalog-40	10-30	14
Triamcinolone hexacetonide	Aristospan	10-40	21;59;90

Adapted from: Gray R G, Gottlieb N L. Intra-articular corticosteroids. An updated assessment. Clin Orthop Rel Res 1983; 177:235-6314.

splints and bed rest after joint injection. If this is not possible, limitation of activity with minimal weight bearing may be helpful.

Efficacy

Intra-articular steroids are rapidly taken up by synovial cells and clinical improvement is often seen within hours to days,^{7,8} and usually maintained for several weeks or months. The response rate is generally high with a marked degree of improvement. Failures are usually related to poor general disease control or intra-synovial septa.

In the majority of patients reported, the duration of effect was long lasting. Between 60% and 70% of injected joints followed up remained in remission for at least 6 months.⁵⁻⁷ At one year, 45% to 55% were still in remission.^{5,6,8,37} At 2 years, 16% to 37%^{5,7} were still in complete remission. Relapses can occur with or without a trigger, but the percentage of cases needing re-injection is low and response to subsequent injections remains good (Table III).

Predictor of Response/outcome

Allen et al⁵ reported that good outcome was correlated with boys and young age, however Hertzberger-ten Cate et al⁷ did not find any correlation with sex or age of onset. The beneficial effect of injection did not correlate with erythrocyte sedimentation rate,^{6,7} antinuclear antibody status, HLA status,^{5,7} size of involved joint at onset or uveitis.⁷ Luukkainen et al⁴³ found synovial fluid protein, lactate, IgG and IgM to be lower in patients with improved tenderness score after steroid injection but unrelated to decrease in circumference of the knee joint.

Failure of steroid injection could be due to incorrect placement of steroid, insufficient or short-acting steroid, intra-synovial septa (which can be visualised on ultrasound)⁴⁴ or poor general disease control⁶ (for example in polyarticular disease).

Early *relapse* is associated with poor general disease control (i.e. active disease), early spread, extending dis-

ease in pauciarticular JCA,⁶ longstanding disease,^{5,7} and insufficient or short-acting steroid.⁷ Relapse may be associated with viral infection, trauma or vaccination, or may occur without a precipitant. Recurrent or resistant cases which fail to respond to repeated steroid injection may need synovectomy (medically for example with osmic acid, or surgically).

Contraindications

Infection in the form of definite or even suspected articular infection (including tuberculosis), peri-articular cellulitis or sepsis,¹ is an absolute contraindication to intra-articular steroid injection. Steroid injections should also be avoided in the presence of joint prosthesis, during arthroscopy or joint surgery and within the few days preceding such procedures as sepsis may occur.³¹ Damaged and unstable joints should not be injected for fear of accelerated cartilage destruction. Allergy or hypersensitivity to corticosteroids or its vehicle are also contraindications. Hemarthrosis per se is not a contraindication, but may reflect underlying infection, fracture or ligamentous tear.¹⁴

Complications

When used carefully and judiciously, intra-synovial steroid injections are well tolerated with few complications. These are summarised in Table IV. The commonest complication is subcutaneous fat atrophy⁴⁵ while infection can be serious.³¹⁻³³ Other potential side effects^{1,14} include flare (crystal synovitis), haemorrhage, tendon rupture, nerve injury, peri- and intra-articular calcification, articular damage, bony change, systemic absorption, depression and facial flushing.

Subcutaneous atrophy^{5-7,45-49} is the commonest complication of intra-articular corticosteroid injection and has been reported in 8.3% of injections. Steroid leak can result in fat atrophy with thinning and depigmentation appearing over the first few months following injection. It appears more frequently in young children⁴⁶ and smaller joints such as the metatarsal phalangeal joints (50%) as opposed to wrists (22%), ankles (16%) and

TABLE III: EFFICACY OF JOINT INJECTION-REMISSION, REINJECTION PERCENTAGES

Author	Number of children	Number of joints	Diagnosis	Remission at 6 months	Remission at 1 year	Remission at 2 years	Percentage joints reinjected 2x, 3x, 4x
Hertzberger-ten Cate ⁷ (1990)	21	27	Pauci-JCA	70%		37% (30 months)	
Allen ⁵ (1986)	40	49	JCA/SPA	63%	45%	16%	16%, 5%, 2%
Earley ⁶ (1988)	60	83	Pauci-JCA	60% (at 3 months)	55% (excellent) 77% (good or excellent)		13%, 2.5%, 0
Hupertz ⁸ (1995)	21	21	Pauci/Poly JCA/SPA	-	50% normal		5%, -, -

Pauci-JCA: pauciarticular juvenile chronic arthritis; Poly-JCA: polyarticular juvenile chronic arthritis; SPA: spondyloarthropathy

TABLE IV: COMPLICATIONS OF INTRA-SYNOVIAL STEROID INJECTIONS

	Early (within hours to days)	Late (days, weeks or months later)
Local	Flare (crystal synovitis) Vascular injury/haemorrhage Nerve injury Infection	Subcutaneous atrophy Tendon rupture Periarticular calcification Articular and bony damage
Systemic	Flushing Depression Effect on hypothalamic-pituitary axis	?Effect on growth

knees (5.6%). It has been observed on the skin along the course of lymphatic vessels which drained an injected knee.⁴⁹

Spontaneous improvement can occur over months or years but is not universal.^{6,46} It can be minimised by preventing steroid leak into the subcutaneous tissue.* This is done by careful placement of needle into the joint, ensuring that either synovial fluid is obtained or that saline flows in easily before instilling steroids, by relieving pressure in the joint by aspirating to as near dryness as possible before instilling steroid, by obliterating the track by "Z" entry, by flushing the needle track after injection with saline and by avoiding excessive movement and weight bearing after injection.

Post injection steroid flare (crystal-induced synovitis)^{7,14,50} has been reported in about 2% cases.⁵⁰ It is thought to be a crystal-induced arthropathy, in which crystals of long-acting steroid are phagocytosed, releasing inflammatory mediators. The joint becomes painful, red and swollen within hours of steroid injection but usually subsides spontaneously or with an ice pack. Accompanying synovial fluid pleocytosis and fever may last 72 hours.⁷ Occasionally it may require the injection of a water soluble steroid preparation such as hydrocortisone.¹ If post injection synovitis is severe or prolonged re-aspiration is mandatory to exclude septic arthritis.

Infection can be very serious but is reportedly rare in adults³¹⁻³³ and has not been reported in children. An adult with fatal staphylococcal sepsis was reported following injection of the hip with TH.³³ Using a strict aseptic technique, the Mayo Clinic⁴⁷ orthopaedic department reported no cases of infection from over 3000 joint injections done annually. Using sterile skin preparation but no gloves, infection has complicated 1/14 000 to 1/50 000 steroid injections in adults.^{12,48} Intra-articular corticosteroids should not be injected during surgery or arthroscopy, or into joints with prosthesis as septic arthritis has complicated steroids injected under these conditions.^{31,32} Organisms include *Staphylococcus aureus* (commonest), gram-negative organisms (rarely, usually when there is underlying gastrointestinal or gastro-

urinary disease, or intra-abdominal infection), mycobacteria⁵¹ and fungi.

Tendon rupture is rare and may be due to direct injection of steroid into a ligament which decreases its tensile strength and destroys fibroblasts.⁵² Tendon rupture may be prevented by carefully injecting steroid into the sheath of the tendon and not into its substance, by avoiding frequent injections and by using hydrocortisone instead of TH for tendon sheath injections.

Vascular injury is a potential complication especially around the flexor hallucis tendon near the ankle (posterior tibial artery), anterior ankle joint (dorsalis pedis artery), back of the knee (popliteal artery) and anterior hip (femoral vessels). Proper care, knowledge of anatomy, palpation of pulses and aspiration before injection will avoid vascular injury.

*Haemorrhage*⁵³ is rare. Careful injection and adequate analgesia to prevent movement will minimise traumatic aspiration. A minimal amount of blood leak is not unexpected but if a large amount of blood is found on aspiration, one should exclude haemarthrosis from trauma (such as fracture by X-ray, or ligaments injury by MRI), bleeding dyscrasia (by checking platelet count and coagulation profile), as well as villonodular synovitis or haemangioma (by MRI).

Peri-articular or intra-articular calcification^{46,50,54-58} has been reported to occur in 1 %⁵⁴ to 34%⁵⁵ of joints injected, and is associated with long-acting corticosteroids and injection through the infra-patellar fat pad of the knee (50%).⁵⁵ It is not considered one of the radiological features of JCA and its cause is uncertain.⁵⁸ Calcification may be noted to appear from months to years after injection⁴⁶ and may be linear, granular⁴⁶ or punctate. It may be periarticular,⁴¹ on the joint capsule,^{46,57} intra-articular⁴⁶ or on tendon sheaths.⁵⁶ The majority of steroid-related calcification is asymptomatic and spontaneous resolution can occur.⁴⁶

Articular and Bony Damage

Intra-articular corticosteroid use in JCA has not been associated with significant joint or bony damage, even

after repeated injections.⁵⁴ It is potentially toxic to articular cartilage with the concept of "corticosteroid arthropathy" largely based on subprimate (rabbit)⁵⁹ animal studies and a few anecdotal case reports. However, limited investigations of primate cartilage⁶⁰ (monkeys) and human explant models⁶¹ have shown no significant long-term adverse effect on cartilage. Steinberg et al⁶² showed that the negative effects of corticosteroids on proteoglycan synthesis are more than offset by its favourable action on lysosomal enzymatic proteoglycan breakdown.

Sparling et al⁵⁴ reported a case of avascular necrosis occurring after steroid injection in a hip which was painful and already rapidly degenerating before steroid injection but it is not certain whether the avascular necrosis was due to steroids, to the underlying chronic arthritic disease, or to the effect of a combination of steroids on a degenerate weight bearing hip joint.

Charcot-like joints (clinically and radiologically) may result from overuse of diseased weight-bearing joints after pain relief from steroid injection, with bone fragmentation producing loose bodies.^{47,63}

Systemic absorption of steroid from the joint space definitely occurs as evidenced by decreased joint swelling at distant sites and decreased plasma cortisol reflecting hypothalamic pituitary adrenal (HPA) axis suppression.⁶⁴ Greater systemic effect is seen if multiple joints are injected and if the same dose of steroid is split into 2 joints instead of given into one joint due to greater absorption.

The beneficial side effect is that inflammatory activity in uninjected joints may also decrease. Although suppression of the HPA axis may occur especially if several joints are injected, it is almost always clinically insignificant and brief if injections are not given at close intervals. Hupertz et al⁸ did not find impaired statural growth in children after intra-articular steroid injection.

Radioimmunoassay^{65,66} shows peak levels between 2 and 12 hours after injection. Cortisol (adrenal) suppression may last from 12 hours to 7 days depending on the dose and type of corticosteroid used.

Rarely, other side effects^{1,14} have been reported such as transient facial flushing, nausea, weakness, depression or dysphoria as well as hypersensitivity reactions to the corticosteroid, the vehicle or the local anaesthetic.

Conclusion

Intra-synovial corticosteroids are safe, have rapid action, and provide clinically worthwhile remission. They are useful in pauciarticular JCA or polyarticular JCA to target a small number of inflamed joints, tendon sheaths or bursae.

Triamcinolone hexacetonide is a long-acting microcrystalline steroid suitable for injection of large

joints. A shorter acting soluble steroid such as hydrocortisone acetate may be safer for small joints and tendon sheaths. Appropriate medication, rest, physiotherapy should be continued as necessary. Intra-synovial steroids are generally well tolerated. The commonest complication is subcutaneous fat atrophy while other potential complications are rare.

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