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Intra-articular corticosteroid injections in juvenile idiopathic arthritis

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Therapeutic intervention with intra-articular steroid injections in juvenile idiopathic arthritis (JIA) has evolved from experience with adults with inflammatory joint disease, with the earliest report being published in 1951.¹ The technique has subsequently been introduced into paediatric rheumatology practice, although much of the evidence supporting its use remains anecdotal or based on open, non-controlled studies. This review examines the body of evidence relating to many aspects of treating children with JIA with intra-articular steroids, and is approached from both a medical and a physiotherapy perspective. Where appropriate, important areas for future research are identified and discussed.

For readers unfamiliar with the current classification of arthritis in children, the International League of Associations for Rheumatology (ILAR) has recently proposed criteria by consensus for the classification of childhood arthritis under the term JIA.² This replaces and unifies the previous classification criteria, juvenile chronic arthritis and juvenile rheumatoid arthritis, which were largely used according to geographical location. JIA describes the disease manifest by arthritis developing before the age of 16 years for which no specific cause can be found. JIA, as in the classification criteria it replaces, is further subdivided according to the onset pattern of the arthritis into: oligoarthritis (arthritis affecting one to four joints in the first six months of disease); polyarthritis (more than four joints affected during the first six months); and systemic arthritis (arthritis accompanied by a range of systemic features). The remaining subgroups are psoriatic arthritis, enthesitis related arthritis (largely made up of HLA B-27 related disease), and finally a group undefinable according to current knowledge referred to as "other arthritis".

INDICATION FOR INTRA-ARTICULAR STEROIDS IN JIA

The goal of directing potent anti-inflammatory treatment into an inflamed joint is the rapid resolution of synovitis. In oligoarthritis local treatment may lead to complete resolution of the signs and symptoms of arthritis, thus obviating the need for regular systemic therapy. In children with polyarticular JIA, the strategy of multiple intra-articular injections to induce disease remission, while simultaneously initiating therapy

with disease modifying agents, has been proposed.³ Others have instead used systemic steroid therapy as an alternative.⁴ In other situations local intra-articular steroids may be used to treat an arthritis flare in children already maintained on second line agents. This may avoid increasing the dose and hence potential toxicity of such drugs. To date there have been no controlled trials of intra-articular steroids versus systemic agents in any of these contexts in children with JIA.

Although effective in all subtypes of JIA, it is to treat oligoarthritis that intra-articular steroid injection is most frequently used. In oligoarthritis, intra-articular corticosteroids have traditionally been reserved for use in children with arthritis where non-steroidal anti-inflammatory drugs (NSAIDs) have been ineffective in controlling the disease.⁵ However, many paediatric rheumatologists now use intra-articular steroid injection early in the disease to rapidly resolve synovitis, provide pain relief, facilitate or obviate physiotherapy and rehabilitation, and allow the withdrawal or avoidance of regular systemic treatment.⁶ The patient may return to normal activity much more rapidly than when treated with NSAIDs alone. Complications such as joint contracture may be avoided. When used within two months of diagnosis, and if necessary repeatedly, intra-articular steroids have been shown to prevent leg length discrepancy in oligoarthritis, which is a well recognised complication.⁷ There remains the possibility that the very early use of intra-articular steroids in inflammatory joint disease would mean treating some children whose arthritis may have been naturally self limiting, but in doing so these children would have a more rapid relief of symptoms and subsequent return to normal function.

CHOICE OF INTRA-ARTICULAR STEROID PREPARATION

Several steroid preparations with different pharmacological properties are available for intra-articular injection in children (see table 1). In general those with lower solubility have a longer duration of action. In oligoarticular disease, triamcinolone hexacetonide induced significantly better improvement in knee swelling and stiffness

See end of article for authors' affiliations

Correspondence to:
Dr G Cleary, Royal
Liverpool Children's
Hospital, Eaton Road,
Liverpool L12 2AP, UK;
gavin.cleary@talk21.com

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Abbreviations: AVN, avascular necrosis; JIA, juvenile idiopathic arthritis; MCP, metacarpophalangeal joint; MR, magnetic resonance; MTP, metatarsophalangeal joint; NSAID, non-steroidal anti-inflammatory drug; PIP, proximal interphalangeal joint

Table 1 Relative solubility and potency of intra-articular corticosteroids

Preparation	Solubility	Efficacy
Hydrocortisone acetate	High	Poor
Methylprednisolone acetate	Medium	Moderate
Triamcinolone acetonide	Low	Good
Triamcinolone hexacetonide	Low	Excellent

than betamethasone in the first randomised controlled trial of intra-articular steroid preparations.⁸ In an important randomised controlled trial of triamcinolone hexacetonide (mean dose 1 mg/kg) versus triamcinolone acetonide (mean dose 1.1 mg/kg) in oligoarthritis, a significant improvement in the hexacetonide group was maintained at two years follow up.⁹ Similar benefit from triamcinolone hexacetonide over acetonide, with poor response to hydrocortisone, was noted in the adult rheumatoid knee.¹⁰ In a non-randomised retrospective comparison of triamcinolone hexacetonide (mean dose 0.7 mg/kg) versus methylprednisolone acetate (mean dose 1.5 mg/kg) for knee injections, Honkanen *et al* found that the remission rate was significantly higher in the triamcinolone group.¹¹ On the basis of these studies and from considerable anecdotal evidence, triamcinolone hexacetonide is established as the agent of choice, making the current worldwide difficulties of obtaining the product all the more disappointing.

The dosage regime for triamcinolone hexacetonide (Leder-span) currently used by the major paediatric rheumatology centres in the UK is 1 mg/kg for large joints (knees, hips, and shoulders) and 0.5 mg/kg for smaller joints (ankles, wrists, and elbows).¹² For the hands and feet, 1–2 mg/joint for MCPs/MTPs, and 0.6–1 mg/joint for PIPs may be used. If triamcinolone acetonide is being used, doses are doubled, although because of the concentration of the preparation (Kenalog) the volume of fluid injected remains the same.

SEDATION FOR INTRA-ARTICULAR INJECTION IN CHILDREN

Intra-articular injection in JIA may be performed under general anaesthesia, conscious sedation, or local anaesthesia alone. Young children, or those requiring multiple joint injections, will require general anaesthesia. Some paediatric rheumatology units routinely use general anaesthesia for intra-articular injection. With modern anaesthesia techniques the children can often receive their joint injection in the anaesthetic room under a short general anaesthetic, and can be treated as day cases.

Conscious sedation may be achieved with intravenous benzodiazepines such as midazolam. In our experience the distress resulting from insertion of the intravenous cannula has often rendered this technique unsatisfactory. The potential for respiratory depression means this method should only be used when adequate facilities for paediatric resuscitation are available. However, some units have developed expertise with its use, and the additional amnesic effect is well recognised.¹³

The readily available inhaled mixture of 50% nitrous oxide and 50% oxygen (Entonox) is a safe and effective agent in children undergoing painful procedures.¹⁴ When used to facilitate joint injection in children with JIA the technique allows for a short stay in hospital, avoids the risks associated with either intravenous sedation or general anaesthesia, and usually the procedure can be performed quickly after the need is recognised. In an open study, children with JIA reported a median pain score of 1 on a 0–10cm visual analogue scale following the use of Entonox during intra-articular injection.¹⁵

Whichever technique is used, adequate anaesthesia or relaxation must be obtained to ensure accurate injection. It is likely that local facilities and individual preferences and experiences will be important factors in the choice of technique.

SPECIFIC JOINT INJECTION TECHNIQUE

A survey of adult rheumatologists revealed wide variations in individual practice with respect to joint injection technique.¹⁶ Of particular interest was that only 9.8% of respondents to this postal survey reported the routine use of surgical gloves. A recent telephone survey of paediatric rheumatologists in the UK also revealed wide inconsistencies in practice (P Livermore, personal communication). There was no consensus of opinion over issues such as flushing of the needle track with saline or local anaesthetic, mixing the corticosteroid preparation with local anaesthetic, and “pulsing” (administration by several small increments into an individual joint) of injections, especially into small joints, to minimise the risk of steroid leakage and subcutaneous atrophy. There is no evidence that wearing gloves reduces the risk of infection providing that a scrupulous no touch technique is employed, or that flushing the needle track or pulsing the injection is associated with a lower complication rate.

Prior to intra-articular steroid injection, aspiration of as much synovial fluid as possible is routinely performed by most clinicians. Although this practice has never been subject to controlled trials in JIA,¹⁷ it seems logical and may provide immediate symptomatic relief.

In adult patients rates of inaccurate injection as high as 50% have been reported.¹⁸ Similar studies have not been performed in JIA. Radiographic guidance for injection of certain joints is strongly recommended to ensure accuracy of injection. The subtalar joint in particular may be difficult to assess clinically. An improved outcome after the use of magnetic resonance (MR) scan to show synovitis in the subtalar joint, and injection into both tibiotalar and subtalar joint using radiographic guidance was shown by Remedios and colleagues.¹⁹ Injection into the hip joint, subtalar joint, and the shoulder should be done using radiographic guidance.²⁰ Accurate placement of the needle within the joint space can be determined by either ultrasound or by injection of radio-opaque contrast medium, with the choice of technique dependent on local expertise. For an overview of intra-articular injection technique, including joint specific landmarks, see Southwood²¹ and Doherty and colleagues.²²

PHYSIOTHERAPY INTERVENTION FOLLOWING INTRA-ARTICULAR STEROID INJECTION

The issue of post-injection rest, splinting, and physiotherapy regime remains controversial and has never been studied in a controlled trial in children. In adults the evidence is confusing and inconclusive. Chakravarty *et al* found a sustained and significant difference in improvement in clinical and laboratory features in patients who had 24 hours of strict bed rest post-injection.²³ McCarty *et al* concluded that longer periods of rest were useful,²⁴ while other studies have suggested that a rest period is not essential for intra-articular steroid injections to be beneficial.²⁵

In published paediatric studies there is no consensus approach, and wide variations in individual practice are revealed in table 2. With the paucity of information available to guide post intra-articular steroid injection management, a telephone survey of physiotherapists working with children with JIA in the UK was carried out (HD Murphy, unpublished data). A number of units treated all children as day cases, while a few admitted them for up to a week for intra-articular steroid injection followed by daily in-patient physiotherapy. The rest periods varied considerably and policies included 24 hours strict bed rest, 24 hours of light activity, 48 hours of

Table 2 Summary of post intra-articular injection management by study

Study	Post-injection management
Breit <i>et al</i> ²⁷	Daily physiotherapy, ice packs 3 or 4 times a day, rest for 24 hours (bed, wheelchair, splints)
Sparling <i>et al</i> ⁶	Immobilise joints only to treat flexion contractures
Job-Deslandre and Menkes ³¹	Immobilise with bandage 48 hours Night splints 1 to 2 months for contractures
Padeh and Passwell ²⁶	Non-weight bearing 24 hours
Allen <i>et al</i> ⁶	Splinting for contractures
Honkanen <i>et al</i> ¹¹	Non-weight bearing 24 hours

minimal weight bearing. The use of splints was also inconsistent; some therapists did not use splints, others only used them for the problem joint, and some applied them following every injection. The follow up physiotherapy was very variable: some children attended therapy 48 hours following injection, others were treated 1–2 weeks later or as the therapist's case load permitted. This survey showed that there is no consistent therapy regime following administration of intra-articular steroids in the UK. It is the author's belief that the majority of intra-articular injections can be performed on a day care basis, followed by 24 hours minimal weight bearing, followed by physiotherapy. It is not possible to enforce rest in ambulatory children, particularly the very young. In our experience splinting is rarely necessary to correct joint contractures because of the efficacy of the intra-articular treatment. All patients will benefit from physiotherapy post-injection. In those patients with contractures and decreased muscle power an intensive physiotherapy programme post-injection will be necessary, with individual treatment programmes being tailored to individual cases. With such a variety of regimes following intra-articular steroid injections there are no conclusions to be drawn. There is a need for controlled clinical trials to evaluate post-steroid injection management.

OUTCOME FOLLOWING INTRA-ARTICULAR STEROID INJECTION

Published studies on outcome following joint injection in JIA need to be interpreted with caution, as there is little consistency in the disease subtypes studied, definitions of improvement used, and the time scale used to measure response or failure of the treatment between studies. It is not established whether intra-articular steroid injection modifies the eventual outcome in JIA, and long term follow up studies are needed.

Padeh and Passwell reported complete resolution of joint inflammation in 246 of 300 joint injections in children with all subtypes of JIA.²⁶ Other positive outcomes reported in this study were the discontinuation of oral medication in 74.4% of children with oligoarthritis, and also the correction of joint contracture, slowing of the rate of discordant leg growth, resolution of Baker's cyst, and treatment of tenosynovitis.

The largest single cohort studied was that published by Breit and colleagues.²⁷ Of 1439 triamcinolone hexacetonide injections given to 194 patients with JIA, the median duration of improvement was 74 weeks, with the best effect seen after the first injection into an individual joint. The definition of improvement used in this study was a 50% reduction in a composite of six clinical examination features of synovitis. Furthermore it was noted that those with oligoarthritis presenting before the age of 5 years had the longest median duration of effect, and those with systemic onset arthritis the shortest. When the response in specific joints was analysed,

the median duration of efficacy varied according to joint and disease subtype. Duration of effect ranged from 34 to 120 weeks in the knee, to 11 to >48 weeks in the hips. The outcome of intra-articular steroid injection into individual joints has been reported in other studies. A good outcome following wrist injection was reported by Evans and colleagues.²⁸ Earley and co-workers achieved a remission rate of 77% at one year in knees injected with triamcinolone hexacetonide.²⁹

Other studies have utilised a total resolution of signs of arthritis as their outcome measure, with 60% of knees injected with triamcinolone responding to the treatment.¹¹ The only significant predictor of outcome in this study was the synovial fluid polymorphonuclear leucocyte proportion, with those children with higher counts having the poorest response to triamcinolone hexacetonide. Other studies have also attempted to identify predictors of outcome to intra-articular steroids. A logistic regression procedure was used for the analysis of response to triamcinolone hexacetonide in 94 patients (81 with oligoarticular onset disease) treated in one or both knees, in whom response was defined as complete resolution of synovitis at six months.³⁰ Erythrocyte sedimentation rate (ESR) was the only significant predictor of a favourable outcome. Sustained responders had a significantly higher ESR than those with recurrence of joint inflammation, leading the authors to speculate that in some patients the synovial inflammatory process is particularly sensitive to intra-articular steroid injection.

SIDE EFFECTS OF INTRA-ARTICULAR INJECTION

Although many studies have reported adverse effects, there is little conformity in the effects chosen to report, and to date there have been no prospective studies designed to specifically evaluate adverse effects resulting from intra-articular steroids in children with JIA. Subcutaneous atrophy is a well recognised adverse effect,^{5 8 26–29 31} with the highest incidence in a single study of 8.3% of patients.³¹ Resolution of the subcutaneous atrophy was noted in all cases after two years in one single study,²⁶ but persistent at four years in another.³¹ The risk of subcutaneous atrophy is minimised by scrupulous injection technique and by ensuring accuracy of injection (including by radiographic techniques). Conversely the risk is increased with the potency and duration of action of the injected preparation—that is, high for triamcinolone and low for hydrocortisone. Risk of extravasation is higher in small joints

There have been concerns that intra-articular injection may damage intra-articular structures. Objective evidence of safety of intra-articular steroid injection into joints in JIA was reported by Huppertz *et al*, by means of MR scans pre and post-procedure.³² In this study at 13 months follow up, cartilage integrity was well preserved in all joints treated with intra-articular steroids. Prior to intra-articular steroid injection, pannus was noted in seven joints, and at 13 months follow-up pannus was only present in two of these joints. By means of MR scan, Eich *et al* reported resolution of pannus that had replaced articular cartilage in the knee one month after intra-articular triamcinolone hexacetonide.³³

It is likely that following multiple intra-articular steroid injections (10 or more joints, including large joints), there is sufficient systemic absorption of steroid to produce a cushingoid appearance.³⁴ Although cosmetically unappealing, this is not associated with long term adverse effects and is short lived. Huppertz and Pfüller reported transient suppression of cortisol release detected by a low morning peak value of salivary cortisol.³⁵ In all cases studied (n = 22), the morning peak value of cortisol returned to normal after a median of 16 days (mean 10 to >31 days). No adverse events were recorded secondary to this transient adrenal suppression.

Other clinical and radiological parameters have been studied. In a retrospective non-blinded study, Sparling and colleagues discovered radiological abnormalities in 16 joints of 11 patients from a study cohort of 55 children.³⁶ The abnormalities included small patella, patellar osteochondritis dissecans, periarticular calcification, intraarticular tibial bony spur, and avascular necrosis (AVN) of the proximal femoral epiphysis and of the hip. However, all the abnormalities reported might have been attributable to the underlying inflammatory disease. In this study, the patient with symptomatic AVN of the hip showed progressive changes on serial radiographs of the joint taken before the injection. A series of intra-articular hip treatments was reported by Boehnke and colleagues,³⁷ in which no cases of avascular necrosis of the femoral head were noted.

In a different series of 15 children who underwent radiographically guided intra-articular hip injection for JIA, three developed avascular necrosis of the femoral head.³⁸ As it has been speculated that AVN of the femoral head arises as a consequence of increasing the intra-articular pressure with the steroid injection, the intra-articular pressure was allowed to equilibrate with atmospheric by removing the syringe from the needle hub before withdrawal. In this group the injected hip was immobilised with skin traction for three days, and night splinting or traction used for a further three months. Controlled trials of post-injection technique are needed to determine whether any particular technique is associated with an increased risk of AVN of the femoral head. AVN is a recognised complication of uncontrolled synovitis of the hip per se, and it remains controversial whether injecting a hip with pre-existing degenerative changes alters the risk of AVN subsequently developing. This is another question that can only be answered by a controlled clinical trial.

In a blind retrospective study, Gilsanz and Bernstein³⁹ reported a higher incidence of periarticular or joint capsule calcification, in 32 of 92 joints injected. The majority were non-symptomatic and detected coincidentally on radiological follow up, but in one case surgical removal of calcium deposit from the infra-patellar fat pad was necessary. The route of injection into the knee in this study (through the infrapatellar fat pad) was associated with an unusually high incidence of periarticular calcification.

There are no reported cases of septic arthritis in children in the actual joint injected with corticosteroids. Septic arthritis of the ankle 48 hours after intra-articular knee injection in a child with a respiratory infection has been reported.⁴⁰ The procedure should be postponed if the child has evidence of inter-current infection. A risk of 0.002% of septic arthritis associated with intra-articular corticosteroid injection is reported in the adult literature.⁴¹ Asepsis measures incorporating a good no touch technique must always be taken to prevent such a serious complication.

Unusual adverse effects also encountered include post-injection joint erythema and pain. This is thought to be a result of crystal induced synovitis, in which phagocytosis of steroid crystals in the joint results in the release of inflammatory mediators.⁴² This usually subsides spontaneously or with local ice application within a few days. Subluxation of the shoulders has been reported.⁴³ Acute anaphylaxis in adult patients given a combined preparation of methylprednisolone and local anaesthetic has been described.⁴⁴ Such an episode has never been reported in a child.

CONCLUSION

Intra-articular injection in JIA is a safe and rapidly effective treatment for synovitis. The procedure can be facilitated in an ambulatory care setting using local anaesthesia with or without conscious sedation, or under general anaesthesia, usually involving a day case admission to hospital. The optimum

choice of corticosteroid agent in paediatric practice is triamcinolone hexacetonide, but there are currently worldwide manufacturing difficulties, the outcome of which at the time of writing is uncertain. Triamcinolone acetonide is the most appropriate alternative agent. There is an overwhelming body of anecdotal evidence supporting the use of intra-articular steroid injection, particularly in oligoarthritis, but there is no data to confirm whether the technique is disease modifying in the long term. Because of a lack of controlled trial data it remains unclear whether multiple intra-articular injection of corticosteroid is more effective and less toxic than intravenous boluses of steroid to induce remission or treat a flare of established polyarticular JIA. Differences in reported incidence of adverse effects may reflect differences in individual practice, but at present there is no conclusive data to support particular techniques.

Authors' affiliations

A G Cleary, J E Davidson, Royal Liverpool Children's Hospital, Eaton Road, Liverpool L12 2AP, UK

H D Murphy, Wexham Park Hospital, Slough, UK

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