Intra-articular Steroid Injections in JIA

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Summary

Intra-articular steroids are an effective, important treatment for arthritis in children. Rapid treatment of synovitis is just as important in children as it is in adults. By quickly treating synovitis in a growing child the problems of flexion contracture, leg length discrepancy, and muscle atrophy can be avoided or at least minimized.

Intra-articular steroid injections are an important part of the treatment of childhood arthritis. They generally are very effective at squelching synovitis quickly and restoring normal function. They can be used at any stage in disease – early, later or for persistent disease. A single joint can be injected, or many at the same time. For the later, this usually requires general anesthesia for children. Some pediatric rheumatologists will prefer to use intra-articular injections rather than oral medications for children with only a few joints involved.

Efficacy in children

Canhao et al (1) reviewed 20 patients with childhood inflammatory arthritis that had received intra-articular (IA) triamcinolone hexacetonide. 56/61 (92%) had complete resolution of synovitis. Only 2 patients had no effect at all. Half of these patients however, relapsed 2 to 32 months later (mean 17 months). Over half of the patients were able to taper steroid dose and a third to decrease NSAID use. The dose used was not given in this brief report.

Bloom and colleagues (2) reported 121 IA injections in children with childhood arthritis: 37 pauci, 11 poly, 5 systemic and 8 spondyloarthropathy with a mean duration of disease 12.5 months (0.5-44months). 52% of patients remained in remission after 1 year, however 17% flared before 3 months. Systemic onset patients had the shortest effect, where as patients with poly disease on DMARDs had the longest effect from the intra-articular steroid. Triamcinolone hexacetonide (TH) had a more prolonged effect than methylprednisolone. Those patients with the longest response had >1mg/kg in their knees.

Padeh and Passwell (3) found IAS to be very effective for 71 children with inflammatory arthritis treated with 10 – 40 mg of triamcinolone hexacetonide. 27 patients had this done under general anesthesia, 3 joints were the maximum injected. All patients had resolution of synovitis but 18% experienced recurrence of synovitis within 2-6 months. The authors did not indicate if all active joints were injected or just one or a few. It is possible that complete suppression of synovitis in all joints could have a different effect than treatment of one of several active joints. The authors found correction of joint contractures and leg length discrepancies (decreased from 1.5 cm to 0.8 cm) 2.5 years later.

The issues of LLD and muscle atrophy are important, as these consequences of active synovial inflammation may end up being long term residua for children. Vostrejs and Hollister (4) examined 32 children with pauci-articular JRA involving at least one knee. In addition to aspirin therapy, all patients had daily home exercise programs of passive ROM, isometric strengthening, bicycling, stair climbing, and if indicated a night time splint to treat contractures. At the time of evaluation at a mean follow up of 4.5 years, patients had had active arthritis for 1-10 years. Two thirds of patients had a LLD of up to 2.5 cm and nearly half had measurable thigh atrophy. Of note, the LLD and thigh atrophy occurred primarily in the patients with onset of JRA

prior to 3 years of age. 12/13 children with onset of arthritis less than age 3 had a mean LLD of 1.4 cm while 11/13 children with early onset JRA had an average thigh circumference difference of 1.6 cm. In the patients with early onset arthritis, the length of the first episode of synovitis correlated with the development of a LLD. There was no correlation between the amount of LLD and the magnitude of muscle atrophy or the presence of muscle weakness.

Sherry et al (5) retrospectively evaluated whether IAS could effect this known residua of pauci-JRA. Children with lower extremity pauciarticular JRA before the age of seven that had been treated with IA triamcinolone hexacetonide were compared to a cohort who had received NSAIDS. At a mean of 42 months later the 16 children who were given IA steroids into a knee or ankle within 2 months of diagnosis had significantly less leg length discrepancy, less muscle atrophy and flexion contractures compared to the 14 children who were treated with NSAIDs.

Factors affecting the efficacy of intr-articular steroid injections

Honkanen and colleagues (6) retrospectively reviewed 79 patients with juvenile chronic arthritis with a median duration of disease of 4 months who had received IA steroids in addition to NSAIDs, (17 were also on DMARDs). The probability of a patient staying in remission was significantly greater in those receiving triamcinolone hexacetonide (TH) than methlyprednisolone ($p<0.0005$). The difference was still evident two years after injection. Further, those patients with less than 20% synovial fluid polymorphonuclear leucocytes tended to have longer remissions. Those with >80% PMNs in the synovial fluid had the worst response. Age of the patient, duration of the disease, onset type of arthritis or the ESR had no predictive value for the length of remission.

Ravelli et al (7), however, found that those patients who sustained complete clinical response at 6 months had a significantly higher ESR than those who did not in 94 children receiving IA TH (1mg/kg) in one or both knees. As with other studies, other patient characteristics such as gender, age at onset, disease duration, subtype of arthritis, medications, global assessment, CHAQ, CRP, involvement of other joints and amount of fluid aspirated were not predictive of a prolonged response. 31% had recurrence of synovitis by 6 months.

There are other investigations in patients with childhood arthritis and adult RA that also demonstrate the superior effectiveness of TH compared to other steroid preparations. Blyth and colleagues (8) prospectively compared hydrocortisone succinate, triamcinolone acetonide and triamcinolone hexacetonide (TH) administered IA into the knees of 300 patients with RA. TH was superior for pain relief 4 to 12 weeks later. There was no clear pretreatment measurement that predicted a more favorable response (age, amount of pain, ESR, amount of fluid withdrawn).

Some studies have suggested that there is a difference in response to IA steroids between subgroups of JIA. Breit and colleagues reviewed 1439 IA injections of TH in 194 children (368 were re-injections). The responses were significantly different among subgroups as follows: early-onset pauci = 121 weeks of efficacy, late onset pauci = 47 weeks, RF- poly = 105 weeks, RF+ poly = 63 weeks and systemic onset = 36 weeks. All patients were on an NSAID and many were receiving DMARDs as well.

The influence of synovial fluid withdrawal was prospectively studied by Weiroft and Uddenfeldt at the time of IA with TH into 191 knees of 147 patients with RA (10). After randomization, 95 patients had complete synovial fluid aspiration before IA and 96 did not. There was a significant reduction of relapse in the arthrocentesis group at 6 months ($p= 0.001$). However 6 of 8 patients in whom fluid could not be withdrawn had no relapse of arthritis. Additionally patients were not all followed up with examination, but rather encouraged to call if problems.

The issue of whether to rest the joint after injection or not has not been resolved. Some studies have instructed patients to “rest” the injected joint for 24 hours and a few for 48 hours, others do not feel this is important. This is difficult to accomplish in children, especially if their joints now feel much better.

Dr. Paul Emery took a unique approach with regard to the effectiveness of IAS.

He and colleagues initially treated 51 adults, with recent-onset oligoarthritis (<12 months, median 16 weeks), with IA methylprednisolone into ALL joints with synovitis (11). At 12 and 26 weeks, those patients that had complete resolution of synovitis

by 2 weeks continued their response. At one year, nearly 50% of the patients had return of synovitis. Failure to respond by 2 weeks indicates a high likelihood of persistent disease and may select patients that will need early intervention with other therapies. One wonders what the results would have been had TH been used. Since arthritis in a few joints has the potential to evolve into involvement of multiple joints, the eradication of synovitis early in the course of disease may be more likely to have a more effective and long lasting effect than trying to eradicate disease after it has been long established.

Side effects

Side effects are possible and consist of infection, early chemical irritation, skin atrophy and intra-articular calcification. The rate of infection is estimated to be less than 1 in 100,000. Atrophy of the skin and subcutaneous tissue over the injection area is probably the most common adverse event. Deslandre and Menkes (12) prospectively studied the occurrence of subcutaneous atrophy and calcifications in 48 children with arthritis that received 144 joint injections with TH. The overall occurrence of subcutaneous atrophy was 8.3% with it present after 5.6% of knee injections, 16% of ankles, 22% of wrists and 50% of MTP joints injected. Periarticular calcifications were found in only 4.9% of joints. This is in sharp contrast to the presence of calcifications, in children, after IAS in 30% of joints found by Glisanz and Bernstein (13). The majority of the calcifications that they found were in the periarticular tissues or in the joint capsule, and were rarely intra-articular. In only one of 32 joints with calcification was it symptomatic.

Probably the most important aspect affecting this problem is whether the injection is actually in the joint. Jones et al (14) investigated the accuracy of joint injections in 87 patients that had joint injection with steroid and contrast material. Radiographs of the injected joints revealed that only 56 of 87 injections were actually intra-articular! In the knee, shoulder, wrist, ankle and elbow, the injections were not in the joint 1/3 of the time. This is certainly strong evidence to encourage the use of fluoroscopy or ultrasound guidance at the time of IAS.

Some investigators have worried about the effects of IA steroids on developing cartilage. Huppertz and colleagues (15) assessed 21 joints in children at 7 weeks after IA steroid and 14 joints 13 months after IA steroid with gadolinium enhanced MRI. All joints had improvement. MRI revealed long-lasting suppression of inflammation and pannus without evidence of toxic effects on cartilage. Statural growth was not affected. Of interest were 8 patients who had no synovitis by exam, but had abnormal MRI indicating persistence of pannus.

What about systemic effects? Emkey et al (16) prospectively investigated markers of bone turnover in adults with RA that had received a single IA xylocaine (n=11) or xylocaine + triamcinolone acetonide (n=29). Serum cortisol levels significantly decreased by day 3 in those patients receiving TA, but were back to pretreatment levels by day 28. Markers of bone resorption did not change, but bone formation markers were significantly decreased at days 1-7 and were back to normal by day 14. The authors concluded that the transient systemic effect on bone formation may be better for overall bone metabolism than continuous use of oral steroids.

Investigations using both in vitro human cartilage explants and primate models have not demonstrated long term adverse effects of repeated use of IAS (17). Despite the wide spread use of IAS over many years, there are relatively few anecdotal reports of steroid arthropathy in humans.

Intra-articular injection technique

Every center has their own standard procedures for steroid injections of joints. We use triamcinolone hexacetonide whenever it is available, at a dose of 1mg/kg for large joints, 0.5mg/kg for medium sized joints and generally 0.1 – 0.2 cc for fingers and toes. For TMJs, one usually uses 1 cc for age 12 and above and smaller amounts for younger children.

For the older child we use ethyl chloride spray, followed by 1% buffered lidocaine. Some children prefer to have EMLA cream applied for an hour ahead of time, but others find the anxiety of waiting too great.

Children under age 6 can often do well with oral midazolam (0.3mg/kg), with an oxygen monitor in the clinic. For difficult joints, those that require fluoroscopy (such as subtalar or hip joints), or for

multiple joint injections at the same time, quick general anesthesia is an excellent choice. Cleary et al (18) reported good pain control during IAS in children with patient administered nitrous oxide. With a quiet child accurate injections can quickly be accomplished.

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