

# Is There a Role for Arthroscopic Synovectomy in Oligoarticular Juvenile Idiopathic Arthritis?

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**ABSTRACT.** *Objective.* To evaluate the longterm efficacy and safety of arthroscopic synovectomy (AS) in children with oligoarticular juvenile idiopathic arthritis (JIA).

*Methods.* Patients with oligoarticular JIA and persistent monoarticular involvement, refractory to non-steroidal antiinflammatory drugs (NSAID) and/or intraarticular corticosteroid (IAC) treatment underwent AS followed, one month later, by IAC. The efficacy of AS was prospectively evaluated, and a good response was defined as absence of synovitis or  $\geq 60\%$  decrease in articular score from baseline. Clinical, laboratory, and radiological variables (radiographs, ultrasound, magnetic resonance imaging) were noted to examine possible factors predictive of the result.

*Results.* Twenty-two patients with JIA (15 female, 7 male) entered the study. Age at disease onset was 77 months (range 13-168). Mean disease duration at the time of AS was 50 months (3-324). Nineteen knees, 2 temporomandibular joints, and one shoulder were treated; the mean followup was 57 months (12-168). Thirty-six percent of patients relapsed within 12 months of the procedure, 14% within 24 months, and 14% thereafter. Eight patients (36%) remain in remission after a mean 65 months' followup. Variables found to be predictive of good response were persistent monoarticular course ( $p = 0.004$ ), short disease duration at the time of AS ( $p = 0.03$ ), and normal erythrocyte sedimentation rate and C-reactive protein at baseline ( $p = 0.008$  and  $0.01$ , respectively).

*Conclusions.* AS is a safe but only partially effective procedure in patients with oligoarticular JIA. Best results are achieved early in the disease course in children with persistent monoarticular involvement and no evidence of systemic inflammation. (First Release Aug 1 2006; J Rheumatol 2006;33:1868-72)

## Key Indexing Terms:

JUVENILE ARTHRITIS

SYNOVECTOMY

THERAPY

ARTHROSCOPY

Juvenile idiopathic arthritis (JIA) is a heterogeneous group of diseases, each subtype showing different clinical features, response to therapy, and outcome. Oligoarthritis affects up to 60% of patients with JIA and presents various degrees of articular involvement, ranging from monoarthritis, persistent oligoarthritis in which 4 or fewer joints are involved, to extended oligoarthritis in which more than 4 joints are involved after the first 6 months of disease<sup>1</sup>. Longstanding disease may lead to periarticular muscle atrophy, ankylosis, and leg length discrepancy.

Arthroscopic synovectomy (AS) is a relatively simple procedure that enables subtotal removal of synovial tissue. When compared to open synovectomy, AS shows many advantages such as less invasiveness, low morbidity rate, and rapid func-

tional recovery<sup>2-4</sup>. In children, this procedure represents a valid tool for the diagnosis of monoarticular pathology<sup>5</sup> and for treating other conditions such as traumatic articular lesions, pigmented villonodular synovitis, and hemophilic joint disease<sup>6-8</sup>. The indication for AS in patients with JIA is still controversial.

We evaluated the longterm efficacy and safety of AS in a cohort of children with oligoarticular JIA.

## MATERIALS AND METHODS

*Patients.* The study group comprised children followed at the Paediatric Rheumatology Unit of the University of Padua. All patients fulfilled diagnostic criteria for oligoarticular JIA<sup>1</sup>, had persistently active single joint involvement refractory to nonsteroidal antiinflammatory drugs (NSAID) and/or to one or more intraarticular corticosteroid (IAC) treatment. Patients with polyarticular, systemic, or oligoarticular JIA with active disease in more than one joint and/or treated with systemic steroids or disease modifying antirheumatic drugs (DMARD) were excluded from the study.

*Laboratory investigations.* At baseline the following laboratory investigations were performed: blood cell count, antinuclear antibodies (ANA, considered positive with a titer greater than 1:80 on Hep2 cell line), erythrocyte sedimentation rate (ESR, normal  $< 30$  mm/h), and C-reactive protein (CRP, normal  $< 6$  mg/l).

*AS procedure.* AS was performed under general anesthesia using a 2.7-4.0 mm 30° arthroscope for big joints, such as knee and shoulder, and a small-bore 1.9 mm glass lens arthroscope for small joints such as wrist and temporomandibular joint (TMJ).

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A suction chondrotome with rotating blades was used to remove the largest amount of synovial membrane as efficiently as possible. The joint was washed with abundant saline solution during the procedure.

NSAID therapy was stopped one week before AS to avoid excessive bleeding. For patients who had been treated with IAC, AS was allowed after a washout period of at least 6 months. Patients were discharged the next day and an intensive physiotherapeutic and pain management regimen was adopted in an outpatient setting.

To better control residual synovial inflammation, one month after AS, patients received IAC treatment with triamcinolone hexacetonide at a dose of 1 mg/kg of body weight up to 40 mg for large joints (knee, shoulder) or 0.3 mg/kg for smaller joints. Patients were advised to avoid weightbearing for at least 72 hours after injection.

**Joint assessment.** Clinical assessment was performed at baseline and 1, 3, 6, 12, and 24 months after the procedure and then once a year or in case of relapse. On each observation 4 variables were recorded: swelling on inspection, limitation of range of motion, pain on passive movement, and warmth to touch, as proposed as part of the Preliminary Core Set of Outcome Measures for JIA<sup>9</sup>. For each joint, a score ranging from 0 to 3 was attributed to each variable: 0 normal, 1 mild, 2 moderate, 3 severe. The articular score was then obtained by summing the single score of each variable. A good response was defined as absence of synovitis or as a decrease in joint inflammation leading to a reduction of the articular score greater than 60% from baseline. Relapse was defined as reappearance of arthritis after a period of good response, as defined above. Remission was defined as absence of synovitis without therapy for at least 2 years.

Joint radiographs were performed to exclude erosions. Articular ultrasound (US) and/or gadolinium-enhanced magnetic resonance imaging (ge-MRI) were also obtained to document the degree of synovial hyperplasia.

**Data analysis.** The 2 groups of patients, with good or poor response to AS treatment, were compared according to the following variables: sex, age at time of treatment, age at disease onset, disease duration, age at AS treatment, course of arthritis (oligoarticular or monoarticular), type of joint treated, ANA, ESR, and CRP at baseline, and previous therapy. All variables were considered for their potential effect on outcome. Differences between groups were analyzed by t test, chi-square test, or the Fisher's exact test, as appropriate.

The primary outcome variable was defined according to the articular score at 6, 12, and 24 months, then yearly after the procedure. Efficacy of the treatment was expressed as percentage of positive result or in terms of relative risk (RR) of relapse. The 95% confidence interval (CI) defined the degree of significance and the accuracy of the estimate.

A secondary analysis was performed to assess the potential role of each variable as predictor of positive response.

Analysis of time to relapse was undertaken according to the Kaplan-Meier procedure and compared by the log-rank test. The SPSS statistical package was used for data analysis.

RESULTS

Clinical characteristics of patients are summarized in Table 1. Between January 1993 and June 2004, 22 patients entered the study. Fifteen (68%) were female and 7 were male. The average age at onset of disease was 77 months (range 13-168). The mean disease duration at time of AS was 50 months (range 3-324). Sixteen patients (73%) had persistent oligoarticular JIA which was monoarticular in 9 (41%), and 6 patients (27%) had extended oligoarticular JIA. Laboratory examinations at baseline showed elevated ESR in 13 patients (59%) and CRP in 14 (64%). ANA was positive in 9 patients (41%), HLA-B27 in 2 (9%). Two patients (9%) had anterior chronic uveitis. All patients had been treated with NSAID and 18 (82%) with IAC.

Table 1. Clinical characteristics of patients with JIA (n = 22) who underwent arthroscopic synovectomy (AS).

	n (%)
Sex	
Female	15 (68)
Male	7 (32)
Age at onset, mos	
Mean	77
Median	67
Range	13-168
Disease duration, mos	
Mean	50
Median	24
Range	3-324
Age at time of AS, mos	
Mean	124
Median	109
Range	34-408
Oligoarticular JIA subtype	
Persistent	16 (73)
Extended	6 (27)
Monoarticular	9 (41)
Laboratory variables at baseline	
ESR, mm, mean ± SD	54 ± 29.1
CRP, mg/l, mean ± SD	36.5 ± 34.2
ANA, > 1:80	9 (41)
HLA B27	2 (9)
Previous treatment	
NSAID	22 (100)
IAC	18 (82)
Treated joints	
Knee	19 (86)
TMJ	2 (9)
Shoulder	1 (5)
Followup, mos	
Mean	57.5
Median	55
Range	12-168

ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; ANA: anti-nuclear antibody; NSAID: nonsteroidal antiinflammatory drugs; IAC: intraarticular corticosteroid; TMJ: temporomandibular joint.

The mean followup was 57.5 months (range 12-168). Joint radiograph, performed at baseline in all patients, did not show any joint-space narrowing or erosions. Articular US, performed in 18/22 patients (82%) and ge-MRI, performed in 8/22 (36%) before the procedure confirmed the presence of various degrees of synovial hyperplasia.

AS was performed in 19 knees, 2 TMJ, and one shoulder. **Patient details.** Two patients with TMJ involvement experienced orofacial pain during mastication and mandibular movement. In one, symptoms were so intense to cause difficulty in feeding properly and weight loss. On physical examination both patients had TMJ deviation, crepitations at mouth opening, mandible protrusion, and decreased maximal mouth opening (25 and 30 mm, respectively). In both, ge-MRI confirmed severe deformity of the mandibular condyles, synovial fluid, and extensive synovial proliferation. They underwent AS under general anesthesia followed, one month later, by

IAC treatment. Within 6 months after treatment, a dramatic, clinical improvement was observed in both patients. On examination the mandibular range of motion greatly improved with wider mouth opening distance (37 and 42 mm, respectively), symmetry at opening, and disappearance of crepitations.

Another patient presented with a one year history of arthritis of the left shoulder and right ankle. She had been treated with NSAID but significant improvement was obtained only on the ankle. Ge-MRI of the shoulder revealed a massive synovial proliferation completely covering the glenoid surface and causing enlargement of the glenohumeral space. Arthroscopy, performed under general anesthesia, showed the glenoid covered with inflammatory synovium, which was completely removed. After an intensive postoperative physiotherapy program, a good, although not complete, range of motion was obtained.

Considering the whole cohort of patients, the rate of arthritis relapse, after AS treatment, was 27% (6 patients) at 6 months, 36% (8 patients) by 12 months, 50% (11 patients) by 24 months, and 64% (14 patients) thereafter. After a mean followup of 65 months (median 60, range 18 to 168), 8 patients (36%) are still in remission without any systemic therapy.

The mean time to relapse was significantly longer in patients with persistent isolated, unique monoarticular involvement (65 ± 48 mos vs 19 ± 17, *p* = 0.004) (Table 2). Patients who underwent AS within one year from disease onset also showed a significantly sustained response with a mean response duration of 60 ± 48 mos versus 23 ± 25 (*p* = 0.03). Other variables found to be predictive of good response were normal ESR and CRP before surgery. In patients with normal ESR, time to relapse was 64 ± 45 mos; in those with elevated ESR, it was 20 ± 24 mos (*p* = 0.008). Similarly, patients with normal CRP had a response duration of 65 ± 48 mos; those with high CRP relapsed after 23 ± 25 mos (*p* = 0.01). No clear relationship between response to treatment and other demographic and laboratory variables at baseline were found.

Table 2. Predictors of good response to AS in patients with oligoarticular JIA.

	Remission Duration, mo		p
	Mean	SD	
Monoarticular course	65	48	0.004
Oligoarticular course	19	17	
Disease duration at the time of AS			0.03
≤ one year	60	48	
> one year	23	25	
ESR at baseline			0.008
< 30 mm	64	45	
≥ 30 mm	20	24	
CRP at baseline			0.02
< 6 mg/l	64	48	
≥ 6 mg/l	23	25	

Survival curves, regarding the analysis of time to disease flare, are shown in Figure 1. The Kaplan-Meier estimate of incidence rate of arthritis flare was 0.68/100 months/person of followup for the monoarticular course group and 4.07/100 months/person for the oligoarticular course group (incidence rate ratio 5.98, 95% CI: 1.72-26.1). The log-rank test showed the probability to achieve joint remission was higher in patients with monoarticular than oligoarticular course (78% and 62% after 12 mos and 78% and 38% after 24 mos, respectively, *p* = 0.01).

The Kaplan-Meier estimate of incidence rate of arthritis flare for patients with disease duration greater or lower than one year at the time of AS revealed a consistent difference between the 2 groups without reaching statistical significance (*p* = 0.063).

### DISCUSSION

The general approach to treating oligoarticular JIA includes the use of NSAID and IAC as first line therapy<sup>10</sup>. However, when a patient is refractory to such a treatment or several IAC injections are not able to control the inflammatory process, second line agents such as methotrexate (MTX) or even biological agents are indicated. The indication for AS in JIA patients is still controversial.

In adult patients with rheumatoid arthritis AS is indicated, after failure of an adequate trial of medical management, in patients with persisting synovitis, little or no degenerative changes on radiographs, and functional class I or II according to the American College of Rheumatology criteria<sup>3</sup>. Patients with greater functional impairment are usually candidates for more extensive surgery.

In children, AS has been proposed when a single joint is persistently affected, refractory to treatment and painful, or when mechanical impairment is present<sup>11</sup>.

In our study, the largest ever reported, we found AS is a safe but only partially effective procedure for the majority of patients with oligoarticular JIA. In fact, one-third of our patients relapsed within 12 months of AS and two-thirds within 24 months of AS. Interestingly, one-third of our patients were still in remission at the last evaluation, after a mean 5 years of followup. These patients, at the time of AS, had persistent monoarticular involvement with no signs of systemic inflammation as confirmed by low ESR and CRP plasma levels.

Disease duration prior to AS was variable in our group of patients and ranged from 3 to 324 months. The patient with the shortest disease duration underwent AS just 3 months after disease onset for diagnostic purposes at a peripheral hospital. As histology had revealed chronic synovitis compatible with a diagnosis of JIA, he was referred to us and the IAC treatment was performed one month later. The patient with the longest disease duration had disease onset at the age of 7 years. She had several relapses in the same knee and was always treated with NSAID and IAC. She underwent AS 27 years after disease onset, but the outcome was very poor. Soon

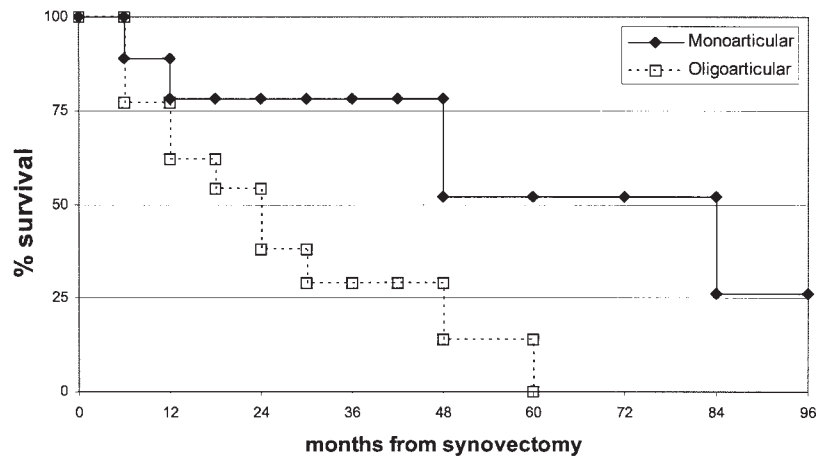


Figure 1. Kaplan-Meier survival estimates of the time to arthritis flare in monoarticular and oligoarticular course groups (log rank test:  $p = 0.01$ ).

after surgery, she developed hemarthrosis and persistent joint effusion. She required prolonged systemic steroids and MTX treatment to control joint inflammation.

Until now, studies reporting the efficacy of AS in patients with JIA are few and often clear indications for this treatment and longterm followup are lacking. The only study in a peer-reviewed journal reported results of 19 AS of the knee in 17 patients with JIA, 12 of whom had oligoarticular subtype<sup>12</sup>. These authors reported a good result in two-thirds of their patients. However, a careful analysis of the data revealed that outcome measures used to evaluate clinical response were joint pain and swelling. If functional variables had been considered, the results would not be so encouraging since 4/19 joints worsened and the remaining joints were unchanged, with the majority of patients in the third functional class. Indeed, the mean followup time was shorter (2.2 yrs) than in our study (4.9 yrs), with half the patients followed for just one year.

More recently, other authors have reported their experience with AS in 21 knee joints of patients with all forms of JIA<sup>13</sup>. At 2 years' followup, they found a 43% relapse rate, very similar to our findings, and predictors of poor outcome were presence of high inflammatory activity and polyarticular and systemic subtypes.

Others reported similar results in a small cohort of 10 patients with JIA with polyarticular, oligoarticular, and systemic subtypes<sup>14</sup>. The 2 patients with systemic onset JIA relapsed soon after AS. Three patients showed postoperative ankylosis complicated by secondary osteoarthritis. Only 2 patients, with oligoarticular subtype, were still in remission after 3 years' followup.

In contrast to these studies, ours was prospective, our inclusion criteria were more selective, the outcome measures more detailed, and the length of followup longer. These distinctions highlight the difficulty in comparing studies and probably account for the minor differences found.

Based on our results, AS seems to be indicated only for

patients with oligoarticular JIA and persistent active arthritis in one joint. The association of AS with IAC injection allows both the gross removal of hypertrophic synovium and the treatment of residual inflammation. This combined therapy was very effective and led to a complete remission in one-third of our patients.

Among the variables predictive of good response to AS treatment, a persistent monoarticular involvement, early treatment, and normal ESR and CRP were found to be the most important. These features characterized a very small group of patients with oligoarticular JIA who seem to be the best candidates for AS.

The differential response related to disease duration could be explained by histological changes observed during the disease. It is well known that during the first months of disease, synovial lining hyperplasia and proliferation of blood vessels are prevalent while the sublining inflammatory infiltrate is mild<sup>15,16</sup>. The second phase, subacute, is characterized by formation of granular tissue and dramatic increase of the cellular infiltrate, mainly macrophages, whose presence appears to correlate with erosive changes<sup>17</sup>. The third, chronic stage, is characterized by the formation of pannus, a "tumor-like fibrotic proliferation" with potential invasiveness and ability to destroy the joint.

It is possible that the mechanical removal of synovial tissue during the subacute phase of the disease, in patients with persistent monoarticular involvement, may prevent pannus formation and lead to complete, long-lasting remission of arthritis.

In conclusion, our study shows that AS is a relatively safe procedure for patients with JIA. Best results are achieved in children with persistent monoarticular course with no evidence of systemic inflammation. In this particular group of patients, AS should be performed early in the course of the disease, after first line therapy has failed. In patients with persistent or extended oligoarticular JIA, other therapeutic options such as MTX or even biological agents should be preferred.

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