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Synovectomy in juvenile idiopathic arthritis
A systematic review and meta-analysis

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Abstract

Background: Juvenile idiopathic arthritis (JIA) is an inflammatory arthropathy with onset in children younger than 16 years. Treatment is primarily medical; however, surgical interventions, such as arthroscopic or open synovectomy, can be beneficial. Many studies have investigated synovectomy in JIA, but the results of these studies have not been synthesized to our knowledge. Therefore, we performed a systematic review of the literature reporting synovectomy as a treatment for JIA to provide clinical recommendations regarding its risks and benefits.

Methods: On March 8, 2022, we searched the Cochrane Library, Embase, PubMed, Scopus, and Web of Science for studies evaluating clinical outcomes of open or arthroscopic synovectomy to treat JIA in patients younger than 18 years. We included only studies published in English and excluded studies of synovectomy to treat other arthropathies, septic arthritis, hemophilia, or foreign body arthropathy. The level of evidence for included studies was determined by using the Oxford Centre for Evidence-Based Medicine criteria. We qualitatively analyzed clinical outcomes data, including patient-reported pain relief, rates of symptom recurrence, and postoperative complications.

Results: Of 428 articles assessed, 14 were included in our analysis. One was a randomized trial, 1 was a case-control study, and all others were case-series. Studies consistently reported that synovectomy was associated with improved function and decreased pain postoperatively. However, comparisons with modern medical therapy were lacking. Rates of arthritis recurrence varied, with increasing symptom recurrence with longer follow-up and re-synovectomy rates up to 15%. Oligoarticular disease and early disease course were associated with better response to synovectomy, whereas systemic and polyarticular disease were associated with poor response. Stiffness requiring manipulation under anesthesia was the most common complication (4% of all included patients).

Conclusion: Although synovectomy is associated with positive functional outcomes and pain reduction postoperatively, there was inadequate comparison thus inadequate evidence to recommend it over modern medical therapy. The current literature suggests that synovectomy should be offered only to patients for whom medical management has failed, while noting the risks of decreased range of motion and symptom recurrence over time.

Abbreviations: JIA = Juvenile idiopathic arthritis.

Keywords: inflammatory arthropathy, juvenile idiopathic arthritis, pediatrics, synovectomy

1. Introduction

Juvenile idiopathic arthritis (JIA) is a chronic inflammatory disease leading to persistent arthritis that lasts for more than 6 weeks with onset occurring before age 16 years.[1] JIA is one of the most common causes of acquired disability in children.[2] The etiology of JIA is poorly understood and thought to be related to numerous genetic, environmental, and immunologic factors.[3] JIA is categorized as systemic, seropositive polyarticular, seronegative polyarticular, oligoarticular, psoriatic-related, enthesitis-related, or undifferentiated.[4]

The mainstay of treatment for JIA is medical therapy using nonsteroidal anti-inflammatory drugs, conventional and biologic disease-modifying anti-rheumatic drugs, and corticosteroid injections.[3] Medical treatment is effective in improving clinical outcomes, reducing physical disability, and reducing morbidity and mortality rates secondary to JIA.[5,6] Despite advances in medical treatment, many patients do not achieve full remission,

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and pain and functional disability may persist even when remission occurs.[7,8]

Surgical treatment of JIA is controversial. Surgery is generally indicated in patients with pain refractory to medical management, synovial hyperplasia, persistent effusion, or joint destruction.[9] Synovectomy is one surgical option. Potential benefits include removal of the inflammatory pannus and improvement of mechanical symptoms. Conventionally, synovectomy for pediatric inflammatory arthropathies has been considered a salvage approach to palliate pain and loss of range of motion.[9] However, some studies support synovectomy as a means of disease control.[10,11] Despite the abundance of studies of synovectomy for JIA, to our knowledge, this evidence has not been synthesized to provide clinical recommendations. Therefore, we performed a systematic review of the literature to investigate the evidence for synovectomy as a treatment for JIA and to describe the risks and benefits of this procedure. We focused on assessing the outcomes (function, pain, range of movement, recurrence of symptoms, requirement for reoperation for arthroplasty) and complications associated with synovectomy for JIA.

2. Methods

2.1. Protocol

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines. The study was exempt from approval by Johns Hopkins Medicine Institutional Review Boards; it did not meet the 45 CFR 46 definitions of human-subjects research because it was an analysis of publicly available literature.

2.2. Literature search

On March 8, 2022, we searched the Cochrane Library, Embase, PubMed, Scopus, and Web of Science for studies published in English that reported the use of synovectomy to treat JIA. The search methods, developed by a certified medical informationist, are provided in Supplemental Digital Content (Appendix 1 and 2, Supplemental Digital Content, http://links.lww.com/MD/I119). Duplicate studies were removed, and the remaining studies were imported into Covidence (Veritas Health Innovation Ltd, Melbourne, Australia) for management and screening. Title and abstract screening, followed by full-text review, were performed by 2 independent reviewers (D.B. and C.R.L.) based on predetermined eligibility criteria. Conflicts were resolved by a third reviewer (R.S.B.).

2.3. Inclusion and exclusion criteria

We included studies that evaluated clinical outcomes of open or arthroscopic synovectomy to treat JIA in patients younger than 18 years. We included clinical trials, retrospective studies, prospective studies, and case reports or series. Studies using previous names for this group of pediatric inflammatory arthropathies (e.g., juvenile rheumatoid arthritis, juvenile chronic arthritis) were also included. We excluded studies of synovectomy to treat other arthropathies, septic arthritis, hemophilia, or foreign body arthropathy. Abstracts, editorials, in vitro or animal studies, and research letters were excluded.

2.4. Data abstraction

Data were abstracted from included studies by 2 independent reviewers (D.B. and C.R.L.) through manual full-text review. We recorded the following data: publication year, author names, sample size, population demographics, affected joints, intervention used, medical interventions used, follow-up duration, and clinical outcomes (e.g., patient-reported pain relief, postoperative rates of symptom recurrence, and postoperative complications). We evaluated the level evidence of the included studies using the Oxford Centre for Evidence-Based Medicine criteria.[12]

3. Results

Our initial search retrieved 428 articles after removal of duplicates. Fourteen articles met our eligibility criteria (Table 1). A flow diagram illustrating the search is provided in Figure 1.

Publication dates ranged from 1969 to 2013. One article was a randomized trial,[10] 1 was a case-control study,[16] and all others were case series.[9,11,13–15,17–23] Of the 11 articles, 13 were level-IV studies, and 1 was a level-II study (Table 1).

3.1. Function and pain

Despite the high variability between studies, most studies reported at least some improvement in either function or pain after synovectomy.

In a randomized controlled trial involving 30 patients with JIA, 15 of whom underwent synovectomy, Kvien et al[10] found better patient-reported outcomes, pain, and disease activity scores in the operative group compared with the nonoperative group at 2-year follow-up. Mäenpää et al[17] reported pain remission after synovectomy in 8 of 18 joints and good or excellent pain relief in 13 of 18 synovectomies. Joint function did not improve. Hanff et al[11] reported pain improvement in 12 of 20 wrists, 7 of which became pain free. Four wrists had persistent pain that prompted arthrodesis, and 1 wrist developed spontaneous ankylosis. Meanwhile, mean overall grip strength improved. Rydholm et al[20] found significant postoperative improvement in pain, whereas Jacobsen et al[21] found no such improvement. Paus et al[18] reported a significant improvement in University of Colorado Knee Scores at 5-year follow-up. Carl et al[14] found improved mean Merle d'Aubigné hip scores, as well as improved pain, mobility, and walking ability scores after synovectomy at 4-year follow-up. Of 67 hips, 57 (85%) had a great or very great improvement in function.

3.2. Symptom recurrence

Remission rates after synovectomy varied widely among studies, with some studies reporting high recurrence rates and others reporting very low rates.

Toledo et al[15] reported a recurrence rate of 64% (16 of 22) at a mean follow-up of 5.4 years. In contrast, at a mean follow-up of 5.7 years, Dell'Era et al[9] reported recurrence rates of 95% (19 of 20) in patients with polyarticular arthritis, 100% (5 of 5) in patients with psoriatic arthritis, and 67% (4 of 6) in patients with oligoarticular arthritis. Mean time to symptom recurrence was 1 year.

Hanff et al[11] reported symptom recurrence in 9 of 20 wrists and radiographic deterioration in 11 of 20 wrists at a mean follow-up of 3 years. Rydholm et al[20] reported radiographic progression of joint destruction in 47% of knees (24 of 51) at a mean follow-up of 7.5 years. Thirty-four knees (67%) experienced 1 or more symptomatic relapses during the follow-up period. Conversely, Jacobsen et al[21] reported only 1 patient of 41 with recurrent synovitis at 7.1 years, and Albright et al[22] reported 1 case of progressive destruction in 9 hip synovectomies.

Ovregard et al[19] analyzed 389 joints 3 years after synovectomy and classified 78% as responders, 12% as nonclassifiable, and 10% as nonresponders. The authors noted that with longer follow-up, patients went from good results to poor rather than vice versa.

Fink et al[23] found that 97% of joints (38 of 39) had decreased inflammation on clinical examination after synovectomy.

Table 1

Summary of characteristics and findings of included studies.

First Author (yr)	LOE	Population	Joints Included	Intervention*	Medical Therapy (% Patients Receiving)	Outcomes/Findings	Complications
Teramoto (2013)[13]	IV	1 F with early, undiagnosed JIA	2 Knees	Arthroscopic synovectomy	NA	10-yr remission of arthritis	None reported
Dell'Era (2008)[9]	IV	15 F and 4 M with refractory JIA	31 Knees	Arthroscopic synovectomy	NSAIDs (90) Steroids (32) Other DMT (48)	Recurrence rates of 100% for psoriatic arthritis, 95% for polyarthritis, and 67% for oligoarthritis; mean time to recurrence of 1.0 yr	1 Thrombophlebitis; 1 septic arthritis (in patient taking etanercept)
Carl (2007)[14]	IV	35 F and 21 M with refractory JIA	67 Hips	Open synovectomy	NA	Mean Merle d'Aubigné hip score improved from 9.5 at baseline to 16.3 at follow-up ($P < .001$). Pain, mobility, and walking ability scores improved (all, $P < .001$). 85% of hips had great or very great improvement in function; 5 hips required total hip arthroplasty during mean follow-up of 50 mo.	2 Superficial wound hematomas
Toledo (2006)[15]	IV	15 F and 7 M with refractory JIA	23 (19 Knees, 2 TMJs, 1 shoulder)	Arthroscopic synovectomy	NA†	Relapse rates of 36% (first yr) and 14% (second yr); 36% in remission after 65 mo; factors predictive of favorable response were monoarticular course, short disease duration, and low erythrocyte sedimentation rate/C-reactive protein level	1 Hemarthrosis and persistent joint effusion
Lybäck (2004)[16]	IV	45 F and 7 M with knee arthroplasty for JIA	77 Knees	Synovectomy	NA	Equivalent mean age at arthroplasty in both groups	None reported
Mäenpää (2003)[17]	IV	15 F and 4 M with refractory JIA	24 Elbows	Synovectomy	Steroids (12) Methotrexate (21) Other DMT (30)	Pain remission in 44%; "good or excellent" pain relief in 72%; reoperations comprised 4 repeat synovectomies and 2 total arthroplasties	1 Superficial wound infection; 1 elbow stiffness
Paus (1992)[18]	IV	16 F and 2 M with JIA	18 Knees	Open synovectomy	NSAIDs (67) Steroids (22) Other DMT (67)	Improved University of Colorado Knee Scores; factors predicative of favorable outcomes were low IgA-positive plasma cells at 12-mo biopsy and better preoperative function; reoperations comprised 3 repeat synovectomies and 1 total knee arthroplasty	None reported
Hanff (1990)[11]	IV	10 F and 4 M with JIA	20 Wrists	Synovectomy	NA	80% experienced improved pain, 46% became pain free; global improvement in grip strength; 45% recurrence of synovitis; 55% wrists with deterioration at follow-up (vs 100% preoperatively); reoperations comprised 4 cases of wrist arthrodesis	None reported
Ovregard (1990)[19]	IV	212 Children	389 Joints	Open synovectomy	NA	At 3-yr follow-up, 303 joints were classified as responders, 45 as nonclassifiable, and 41 as nonresponders. With longer follow-up, more patients went from good results to poor; 5 joints required re-synovectomy	11 Patients had negative outcomes (deformities, growth disturbance, scarring)
Kvien (1987)[10]	II	21 F and 9 M with JIA	30 (18 Wrists, 8 ankles, 4 knees)	Synovectomy (15); no synovectomy (15)	NSAIDs (100) Steroids (100) Other DMT (59)	In operative group, improvements in swelling, disease activity scale scores, subjective patient-reported outcomes, and pain scale scores	1 Keloid scar removal; MUA for both knee synovectomies; decreased average joint range of motion
Rydholm (1986)[20]	IV	35 F and 16 M with refractory JIA	60 Knees	Synovectomy	NA	Pain improved postoperatively; younger patients more likely to benefit; 40% with progression of joint destruction; 57% with 1 or more relapses; joint destruction and recurrence more common in those with polyarticular and active disease at time of operation; reoperations comprised 4 soft tissue releases, and 1 total knee arthroplasty	2 Superficial wound infections; 21 cases of MUA; 6 cases of hemiepiphysiodesis for valgus deformity
Jacobsen (1985)[21]	IV	33 F and 6 M with refractory JIA	41 (23 Knees, 10 hips, 4 wrists, 4 ankles)	Synovectomy	NA	No improvement in pain or range of motion; swelling permanently decreased; joint destruction continued in those with radiographic changes or systemic disease at time of operation; reoperations comprised 2 repeat synovectomies and 6 cases of total joint arthroplasty	6 Cases of MUA

(*Continued*)

Table 1
(*Continued*)

First Author (yr)	LOE	Population	Joints Included	Intervention*	Medical Therapy (% Patients Receiving)	Outcomes/Findings	Complications
Albright (1975)[22]	IV	5 F with refractory JIA	9 Hips	Synovectomy	NA	4 Patients experienced improved or retained range of motion; 1 patient had progressive destruction of hips	1 Contralateral hip subluxation and additional synovectomy
Fink (1969)[23]	IV	13 F and 10 M with refractory JIA	39 (25 Knees, 5 wrists, 4 ankles, 4 hips, 1 elbow)	Open synovectomy	NA	38 Joints had decreased inflammation clinically after synovectomy; erythrocyte sedimentation rate decreased significantly but by a small magnitude; postoperative range of motion increased in 13 patients and decreased in 10 patients; 1 joint underwent re-synovectomy	None reported

* Presented as either arthroscopic or open unless not specified in primary study.
†Patients on DMT excluded from study.
DMT = disease-modifying therapy, F = female(s), JIA = juvenile idiopathic arthritis, LOE = Oxford Centre for Evidence-Based Medicine level of evidence, M = male(s), MUA = manipulation under anesthesia, NA = not available, NSAIDs = nonsteroidal anti-inflamatory drugs, TMJ = temporomandibular joint.

Teramoto et al[13] reported a case of undiagnosed JIA treated with bilateral knee synovectomy. The patient was asymptomatic for 10 years before recurrence of symptoms and diagnosis of JIA.

3.3. Range of motion

Studies broadly agreed that range of motion was unchanged or decreased after synovectomy. Few studies reported improved range of motion.

Mäenpää et al[17] and Jacobsen et al[21] found no change in range of motion postoperatively. Hanff et al[11] found decreased mean range of motion postoperatively. Albright et al[22] reported that 4 of 5 patients had retained or improved range of motion, whereas 1 patient had worse range of motion at a mean follow-up of 5 years. Fink et al[23] found that range of motion increased in 13 of 39 joints (33%) and decreased in 10 of 39 (26%) joints 4 to 8 months after surgery. In a randomized trial, Kvien et al[10] found decreased passive range of motion after surgery with gradual improvement throughout 24 months of follow-up. However, patients who underwent synovectomy never attained the range of motion observed in the nonoperatively treated group; at no follow-up timepoint did the median change in passive range of motion in the former surpass the 25th percentile in the latter.

3.4. Re-synovectomy and arthroplasty

Studies reported arthroplasty rates after synovectomy ranging from 2% to 15% and repeat synovectomy rates from 1% to 17%, with mean follow-up ranging from 3 to 7 years.[14,17–21,23]

Lybäck et al[16] conducted a case-control study of 77 patients with JIA who underwent total knee arthroplasty. Patients with prior synovectomy had shorter mean time to arthroplasty compared to patients with no synovectomy.

3.5. Predictors of outcomes after synovectomy

Studies reported various predictors of success/failure of synovectomy. Broadly, limited or early disease predicted better response to synovectomy, whereas advanced or systemic disease predicted worse response.

Factors associated with favorable outcomes after synovectomy were younger patient age, oligoarticular joint involvement, short disease duration, low erythrocyte sedimentation rate/C-reactive protein level, paucity of IgA-positive plasma cells in the cellular infiltrate on biopsy, and absence of joint destruction and systemic disease at surgery.[15,18,20,21] Factors associated with worse outcomes were cartilage destruction at the time of synovectomy, early recurrence, polyarticular disease, active disease at the time of surgery, radiographic joint destruction at the time of surgery, and systemic disease.[18,20,21]

3.6. Risks and complications

Of the 830 synovectomies reported in the 14 studies reviewed, 57 complications were reported (7%) in 9 studies.[9,10,14,15,17,19–22] Of these complications, 30 (53%) involved postoperative joint stiffness (29 knees and 1 elbow underwent manipulation under anesthesia),[10,17,20,21] 6 (11%) involved hemi-epiphysiodesis of the distal femur or proximal tibia for progressive valgus deformity,[7] and 4 (7%) were related to infection, including 3 superficial wound infections and 1 case of septic arthritis in a patient prescribed etanercept for immunosuppression.[8,15,18] Six other complications were cases of thrombophlebitis, superficial wound hematomas, hemarthrosis and persistent joint effusion, keloid scar formation, and contralateral hip subluxation.[9,10,15,22]

4. Discussion

Synovectomy for the treatment of JIA has traditionally been reserved for cases refractory to medical management.[9,13,15] Its benefits as an early treatment to prevent joint destruction are still unclear. The absence of recent studies investigating synovectomy in JIA and the abundance of older studies likely reflects the advances of medical treatment and decline in the need for surgical intervention. However, it is important to note that several of these older studies reported benefits of synovectomy.

We found a wide range of rates of symptom recurrence after synovectomy. For example, some studies reported long remission phases of 6 to 10 years,[9,13] whereas others reported high recurrence rates (up to 100%) with short remission phases after synovectomy.[15] This difference may be explained by the small sample sizes, heterogenous indications for synovectomy, and various joint types included in the studies. Moreover, JIA is increasingly thought to be a group of heterogenous disorders with widely different pathophysiological characteristics, as opposed to a single disease.[3] Although the wide variability makes it difficult to derive conclusions, studies consistently reported certain factors associated with the success of synovectomy. Notably, all

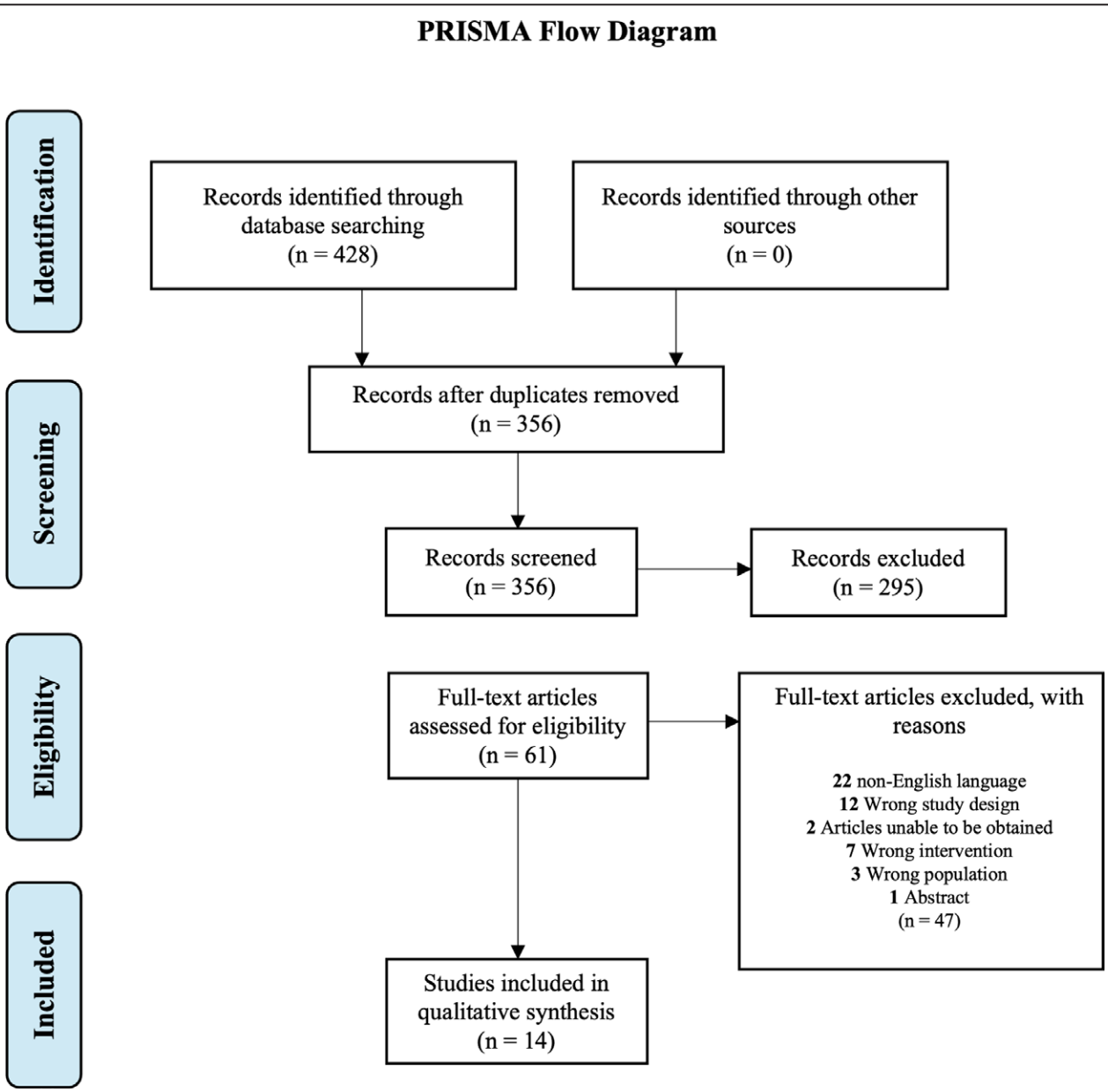

Figure 1. PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analysis) flow diagram detailing the literature search. Search was performed on March 8, 2022, using the Cochrane Library, Embase, PubMed, Scopus, and Web of Science.

of the favorable prognostic factors reported were early, localized, or oligoarticular disease as opposed to systemic, advanced, or polyarticular disease. For example, Dell'Era et al[9] noted considerable differences in recurrence rates between patients with polyarticular JIA (95%) and those with oligoarticular JIA (65%). Toledo et al[15] reported that monoarticular course, short disease duration, and low levels of inflammatory markers were associated with good response to synovectomy. Further, the patient with oligoarticular JIA who underwent synovectomy early in the disease course, reported by Teramoto et al,[13] experienced a remarkably long 10-year postoperative remission. Nonetheless, it is unclear whether these reported advantages of early synovectomy are clinically applicable, because patients with limited and early disease involvement are likely to be eligible for multiple first-line medical treatments that are highly effective.[24,25] Therefore, justifying surgical intervention in this population is difficult.

Most studies reported that synovectomy offered improvements in pain and joint function. Most notably, the randomized controlled trial by Kvien et al[10] found that synovectomy was superior to nonoperative treatment with regard to multiple outcome scales. However, that study analyzed 2-year outcomes, and other studies reported higher recurrence rates with longer follow-up.[19,20] For example, 1 study concluded that, with longer follow-up, patients went from good to poor results rather than vice versa.[19] Moreover, the trial by Kvien et al[10] was performed in the 1980s, before the development of modern medical therapy. Therefore, although most studies reported improvements in pain and function, it is difficult to draw conclusions about the outcomes of synovectomy compared with medical therapy.

It is important to note that most studies were limited by confounding bias because synovectomy was most often offered for persistent or refractory arthritis. This limitation may mask the benefits that early synovectomy might provide in mild or moderate cases of arthritis, particularly because multiple studies reported greater benefits in younger patients and those with milder disease.[15,18,21] For example, Jacobsen et al[21] found that radiographic joint destruction persisted after synovectomy in

patients who had radiographic changes at the time of surgery but did not occur in patients without changes at the time of surgery. This finding is logical from a mechanistic perspective because resecting the inflammatory pannus in mild and early disease may impede the inflammatory cycle. However, as mentioned previously, it may be difficult to offer early synovectomy to patients with mild disease, when most are likely to benefit from medical therapy or even achieve spontaneous remission. Furthermore, patients with oligoarticular disease have a better prognosis regardless of treatment type.[26]

Regarding perioperative complications, the studies we reviewed indicated a mild to moderate postoperative risk profile. In total, 7% of synovectomies involved a complication, with joint stiffness prompting manipulation under anesthesia being the most common. This finding was concordant with the reports of unchanged or decreased range of motion. Considering the importance of activity and range of motion for children, the risk of stiffness or decreased range of motion after synovectomy may weigh against its use, and it is critical to discuss this risk with patients and their families.

This systematic review has several limitations. First, because of the heterogeneity of studies, it was not possible to perform a meta-analysis, and our conclusions are qualitative rather than quantitative. Second, the strength of evidence was limited because most studies were case series without comparison groups. Third, the absence of recent literature on the topic makes it difficult to draw conclusions regarding comparisons between synovectomy and modern medical therapy. Despite these limitations, this study is, to our knowledge, the first systematic review synthesizing the evidence regarding synovectomy in the treatment of JIA.

5. Conclusion

Synovectomy for JIA is associated with improvements in pain and function, but with a risk of stiffness and recurrence of symptoms with longer follow-up. Although earlier, milder, and localized disease was associated with better response to synovectomy, there is inadequate evidence to recommend this procedure over modern medical therapy. We recommend that synovectomy should remain an option for refractory disease only after medical options have been exhausted. At that point, the risks, benefits, and absence of strong evidence should be extensively discussed with patient and family before proceeding with this option.

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