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Synovitis and synovectomy in haemophilia

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Abstract

Joint bleeds cause major morbidity in haemophilia patients. The synovial tissue is responsible for removal of blood remnants from the joint cavity. But blood components, especially iron, lead to a series of changes in the synovial tissue: inflammation, proliferation and neovascularization. These changes make the synovium vulnerable to subsequent bleeding and as such a vicious cycle of bleeding-synovitis-bleeding may develop leading to chronic synovitis. The initial step in the treatment is adequate clotting factor supplementation and immediate physiotherapeutic involvement. If these measures fail, synovectomy may be indicated. Non-surgical options are chemical and radioactive synovectomy. This is a relatively non-invasive procedure to do synovectomy, leading to a reduction in pain and joint bleeds. Radioactive synovectomy seems more effective than chemical synovectomy in larger joints. Surgical options are open and arthroscopic synovectomy. Open synovectomy has been found to decrease the incidence of breakthrough bleeds but at the cost of loss of joint motion. Use of arthroscopic synovectomy has been advocated to reduce bleeding episodes with less morbidity to extra-articular tissue and preservation of joint motion. Use of a continuous passive motion (CPM) machine and early mobilization can decrease the postoperative stiffness and promote early recovery. This review addresses the current understanding of synovitis and its treatment options with specific emphasis on chemical and radioactive synovectomy and surgical options.

KEYWORDS

haemophilia, synovectomy, synovitis

1 | INTRODUCTION

The clinical hallmark of haemophilia is its spontaneous bleeding tendency, affecting primarily the large synovial joints, especially the ankles, knees and elbows.[1] Nearly, all untreated patients with severe haemophilia and half of the patients with moderate disease experience haemarthroses. Consequences of these joint bleeds are the development of chronic synovitis and haemophilic arthropathy. In this paper we will discuss the current knowledge on the pathophysiology of synovitis, the clinical course, and treatment options with specific emphasis on non-surgical synovectomy (ie chemical and radioactive synovectomy) and surgical options.

2 | PATHOGENESIS OF HAEMOPHILIC SYNOVITIS

Synovial joints are characterized by a joint cavity formed by the two bony ends covered with cartilage, connected via ligaments and a surrounding joint capsule. Synovial tissue lines the inner surface

of the joint capsule. It consists of a thin lining (intima) composed of three cell layers, and a sublining (subintima) with fatty and fibrous parts containing blood and lymphatic vessels.[2] Synovial tissue is responsible for the production of synovial fluid, nutrition of cartilage and lubrication of the joint, and removal of debris from the joint space. For this purpose, synovial tissue is highly vascularized and in haemophilia even minimal forces can lead to haemarthroses. The blood vessels and capillaries are located in the sublining, with the highest density of capillaries found just below the lining.[2] The lining consists of macrophages and fibroblasts. These macrophages, which can also be found in the sublining, provide a scavenger function removing blood and other deleterious substances from the joint space. Erythrophagocytosis can be observed as early as four hours after a bleed and is a sign of removing blood remnants from the joint cavity.[3] Complete resolution of blood in the joint, assessed by ultrasonography, may however take up to 20 days (SD 9.4).[4]

The presence of haemoglobin-derived iron in the joint cavity has disturbing effects on all joint components. In the synovium, iron induces an inflammatory response and stimulates cell proliferation. Iron-laden synoviocytes produce pro-inflammatory cytokines such as interleukin (IL)-1β, IL-6, and tumour necrosis factor alpha (TNFα), in addition to tissue destructive proteases like matrix-metalloproteinases (MMPs).[5-7] The normally thin synovial membrane becomes thickened and irregular due to the inflammatory response, but also as a result of synovial hyperplasia. Synoviocytes exposed to iron overexpress the proto-oncogene *c-myc* resulting in cell proliferation and have an increased expression of the *p53* tumour suppressor binding protein mdm2, resulting in an abrogated apoptosis.[8,9]

The oxygen demand of this hypertrophied and inflamed synovium is increased. Growth factors such as vascular-derived endothelial growth factor (VEGF) are released and a rich network of brittle capillaries underneath the hypertrophied synovium is formed.[10,11] This aberrant vascular remodelling persists for months after an induced joint bleed in factor VIII deficient mouse.[12] These new, fragile blood vessels make the joint vulnerable to subsequent (repeated) bleeding and as such can lead to a vicious circle in which the synovial tissue is unable to remove blood remnants completely, further triggering synovial inflammation and proliferation, resulting in chronic synovitis.[5,13]

A possible adaptive response of the synovium to improve iron handling after repeated bleeds is suggested by studying the synovial tissue of patients with end-stage haemophilic arthropathy.[14] A clear upregulation is demonstrated for the iron regulating proteins ferroportin, feline leukaemia virus subgroup C receptor (FLVCR) and haem carrier protein 1 (HCP-1). A similar upregulation was noted for ferroportin, CD163 and HCP-1 in haemophilia mice after induction of a joint bleed. It is hypothesized that these changes help in handling the burden of iron and maintaining iron homeostasis after joint bleeding. In case of a major bleed or recurrent bleeding, even after upregulation of these iron regulating proteins, the removing capacity of the synovium will be overwhelmed.

Besides the synovial changes, joint bleedings will also progressively lead to cartilage degradation and bone changes ultimately resulting in haemophilic arthropathy. This results from both synovial-dependent and synovial-independent processes. The production of pro-inflammatory cytokines and cartilage matrix degrading proteases by the inflamed synovium leads to degradation of the cartilage extracellular matrix.[5,15] Also, direct blood exposition to cartilage causes the production of IL-1β, IL-6, and TNFα.[16,17] In the vicinity of chondrocytes, these mediators activate the chondrocytes resulting in hydrogen peroxide (H_2O_2) production, which in combination with iron derived from erythrocytes leads to apoptosis via radical formation.[18,19] By this chondrocyte death, the repairing capacity of the cartilage is destroyed. In end-stage arthropathy, the synovial tissue becomes fibrotic decreasing the frequency of bleeding.

Treatment aims at reducing synovitis or inducing fibrotic changes and therewith decreasing the frequency of bleeding before end-stage arthropathy has developed.

3 | CLINICAL COURSE

An acute joint bleed leads to a rapid swelling, loss of range of motion, pain and warmth of the skin over the joint.[20] The joint is held in a position of ease of slight flexion to minimize pain and intra-articular pressure. After appropriate and immediate clotting factor substitution and gradually regaining joint loading and physical activity, most joint bleeds will resolve. However, synovitis may become a bleeding-independent process, especially after gross or repeated bleeding. In this condition, the joint appears swollen, but usually not tense, is often painless and only slightly warm.[20] In early stages of synovitis range of movement is usually preserved, but in chronic stages a mild limitation and flexion deformity can develop. The surrounding musculature may become atrophic, the ligaments and fibrous capsule are stretched leading to joint instability. Ultrasound shows inflammatory changes with joint effusion and a thickened synovium usually with a positive Doppler signal.[21] On X-ray initially synovitis will only result in minimal changes such as swelling and osteoporosis. However, information on pre-existing osteochondral bone changes are more clearly visualized compared to ultrasound. Magnetic resonance imaging (MRI) is useful to visualize the extend of synovitis, and minimal alterations such as haemosiderin deposition and synovial hypertrophy as well as minor cartilage damage without joint space reduction.[22]

4 | NON-SURGICAL TREATMENT

Administration of clotting factor is necessary to break the self-perpetuating cycle of bleeding-synovitis-bleeding and to prevent the progressive degeneration of the joint. In contrast to its effect on acute haemarthrosis, clotting factor replacement does not modify the clinical findings immediately and long-term treatment is indicated.[20] Intensified prophylaxis to achieve adequate levels to prevent recurrent bleeding is indicated. Cyclo-oxygenase (COX)-2 inhibitors might be given as they have anti-inflammatory, antiangiogenic and analgesic properties.[23,24] The physiotherapist needs to be

involved immediately. Initially, physical activity needs to be reduced and splinting might be indicated for joint stability. During recovery, a specifically tailored muscle strengthening programme is indicated starting with isometric muscle exercises and gradually increasing loading and activity.[25]

If these conservative measurements fail, (non-)surgical synovectomy needs to be considered (see Table 1).

The principle of the treatment of chronic haemophilic synovitis is the destruction or inactivation of the inflamed and hypertrophic synovial tissue, consequently reducing bleeds and pain. It can be achieved through surgery, or by use of radioactive or chemical intra-articular infiltration of a fibrosing substance. Published studies show that non-surgical approaches have similar benefits to surgeries with less complications and significantly less costs.[26,27]

4.1 | Chemical synovectomy

Chemical synovectomy or chemical synoviorthesis has been used for more than 50 years with different products such as thiotepa, osmic

TABLE 1 Comparative analysis between different synovectomy

	Non-surgical		Surgical	
Parameter	**Rifampicin**	**Radio-synovectomy**	**Arthroscopic synovectomy**	**Open synovectomy**
Invasiveness	Minimal	Minimal	Intermediate	Invasive
Clotting factor requirement	Equal to treatment of a haemarthrosis	Equal to treatment of a haemarthrosis	Intermediate	High
Hospital stay	Outpatient	Outpatient	Indicated, shorter	Indicated, longer
Postoperative bleeding	Very rare	Very rare	Rare	Increased risk
Postoperative stiffness	Not reported	Some reports of post-RSO stiffness due to excessive synovial fibrosis	Low incidence, low morbidity	High incidence, increased morbidity
Range of motion (ROM)	Maintained or increased	Maintained or increased	Post-op ROM preserved	Post-op ROM decreased
Risk of infection	Extremely low	Extremely rare	Low (minimally invasive)	High (open procedure)
Morbidity to extra-articular tissue	Minimal	Potential radionuclide contamination through the needle tract	Less	More
Effectiveness	Effective, but less if compared to RSO and often needs to be repeated	Equivalent to arthroscopic synovectomy	Posterior aspect, posteromedial and posterolateral corners left incomplete	Near complete
Equipment & expertise	Minimal	In accordance to local and international radioprotection guidelines	Required, can be carried out only at specific centres	Conventional surgery
Financial perspective	Low cost of rifampicin, but often needs to be repeated requiring extra factor concentrates (many)	More expensive than rifampicin. Significantly less expensive than surgical synovectomy	More expensive	Expensive considering clotting factor substitution and hospital stay
Contraindications	1. Non-availability of local production or importation of rifampicin 2. Patient's experience of extreme pain during or after procedure 3. Massive acute haemarthrosis (chronic bleeds are nor contraindications)	1. Surgeon unfamiliar with the procedure 2. Non-availability of production or importation of radiopharmaceutical, equipment and setup 3. Children. Selection according to individual decision of risk and benefit 4. Massive acute haemarthrosis (chronic bleeds are not a contraindication)	1. Surgeon unfamiliar with the procedure 2. Non-availability of arthroscopy equipment and setup 3. Advanced arthropathy (relative)	1. High inhibitor titres 2. Advanced arthropathy 3. Non-availability of on-demand factor replacement

Note: Oxytetracycline is as effective as rifampicin.

acid, D-penicillamine, rifampicin and oxytetracycline. To our knowledge, the products still in use are rifampicin and oxytetracycline.[28-30] Rifampicin is employed in its injectable form,[28,30] which is currently not available in some countries. The oxytetracycline is rejected by some ethics committees due to its restricted veterinary use.

The effectiveness of rifampicin in synovitis was demonstrated first in 30 rheumatoid patients with persistent knee effusion.[31] In a double-blind study, patients received either 500 mg of rifampicin or 10 mL of saline solution showing a complete disappearance of the knee effusion in the rifampicin group. Based on this study, chemical synovectomy with rifampicin in haemophilia patients became popular in some countries where it is somewhat easier to obtain compared to the radioisotopes needed for radioactive synovectomy (RSO).[28,30,32] The expected results are pain reduction, improving the range of motion and decreasing the number of haemarthroses, although results are less when compared to the results achieved by RSO.[30] Moreover, repeated injections (up to 10, in knees) are sometimes needed to achieve the expected results. The published methodologies utilized for chemical synovectomy with rifampicin vary considerably. Caviglia et al[32] presented their experience with rifampicin in three services using different protocols. Rifampicin was shown effective especially when used in smaller joints (elbows and ankles) and in joints of small children. A rationale for the variation in rifampicin doses was not mentioned. With higher doses of rifampicin used in the knee compared to the elbows and ankles, in all joints an improvement in the total WFH joint physical scores, as well as a significant reduction of the number of bleeds and pain was described by Suh et al.[33] They also suggested that synovectomy with rifampicin may prevent repeated haemarthrosis and therewith be beneficial especially in the early stage of arthropathy without joint space narrowing by preserving joint status.

A single treatment with rifampicin is relatively inexpensive when compared to RSO. Nevertheless, synovectomy with rifampicin usually demands weekly or fortnightly injections (sometimes up to 10 in knee joints) in order to achieve the expected results. This makes the treatment more expensive compared to RSO, due to the costs of factor concentrate supplementation before each injection. Additionally, pain postinjection of rifampicin is described often and can be a matter of concern, especially in children[30] with complaints of pain reported for up to a week after the first injection.[33]

It is generally accepted that chemical synoviorthesis is a good alternative to RSO when radiopharmaceuticals are not available.

4.2 | Radioactive synovectomy

Radioactive synovectomy or radiosynoviorthesis (RSO) consists of the intra-articular injection of a radiopharmaceutical (RP). The RP should be a beta-emitting radioisotope coupled with a carrier particle. RSO has been used over five decades for the treatment of refractory synovitis in patients with rheumatoid arthritis and other inflammatory conditions, such as haemophilic synovitis.[27-30,34-37] Yttrium-90 (^{90}Y) in the forms of colloid citrate or silicate and rhenium (^{186}Re) sulphide are the preferred beta-emitting radioisotopes in Europe, while chromic phosphorus (^{32}P) is currently the most used RP in North America.[36] These treatments are effective in decreasing the number of joint bleeds and pain, and improving the range of motion.[27-30,34-36] After the initial 48 hours of the limb immobilization post-RSO, it is strongly recommended to initiate a rehabilitation programme. This is also very important after chemical synoviorthesis. Rehabilitation is important to achieve improvement of the range of motion once the joint effusion is reduced and aims at gaining strength and mobility after synovectomy.

Like other nuclear medicine therapies, the success of RSO depends, among other factors, on the therapeutic dose effectively delivered to the target tissue, which in this case is the hypertrophic synovium.[34,35,37] While RPs applied to RSO are mostly absorbed by the synovium, and the remaining tissues receive negligible doses of radiation, the minimization of radiation exposure to non-target structures is advised. In this regard, regulatory agencies recommend the individualization of radiation doses to patients.[34,36] Tailoring doses for RSO, however, is a challenging task due to the difficulty in delineation of the synovial hypertrophic tissue.[37] Some groups perform ongoing studies regarding individualization of ^{90}Y dosing, applying Monte Carlo calculations and density specific anatomic models of the joints.[37,38] The choice of RP, the administered activity, joint size and synovial thickness should be considered when calculating the proper injected activity, in order to achieve the ablation of the synovium without damaging non-target tissues.[37]

Despite the short half-life of the abovementioned radioisotopes a continuous therapeutic effect (up to 8 weeks) after RSO in the deeper inflamed layers of the synovia is expected due to a showering effect of the radioisotopes.[36] Therefore, patients should be evaluated at least 3-6 months after the RSO procedure, in order to avoid over or under treatment. In case of severely thickened synovium fractionated doses of RSO repeated within shorter intervals might be indicated. The individual cumulative activity of ^{90}Y should not exceed 400 mCi,[34,36] which hardly occurs considering the needed activity of around 5 mCi for knee joints.[27,35]

The timing to perform RSO is a matter of debate among musculoskeletal professionals and haematologists.[39] Ideally, this therapy should be employed before joint destruction occurs, and in haemophilia it can be indicated during childhood. Many authors consider that the benefits of RSO in patients younger than 20 years old outweigh the potential risks.[27,35,37]

A good understanding of the pathophysiology of haemophilic arthropathy and the interdisciplinary collaboration for decision-making are mandatory for individualized risk/benefit analysis and justification of RSO.[36] Not every country has the ability to produce radiopharmaceuticals, therefore requiring importation in order to organize a local a RSO programme. This should be done in accordance to strict national and international radioprotection requirements.[36].

Currently RSO presents the best risk-benefit alternative to treat chronic haemophilic synovitis (see Table 1). Alternatively, chemical synoviorthesis can be used, when RSO is not possible.

5 | SURGICAL SYNOVECTOMY

Surgical synovectomy, which warrants removal or destruction of inflamed friable synovial tissue, is a useful tool in the management of recurrent synovitis. The major goals of synovectomy are reduction of bleeding episodes and maintenance of joint function. Indications of synovectomy are patients with subacute or chronic synovitis with no response to medical treatment for at least 6 months with a moderate radiological score for the joint. Sometimes synovectomy can be performed for advanced stage disease when combined with debridement of articular cartilage fragments causing mechanical impingement. Surgical synovectomy is the preferred treatment option over non-surgical synovectomy (radiation/ chemical) in patients with active haemarthrosis, ruptured Baker's cyst, rotator cuff tear, instability and those predisposed to late radiation induced neoplasia (see Table 1). Severe joint space reduction and significant loss of motion are contraindications to synovectomy.[40]

5.1 | Open surgical synovectomy

Open surgical synovectomy for the treatment of haemophilic synovitis was first described by Storti et al.[41] This method is effective in decreasing the number of subsequent haemarthroses (>80%) by removal of the pathologic inflamed synovium. However, the invasiveness of the procedure and the major consequence of loss of movement made open synovectomy a rather undesirable procedure.[42] Additionally, the procedure required large amounts of clotting factor replacement and prolonged hospital stay. The natural progression to end-stage arthropathy was inevitable. Other reported complications following open synovectomy are infection, stiffness, fracture following manipulation and postoperative haemarthrosis.[42]

Mingo-Robinet et al[43] reviewed their experience of open synovectomy of 32 ankle joints in 21 haemophilia patients with a median follow-up of 15.4 years. The procedure was carried out under tourniquet using dual incision: anterolateral and posteromedial. The study reports effective control of pain and even if the bleeding episodes were frequent, they were less severe in intensity requiring less clotting factor replacement. The study reiterates that synovectomy can retard the progression of disease but cannot stop it.

Sneppen et al[44] in their review of open synovectomy on 23 joints (17 knees, five ankles, one hip) asserted that the reduction in the number of bleeds was significant ($P < .01$). However, in the light of complex postoperative rehabilitation and loss of motion, they concluded that synovectomy should be used with strict indications in cases with intractable disease.

Rampal et al[45] studied long-term results of open synovectomy of 23 knees with a median follow-up of 8.8 years. Indications for synovectomy were recurrent bleeding, synovial hypertrophy and chronic synovitis. Complete synovectomy was achieved by the use of a long medial parapatellar incision and a posterolateral incision. The author advocates early initiation of physiotherapy along with continuous passive motion (CPM) machine which has been found effective in reducing the hospital stay. The extensive removal of damaged synovium aided by the use of a posterolateral approach along with adequate factor replacement and early initiation of movements have reduced the incidence of bleeding with less loss of motion postoperatively.

5.2 | Arthroscopic synovectomy

As arthroscopic techniques developed in 1970, arthroscopic synovectomy became a popular treatment modality as compared to the open procedure. This novel technique was first performed at the University of Health Sciences Centre, Colorado in 1980. Weidel[46] presented his work on 5 cases of arthroscopic synovectomy at the World Federation of Haemophilia Congress in Stockholm in 1983. The advantages such as less invasiveness, rapid recovery, decreased postoperative bleeding, reduced hospital stay, improved range of motion advocated the use of arthroscopic synovectomy in knee, ankle and elbow joints.[47]

Patients with single joint involvement having subacute or chronic synovitis not responding to conservative measures after 3-6 months are ideal for arthroscopic synovectomy. All patients planned for arthroscopic surgery should be screened for inhibitors and conventional radiographs prior to surgery. Although advanced arthropathy and high inhibitor titres are considered (relative) contraindications for surgical synovectomy (open and arthroscopic), some cases of advanced stage disease can be managed with arthroscopic synovectomy and debridement of loose cartilage pieces and flaps.

Dunn et al[48] reviewed the success of arthroscopic synovectomy in haemophilic joint disease in 69 joints (39 ankles, 21 elbows, seven knees, two shoulders) over a median follow-up of 79 months. The author used a 4.2 mm arthroscope for most joints and occasionally a 2.7 mm scope for small ankles and elbows. A motorized full-radius synovial resector was used and use of CPM and Cryo-cuff was advocated. Standard 4 portals (anteromedial, anterolateral, medial and lateral suprapatellar) were used for knee synovectomy. Posterior compartment disease may necessitate the use of a posteromedial or posterolateral portal. Ankle synovectomy with 2-3 anterior and two posterior portals with manual distraction provided adequate disease clearance. Elbow procedure in prone position using standard anteromedial, anterolateral and three posterior portals was carried out. This study documented a median reduction in bleeding episodes of 84% ($P < .001$). A retrospective review of 28 arthroscopic synovectomies by Journeycake et al[49] also concluded that this procedure can be considered in young haemophilia patients with chronic synovitis with good clinical outcome.

Arthroscopic evaluation of the posterior compartment of the knee may be difficult in haemophilia patients due to osteophytes and bony deformities resulting in recurrences of breakthrough bleeding. Yoon et al[50] proposed the use of six portals (two anterior, two suprapatellar, two posterior) along with an additional posterior trans-septal portal in all cases to carry out optimal removal of the pathologic tissue. The

average frequency of bleeding and requirement of factor was significantly reduced with this modification. Arthroscopic ankle synovectomy for haemophilia patients is also a viable option as compared to open synovectomy to reduce the incidence of joint bleeding and maintaining ankle function.[51] Use of a mechanical distractor for facilitation of synovectomy was first described by Guhl.[52] A contraindication to the use of a distractor is open physis due to the risk of physeal separation. The combination of arthroscopic techniques which are minimally invasive along with immediate mobilization using CPM has shown to produce maximum benefits with minimum complications of synovectomy.[53] The financial benefit of arthroscopic synovectomy was found to be statistically significant when the average preoperative cost per month was compared to the postoperative cost.[54]

Successful outcome in synovectomies for haemophilic arthritis or synovitis largely depends upon timely surgical intervention. It is suggested that synovectomy should be initiated early as young patients have more favourable improvement in range of motion as compared to older patients.[55] Complications such as postoperative bleeding, pseudoaneurysm, development of AV fistula are reported with very low incidence. Success of arthroscopic synovectomy depends upon a multidisciplinary approach including a well-equipped haemophilia centre with orthopaedic expertise, adequate availability of factor, adherence to postoperative physiotherapy and appropriate patient counselling and motivation.

6 | CONCLUSION

The most common and disabling long-term complication of haemophilia is intra-articular bleeding which can result into chronic synovitis and ultimately crippling arthropathy. Synovitis may develop due to a chronic self-perpetuating cycle of haemarthrosis-synovitis-recurrent haemarthrosis that needs to be interrupted. If factor supplementation and rest with gradual activity increase fails, (non-)surgical therapy may be indicated. Successful outcome in young and adolescent patients with haemophilic synovitis requires a multimodal approach involving appropriate patient screening and preoperative evaluation, adequate on-demand factor availability and timely surgical intervention. The major goals of synovectomy are to reduce bleeding and maintain joint function. The progression of arthropathy after synovectomy is delayed but not completely halted.

DISCLOSURES

The authors stated that they had no interests which might be perceived as posing a conflict or bias.

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