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CHRONIC HEMOPHILIC SYNOVITIS: THE ROLE OF RADIOSYNOVECTOMY

Mauricio Silva
James V. Luck Jr.
International Hemophilia Training Center at Orthopaedic Hospital
David Geffen School of Medicine
California, United States

Adolfo Llinás
Hemophilia Treatment Center
Fundación Santa Fé de Bogotá and Fundación Cosme y Damián
Bogotá, Colombia

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World Federation of Hemophilia
1425 René Lévesque Boulevard West, Suite 1010
Montréal, Québec H3G 1T7
CANADA
Tel. : (514) 875-7944
Fax : (514) 875-8916
E-mail: wfh@wfh.org
Internet: www.wfh.org

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Chronic Hemophilic Synovitis: The Role of Radiosynovectomy

Mauricio Silva, James V. Luck Jr., Adolfo Llinás

Introduction

Intra-articular hemorrhage is the most common musculoskeletal manifestation of hemophilia. An acute hemarthrosis is characterized by a rapid swelling of the joint; it may be preceded by a prodrome of stiffness and pain.[1] With adequate management, a joint that has suffered an acute hemarthrosis generally returns to its normal status. It is common, however, to observe a pattern of repeated bleeding (chronic hemarthrosis), especially in patients with severe hemophilia, that can lead to chronic synovitis, inflammatory arthritis, and progressive arthropathy.[2,3,1,4]

Therefore, the key to the successful prevention of hemophilic arthropathy is an aggressive management of the initial hemarthrosis. This is generally accomplished with the use of clotting factor replacement, joint aspiration in severe bleeds, restorative physiotherapy, and close clinical follow-up. If chronic synovitis develops, synovectomy should be undertaken in order to decrease the progression of the hemophilic arthropathy and to prevent the development of major articular surface erosions that can lead to end-stage arthropathy (severe arthritis and joint deformity).

The purpose of this monograph is to review the pathogenesis of chronic hemophilic synovitis, its clinical characteristics and therapeutic options, with special emphasis on radiosynovectomy performed with ^{32}P Chromic Phosphate.

Pathogenesis of Hemophilic Synovitis

The origin of hemophilic synovitis is clearly related to chronic accumulation of blood within a joint.[2,3,1,4] Blood is not a normal constituent of the synovial fluid. When intra-articular bleeding occurs, the collected blood breakdown products must be removed from the joint by the synovial membrane. Iron, an abundant element of blood, acts as a potent stimulus to the synovial cells, inducing an inflammatory reaction[5,4]

A normal synovial membrane has the ability to absorb the breakdown products of blood after an acute, isolated hemarthrosis. Therefore, isolated joint bleeds occurring early during childhood generally only result in transitory, non-specific synovial inflammatory changes. However, when bleeding occurs repeatedly into the same joint over a period of a few weeks, the amount of blood breakdown products overwhelms the synovial membrane's ability to absorb them and transfer them to the central circulation system. Phagocytic synovial "A" cells (Figure 1) are laden with iron-containing hemosiderin.

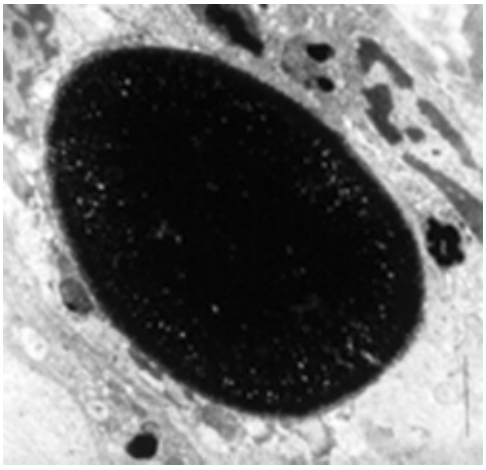

Figure 1: Phagocytic synovial "A" cells laden with iron-containing hemosiderin.

As a result, the synovial membrane becomes chronically inflamed, with a subsequent increase in volume (synovial hypertrophy). Increased blood flow is required by the synovial tissue in order to be able to remove the blood debris from the joint effectively. The result is the development of a rich network of capillaries underneath the hypertrophied synovium, with dilated venous sinusoids.[2,6] The now hypertrophic and highly vascular synovial tissue (Figures 2 and 3) is prone to impingement between the articular surfaces, increasing the likelihood of new bleeding episodes.[6]

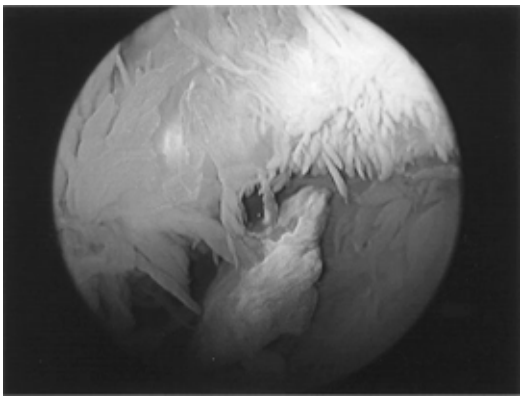

Figure 2: Arthroscopic image of the knee of a hemophilic patient with chronic synovitis. The synovial membrane shows generalized villous formation, with an increased vascularity.

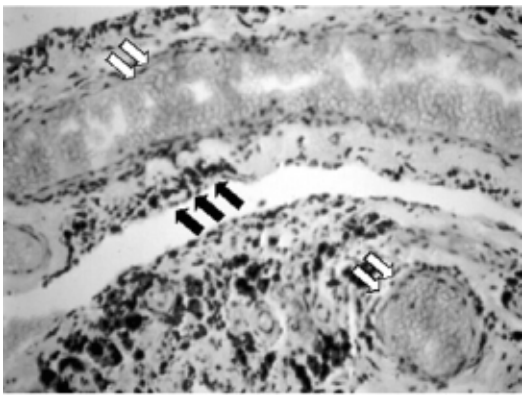

Figure 3: Photomicrograph of chronic synovitis in the stage of chronic hemarthrosis. Note dense hemosiderin deposition in phagocytic surface and perivascular cells (black arrows). Dilated venous sinusoids lie just beneath the surface that can be easily ruptured (white arrows).

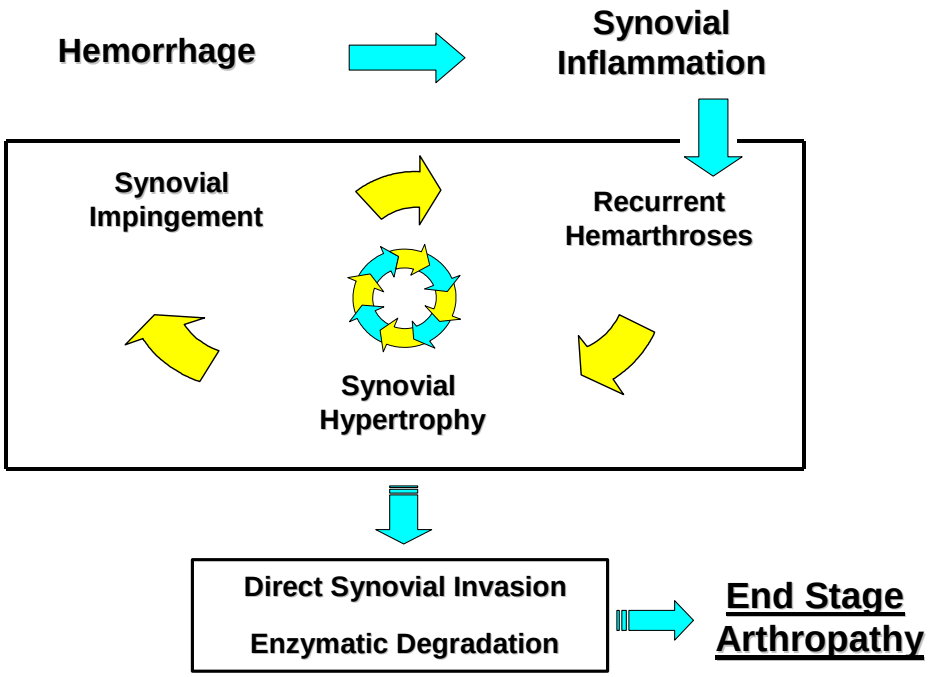

Figure 4: A chronic, self-perpetuating cycle of hemarthrosis-synovitis-hemarthrosis.

A chronic, self-perpetuating cycle of hemarthrosis-synovitis-hemarthrosis is established (Figure 4). This vicious cycle does not usually repair itself. Once this stage of chronic synovitis is reached, mechanical, chemical, and enzymatic mechanisms play a significant role in the destruction of the articular cartilage, and this may lead to a progressive degeneration of the joint.[2,7,8,1,9,5,10,4] Therefore, it is of extreme importance to break the hemarthrosis cycle as early as possible, ideally before any development of articular destruction. If this is accomplished, the patient should be able to reach skeletal maturity with functional

joints, minimal limitations, and a better quality of life.

Clinical Characteristics of Hemophilic Arthropathy

Hemarthrosis is the hallmark of the articular involvement in hemophilia. Although any joint can be involved, the most frequently affected joints are, in decreasing order, the knees, elbows, ankles, hips, and shoulders. Clinically, hemarthrosis can be defined as acute or chronic.

Acute hemarthrosis

This is defined as rapid bleeding into the joint. The origin of the bleeding is usually unrelated to trauma, especially in severe hemophilic patients. A prodrome of stiffness, tingling, and pain is usually noted by the patient [1]. The joint is held in flexion to minimize the resultant higher intra-articular pressure and reduce pain. The joint becomes swollen, reddish, tender, and hot. Characteristically, an acute, isolated accumulation of intra-articular blood in an otherwise healthy hemophilic joint resolves completely after a short period of time (less than two weeks), usually as a result of clotting factor administration. In general, acute hemarthrosis does not result in secondary changes to the synovial cells. Once resolved, the patient generally remains free of new bleeding episodes for prolonged periods of time.

Chronic hemarthrosis

In some cases, a new acute bleeding episode occurs before a previous hemarthrosis has completely resolved. Since it usually takes about two weeks for the synovial membrane to completely absorb the breakdown products of an acute, isolated intra-articular hemorrhage, the presence of more than two to three episodes of acute joint bleeding per month can overwhelm the absorptive capability of the synovial membrane. As a result, the intra-articular joint space becomes chronically filled with blood (chronic hemarthrosis).

Clinically, the patient experiences multiple episodes of acute hemarthrosis during a single month (pain, tingling, and stiffness), indicating that the affected joint never goes back to normal. As with acute hemarthrosis, the joint is held in flexion to decrease pain. However, due to the fact that this position is adopted for prolonged periods of time, the likelihood of developing permanent joint deformities is higher.

During the early stages of chronic hemarthrosis, the physical exam of the affected joint will only reveal signs of acute bleeding. Because prolonged exposure of the synovial membrane to blood is a potent stimulus for synovial cell hypertrophy, physical examination of the joint in patients that have had longer exposure to chronic hemarthrosis will reveal a thickened synovial membrane (chronic synovitis). Figure 5 shows a patient with chronic hemophilic synovitis of the left knee.

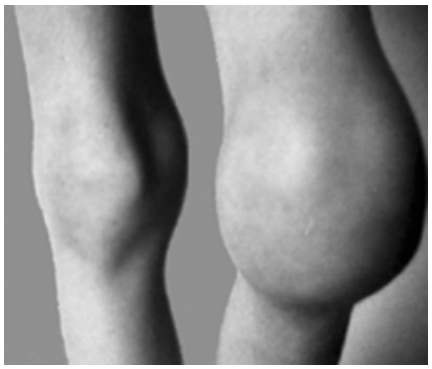

Figure 5: chronic synovitis of the left knee.

Therapeutic Options for the Treatment of Chronic Synovitis

The key to the successful prevention of degenerative arthritis is the management of initial hemarthrosis, before the development of chronic synovitis and articular surface erosions. Therefore, the management of acute hemarthrosis in a normal joint should be aggressive and include aspiration, regular clotting factor replacement, restorative physiotherapy, and close clinical follow-up.[11]

It is very important to initiate a physiotherapy program as soon as the patient can tolerate it, taking precautions to avoid recurrent bleeding. The goals of physiotherapy are muscle strengthening, recovery of range of motion, and improvement in propioception or joint position awareness and gait patterns.[12] Improved strength and mobility will help reduce the risk of recurrent joint bleeding. For patients with early chronic hemarthrosis, the use of short-term oral

or intra-articular steroids has shown beneficial effects, decreasing the synovial volume and, therefore, the risk of impingement.[13]

Prophylactic clotting factor replacement

In an attempt to limit and control joint bleeding, primary and secondary prophylactic clotting factor replacement regimens have been developed. With "primary" prophylaxis, initiated prior to, or shortly after, a child's first joint bleeding episode, patients are given enough clotting factor every other day, or on some other feasible schedule, so that the clotting factor level will be maintained above 1% at all times in order to prevent spontaneous hemarthrosis and the development of a target joint.[14] With "secondary" prophylaxis, the goal is to prevent additional damage to a joint that has bled previously.[15] Clotting factor is given every day, or every other day, until the joint has returned to normal. However, once recurrent bleeding and chronic synovitis has developed, the use of prophylactic clotting factor does not yield very impressive results. It has been reported that, in hemophilic patients with synovitis, only about 40% obtained adequate bleeding control with a carefully supervised clotting factor prophylaxis protocol, using higher doses than are recommended for primary prophylaxis, for up to nine months.[16] Besides a limited therapeutic benefit, the other major concerns with this type of treatment include the high associated costs and the inherent risks to prolonged exposure to plasma products, especially if they are not viral inactivated.

Synovectomy

It has long been recognized that the emergence of chronic hemophilic hemarthrosis is incited by a hypertrophic and highly vascular synovium and that removal of this synovium is the key to prevention of further joint damage.[17] Removal of the synovium can be accomplished through surgical and non-surgical procedures.

A. Surgical synovectomies

Surgical excision of hypertrophic synovium can be accomplished through open or arthroscopic procedures. Historically, synovectomy for chronic hemophilic synovitis was performed through an open arthrotomy.[18,3,19,20,21,22] With extensive surgical approaches, most of the synovium can be removed from a joint. The success rate of open synovectomy in controlling recurrent bleeding was over 80%. Most of these procedures were performed in patients who already had extensive joint surface destruction, however, and a natural progression to end-stage disease was eventually observed. Many patients had difficulty regaining range of motion following open synovectomy. Additionally, the procedure required massive amounts of clotting factor replacement and prolonged hospitalization. For these reasons, open synovectomies have been largely abandoned.

With the advent of arthroscopy, open procedures were replaced by arthroscopic synovectomies.[23,24] In terms of their ability to remove synovium, arthroscopic synovectomies are nearly equivalent to open synovectomies. The success rate of arthroscopic synovectomy in terms of recurrent hemarthrosis is slightly less than that of open synovectomy. However, the procedure is associated with less frequent loss of motion. A drawback is that patients undergoing arthroscopic synovectomy still require hospitalization, massive amounts of clotting factor replacement, and exhaustive physiotherapy. Moreover, most patients with clotting factor inhibitors are not candidates for surgical synovectomies (open or arthroscopic).

B. Non-surgical synovectomies

Certain substances, once injected intra-articularly, have the ability to decrease the volume and activity of the synovial tissue. Among them are chemical and radioactive agents which have been used for the treatment of chronic synovitis. Due to the minimally invasive nature of these procedures, non-surgical synovectomies are of special importance for hemophilic patients with inhibitors to clotting factors.

B.1 Chemical synovectomies:

Chemical synovectomies, using thiotepa, osmic acid, D-penicillamine and other agents, have been used in the distant past. These early agents used for chemical synovectomies had the advantage of being easily available and relatively inexpensive. However, their use was associated with limited clinical success.

Rifampicin, which has been in the therapeutic armamentarium for several years as an antibiotic, is now the most commonly used

chemical for the purpose of synovectomy, and the one that has shown better results in terms of decreasing hemarthrosis.[25] A weekly intra-articular injection of rifampicin, performed on an outpatient basis, is required for as long as the synovitis persists. Each one of the injections should be accompanied by prophylactic administration of clotting factor concentrate. Excellent results (no synovitis and restoration of previous function) in up to 83% of patients have been reported at an average of 2.4 years after the intra-articular injection of rifampicin.

As the pathology of the joint becomes more severe, however, the number of injections required to achieve improvement increases. Younger patients and smaller joints benefit more from this procedure. Since rifampicin is inexpensive, readily available, and does not deteriorate on storage, it seems an appealing alternative for the treatment of chronic hemophilic synovitis. Injections are painful, however, despite the fact that the joint is usually injected with a local anesthetic. Multiple injections are required to obtain satisfactory results. This method is used when more effective and comfortable alternatives are not available. Savings in cost of agent used are offset by the need for multiple procedures.

Due to the limited availability of rifampicin in some developing countries, oxytetracycline clorhydrate, a broad-spectrum antibiotic with sclerosing properties, has been used recently in South America to perform synovectomies in hemophilic patients**.** Although it appears to be as effective as rifampicin to control synovitis, this antibiotic also requires the use of multiple injections which are associated with significant local pain.

B.2 Radiation synovectomies:
Radiosynovectomy and radiosynoviorthesis are common terms used to describe the synovial ablation accomplished by intra-articular injection of radioisotopes. Although multiple isotopes have been used with this purpose, the "ideal" isotope would have pure beta-emissions, a shallow depth penetration (to focus the effect on the synovium and to avoid the potential risk of radiation to surrounding tissues), and a moderate half life (to allow a gradual energy deposition and avoid immediate inflammatory reactions seen with very rapidly decaying isotopes).[26] In order to keep the radioactive material from escaping outside the joint and to avoid whole-body radiation and its systemic effects, isotopes should be bound to carriers of sufficient molecular size. The "ideal" carrier would have a particle size of about 10 microns, would be non-toxic, easy to use, and would degrade at the same rate as the isotope.

B.2.1 Choice of isotope:
Multiple radioisotopes, such as $Gold^{198}$, $Yttrium^{90}$, $Rhenium^{86}$, $Dysprosium^{66}$, and ^{32}P Chromic Phosphate, have been used to perform radiation synovectomies in hemophilic patients. $Rhenium^{186}$ and $Gold^{198}$ have been associated with an increased risk of chromosomal breakage due to gamma radiation and systemic absorption, and are mostly in disuse.[27,28,29,30,31,32,33,34] $Yttrium^{90}$, a pure beta emitter with adequate particle size and depth penetration, has been used successfully for the treatment of hemophilic synovitis. Due to its short half-life, however, secondary inflammatory reactions have been described [35,26,36]. ^{32}P Chromic Phosphate, the current agent of choice in the United States and Canada, is a pure beta emitter, with a particle size between 6 and 20 microns, 3 to 5 mm of penetration, and a half-life of 14 days.[37,38,39,40,41] (Table 1)

B.2.2 Safety:
Safety is a function of local (growth plate and articular cartilage) and remote effects of radiation. There have been no reported cases of growth plate disturbance after radiosynovectomy, even after the use of gamma-emitters such as $Gold^{198}$.[27,31] Articular cartilage is highly resistant to radiation and, although damage is theoretically possible, none has been reported. Progressive degeneration of treated joints does occur, but the rate is slower than the one expected without radiosynovectomy.

The principal concern is the potential of late, radiation-induced neoplasia. External beam radiation has been extensively studied and carries a small risk of osseous sarcoma induction. Because of the low penetration of ^{32}P Chromic Phosphate, bone exposure is minimal. Furthermore, the intra-articular site is extremely rare for sarcomas of any type.

Table 1. Features of radioisotopes more frequently used for synovectomy in hemophilic patients

	^{32}P	^{90}Y	^{198}Au	^{86}Re	^{165}Dy
Radiation	β	β	β and γ	β and γ	β
Particle Size (μ)	6-20	10-20	3	0.1	3-5
Penetration (mm)	3-5	4-10	1-4	1-4	6
Half Life (days)	14	2.4	2.7	3.8	0.1

Probably the strongest argument for the safety of intra-articular radioisotopes is the long-term follow-up of the more than 5,000 radiation synovectomies performed for rheumatoid arthritis, none of which have reported development of radiation-induced malignancies.[42]

Chromosomal changes after radiation synovectomy have been studied extensively. Even though non-specific chromosomal changes have been described in a very small proportion of patients soon after radiation synovectomy with pure beta-emitter isotopes, these changes disappear by the end of the first year post-procedure. More importantly, no pre-malignant chromosomal structural changes have been described in these patients.[29,30,14]

B.2.3 Indications:
Joint destruction can be prevented if frequent joint bleeding is effectively eliminated before the onset of arthropathy. Therefore, radiation synovectomy should be performed before irreversible joint destruction occurs. Following this principle, the ideal candidate should be a hemophilic patient with frequent hemarthrosis (two to three bleeds per month) in a target joint, who has failed conservative treatment with clotting factor replacement and physiotherapy, and who has no radiological evidence of joint damage. In reality, most patients seen at hemophilia centres for chronic hemarthrosis and synovitis already have some degree of articular deterioration. This should not disqualify them as candidates for radiosynovectomy, although patients must clearly understand that articular degeneration already present cannot be improved with the procedure. The aim is to control joint bleeding and prevent further damage.

B.2.4 Procedure:
Radiation synovectomy can be done on an outpatient basis. Some inhibitor patients are kept in the hospital overnight to be monitored for possible bleeding. In general, patients receive a dose of clotting factor to attain a plasma level of 50% of normal. To the authors' knowledge, doses as low as 10 I.U./kg have been used with satisfactory results in developing countries where access to clotting factors is limited. Inhibitor patients receive the clotting factor historically most effective in controlling their bleeding episodes.

The joint involved is prepped with providone iodine and draped with sterile towels. Xylocaine 1% is infiltrated into the skin, subcutaneous tissue, and capsule, using a 27-gauge needle. After satisfactory anesthesia, a larger needle is inserted into the joint. Generally, 22-gauge needles are used for elbows and ankles and 20-gauge needles for knees and shoulders. If needed, a larger bore needle can be used. However, smaller bore needles reduce the likelihood of radioisotope backflow, especially in subcutaneous joints. Achievement of an intra-articular position of the needle is critical, and should be confirmed by aspiration of blood or synovial fluid (Figures 6 and 7).

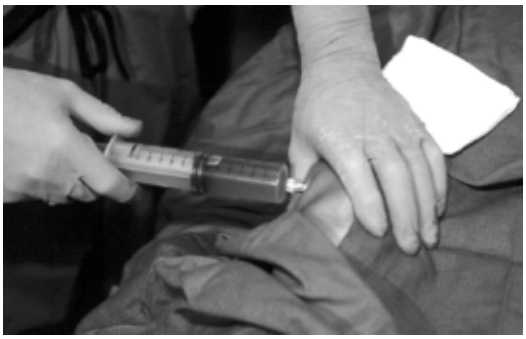

Figure 6: The accumulated blood should be removed from the joint as thoroughly as possible before the injection of the isotope.

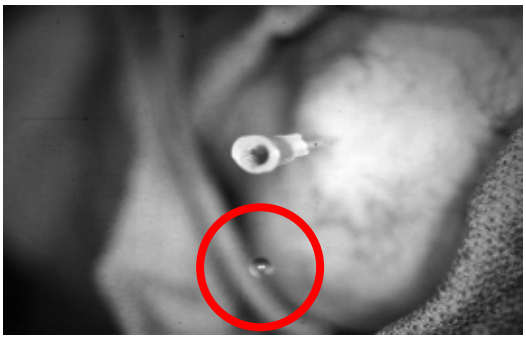

Figure 7: Confirmation of intra-articular position of the needle should be obtained by aspiration of synovial fluid or blood. The circle indicates a drop of synovial fluid that has just fallen from the needle.

In cases where fluid cannot be aspirated, the intra-articular position of the needle can be confirmed by injection of a radiographic dye under image intensifier visualization. Once the needle's position inside the joint space is confirmed, the selected radioactive isotope is injected into the joint using a separate syringe. (Figure 8)

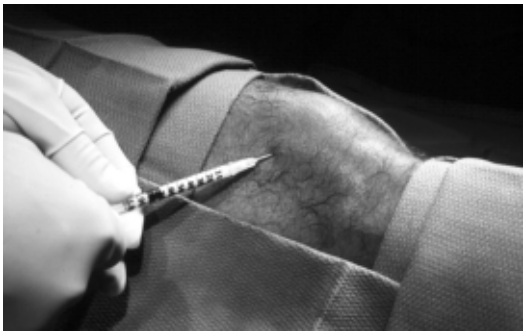

Figure 8: Radioactive isotope is injected into the joint using a separate syringe.

In adults, a dose of 1 mCi is used for large joints (knees and shoulders) and a dose of 0.5 mCi for smaller joints. In children, these doses should be halved. Following injection of radiocolloid, a mixture of xylocaine and dexamethasone acetate is injected into the joint through the same needle, to minimize synovial inflammatory reactions. As the needle is withdrawn from the articular space, the needle track should be bathed with the anesthetic-steroid mixture to reduce the risk of backflow isotope leakage. Pressure on the injection site should be applied for about two minutes. A small adhesive bandage is usually enough to cover the injection site.

After finishing the injection procedure, the joint should be put through range of motion in order to disperse the radioisotope throughout the synovial surface. While flexing the joint, pressure should be maintained on the injection site. The treated joint should be immobilized for two days, and the patient advised to avoid strenuous activities for two weeks.

B.2.5 Clinical results of radiation synovectomy:
Results of ^{32}P Chromic Phosphate radiosynovectomies from several centres have shown very similar, good clinical results averaging 75% reduction in hemarthrosis.[37,39,40,41,43] A recent report of our experience included the outcome of 130 procedures, of which 115 were primary and 15 repeat procedures, with follow-ups between six months and 12 years. A 75-100% reduction in hemarthrosis frequency was obtained, on average, in 80% of the primary cases and 62% of the repeat cases.[41]

Compared to surgical synovectomies, radiosynovectomy is minimally invasive which results in better preservation of range of motion, does not necessitate hospitalization and requires minimal coverage with clotting factor. Since procedure costs are closely related to hospitalization time and clotting factor requirements, radiosynovectomies are much less costly than surgical synovectomies. In the U.S.A., the average cost of radiosynovectomy is about US$3,000, compared to US$61,000 for surgical synovectomy.[41]

Overview

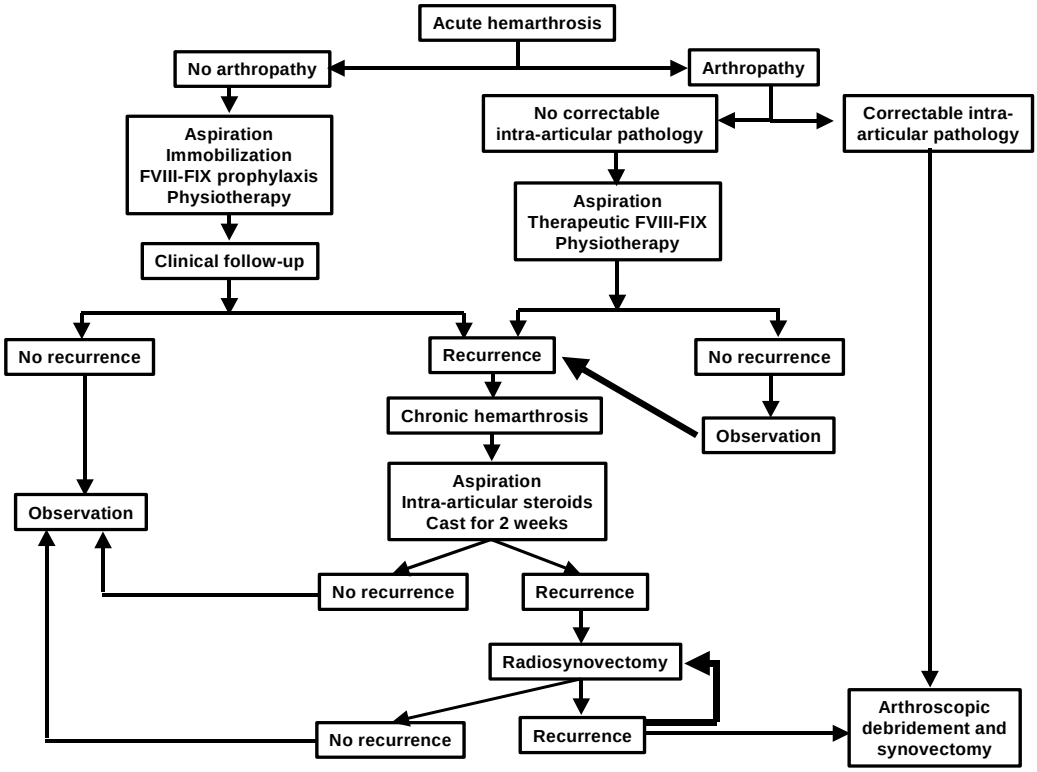

Figure 9: A suggested algorithm for the treatment of patients with acute hemarthrosis and chronic synovitis.

The key to the successful prevention of hemophilic arthropathy is an aggressive management of initial hemarthrosis, before the development of chronic synovitis. Figure 9 summarizes a suggested algorithm for the treatment of patients with acute hemarthrosis and chronic synovitis [44].

The treatment of an acute hemarthrosis should be accomplished with the use of regular clotting factor replacement, restorative physiotherapy and close clinical follow-up. However, if chronic synovitis develops (arthropathy), synovectomy should be undertaken in order to decrease the progression of the hemophilic arthropathy and to prevent the development of end-stage arthropathy.

When available, radiosynovectomy with an adequate isotope is the treatment of choice. The use of rifampicin should be considered in cases where isotope synovectomy is not accessible, while recognizing that multiple injections may be required.

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