

SYNOVIORTHESIS IN HAEMOPHILIA

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Abstract

Introduction

Recurrent haemarthroses will inevitably lead to significant hypertrophic synovitis in patients with haemophilia (PwH), progressive joint cartilage degradation, ultimately resulting in haemophilic arthropathy with significant functional impairment of the affected joints. The degree of haemophilic synovitis is directly related to an increase in bleeding frequency in the affected joint.

Synoviorthesis or non-surgical synovectomy is a therapeutic method which consists in injection into the joint of a substance acting on the synovial membrane by means of a fibrosis that constricts the subsynovial plexus and thus prevents future bleeding. Synoviorthesis can be medical or pharmacological. There are two groups of preparations: chemical and radioactive isotopes.

Chemical synovectomy uses osmic acid, rifampicin. Joint injections with hyaluronic acid, intra-articular corticosteroid therapy and per os D-penicillamine have been proposed as therapy. Radioactive synovectomy uses isotopes like ¹⁹⁸Au (gold), ⁹⁰Y (yttrium), ¹⁸⁶Re (rhenium), ¹⁶⁹Er (erbium).

Material and methods

A review of the international literature on the subject of synoviorthesis and alternative options in case of its failure has been conducted.

Results and discussions

Synoviorthesis should be the first choice of treatment for persistent synovitis of the joints. It is a simple procedure, which eliminates the risks associated with surgery. Chemical synoviorthesis with osmic acid has been partially abandoned because of occurred complications and semicritical pain associated with this procedure. Radioactive synoviorthesis has a higher overall efficiency than chemical synoviorthesis, but is associated with the risk of malignancy, as recently published studies show. Rifampicin has similar results to ⁹⁰Y when used in small joints, but needs multiple injections. Besides that it is not suitable for knee synoviorthesis. If three consecutive synoviortheses at 3 to 6 month intervals, as well as 7-8 chemical synoviortheses fail, arthroscopic synovectomy is indicated, which is a surgical method presenting the risk of general anesthesia and associated complications.

Conclusions

Synoviorthesis is a highly effective procedure that decreases both the frequency and the intensity of recurrent intra-articular bleeds related to joint synovitis. The procedure should be performed as soon as possible to minimize the degree of articular cartilage damage, which, based on many studies, is irreversible. It can also be used in patients with inhibitors with minimal risk of complications.

On average, synoviorthesis has a 75-80% satisfactory outcome in the long term. Global results of treatment with chemical synovectomy seem to be less favourable than with radionuclides. In cases where the synovium is thicker than 5-10 mm, and haemarthroses persist following synoviorthesis, arthroscopic synovectomy is indicated.

Key words: hemophilia, chronic synovitis, synoviorthesis

Introduction

A synoviorthesis consists of the intra-articular injection of a certain material with the aim of 'stabilizing' (orthesis) the synovial membrane of a joint (synoviorthesis). There are two basic types of procedures for synovial control: medical synovectomy (or synoviorthesis) and surgical synovectomy (open or arthroscopic.) It is commonly accepted today that synoviorthesis is the procedure of choice, and that surgical synovectomy should be performed only if a number of consecutive synoviortheses fail to stop or diminish the frequency of recurrent haemarthrosis. Thus, the main indication for a synoviorthesis in a haemophilic joint is hypertrophic synovitis and recurrent bleeding. Synoviorthesis has been utilized for more than 25 years.

In 1959, Margaret Swanton¹, in a landmark study of haemophilic dogs, showed that the synovium was the initial site of bleeding in the development of an haemarthrosis. Diffuse intrasynovial bleeding was followed by extravasation of blood into the joint space, an inflammatory response with secondary hyperaemia of the synovium, and recurrent bleeding. Untreated haemarthroses resulted in a pattern of joint destruction termed 'Haemophilic Arthropathy'². In 1968 an article appeared in the Lancet entitled, 'Synovectomy for Haemophilic Haemarthrosis'³. Professor Storti felt that by eliminating the site of intra-articular bleeding one could eliminate recurrent bleeding and possibly prevent the development of arthropathy. Other authors, Pietrogrande et al.⁴, Mannucci et al.⁵, McCollough et al.⁶, and Kay et al.⁷, reported that most patients studied showed a reduction in bleeding frequency but noted that synovectomy was not without its problems. Kay et al.⁷ concluded that 'the post operative complication rate was high'. They reported secondary haemorrhage, infection and a supracondylar fracture of the femur during manipulation under anaesthesia in addition to post operative loss of motion. At the same time that surgical and arthroscopic synovectomies were being investigated there were attempts to limit the sequelae of bleeding and inflammation by nonsurgical means.

Fernandez-Palazzi⁸ reviewed his experience in the treatment of recurrent haemarthrosis and chronic synovitis by non-surgical means. Experience with synoviorthesis with

rifampicin and radioactive colloids was analysed, and a multiple chromosomal study to demonstrate safety of radioactive injections was described. The results obtained were adequately satisfactory to recommend synoviorthesis as the treatment of choice to prevent recurrent haemarthrosis.

Rodriguez-Merchan⁹ stated that the goal of both synoviorthesis and surgical synovectomy is to remove the inflamed and hypervascular synovium as soon as possible in order to prevent the onset of haemophilic arthropathy. Ideally, these methods should be performed before the articular cartilage has eroded. Radioactive synoviorthesis is an effective, relatively simple, virtually painless and comparatively inexpensive technique for the treatment of chronic haemophilic synovitis, even in patients with inhibitors. Thus, radioactive synoviorthesis is the best choice for patients with persistent synovitis. The current recommendation among orthopaedic surgeons and haematologists is that when three early consecutive synoviortheses (repeated every 6 months) fail to halt synovitis, a surgical synovectomy (open or arthroscopic) should be immediately considered⁹.

The indication for synoviorthesis is chronic hypertrophic synovitis associated with recurrent haemarthrosis that does not respond to haematological

treatment. Synoviorthesis should be performed under clotting factor coverage to avoid the risk of bleeding during the procedure. In patients with inhibitors, synoviorthesis can also be performed with minimal risk. In fact, the procedure is especially indicated in patients with inhibitors because of its ease of performance and low rate of complications compared to surgical synovectomy.

It is important to differentiate between haemarthrosis and synovitis. Acute haemarthrosis is associated with severe pain, and the joint is maintained in a position of comfort (typically in flexion). In contrast, chronic hypertrophic synovitis is not associated with as much pain. The synovium is palpable as a soft-tissue mass whereas a haemarthrosis will have a fluid characteristic. Before making the recommendation of a synoviorthesis, the diagnosis should be confirmed by radiographs, ultrasound and/or magnetic resonance imaging (MRI). Radiographs should also be taken in order to assess the degree of haemophilic arthropathy at the time of diagnosis. In many situations, synovitis and haemarthrosis coexist. (Table 1)¹⁰ The objective of the present paper is to see which are the indications for each type of synoviorthesis, depending on the degree of haemophilic synovitis/arthropathy and the results of these procedures.

Table 1 – Grading system developed by Fernandez-Palazzi and Caviglia to indicate suitability of synoviorthesis¹⁰

Stage	Indications
I Transitory synovitis	With no post-bleeding sequelae. Synoviorthesis is indicated as preventive if there are more than two episodes of haemarthrosis in 6 months.
II Permanent synovitis	With persistent thickening of the synovial membrane and diminution of range of motion. Synoviorthesis is mandatory
III Chronic arthropathy	As for grade II plus muscular atrophy and axial deformities of the limb. Synoviorthesis is helpful.
IV Fibrous or osseous ankylosis	Synoviorthesis is contraindicated.

Material and methods

A review of the international literature of the last 50 years on the subject of synoviorthesis and alternative options in this case has been conducted.

Results and discussions

The results of each type of synoviorthesis will be presented separately:

1) Intra-articular injection of corticosteroids

As far back as 1952, before the availability of concentrated factor replacement, MacAusland and Gartland advocated the use of intra-articular Hyaluronidase¹¹. Other methods of intra-articular destruction of the synovium were also investigated.

Shupak et al.¹² were among the first to report satisfactory short-term results with the intra-articular injection of corticosteroids in haemophilia.

Rodriguez-Merchan et al.¹³ performed a pilot prospective study to investigate the role of the procedure, initially in the short term and later with long-term follow-up. The primary objective of the study was to investigate a less aggressive method for the treatment of haemophilic

synovitis, given that the alternative procedures were synoviorthesis (intra-articular injections of radioactive materials) and surgical synovectomy (open or arthroscopic).

This prospective study evaluated the effectiveness of intra-articular methylprednisolone (80 mg) in 10 knees of 10 haemophilic patients with chronic synovitis. The patients were evaluated by radiographs and ultrasound before initiating treatment, and thereafter periodically for a 5-year follow-up period. One year after injection improvement in pain level was satisfactory, but pain recurred shortly thereafter. Five years after completion of treatment, all results were poor. Thus, it appears that injection of intra-articular methylprednisolone may be beneficial in relieving pain associated with arthropathy for up to 1 year but is not comparable to radiosynoviorthesis in reduction of haemarthrosis.

Fernandez-Palazzi et al.¹⁴ reported that from 1966 to 1988, 34 patients with advanced chronic haemophilic synovitis (25 grade III and nine grade IV of their own scoring system) were treated with intra-articular injections of long-acting dexamethasone (sodium phosphate of dexamethasone plus acetate of dexamethasone) in cycles of three injections with 3-week intervals between each

injection and 6-month rest intervals between cycles for as many as three cycles, depending on the evolution of each case. All patients had chronic severe synovitis, axial deformity, muscular atrophy and diminution of range of movement. The group included 31 knees, two ankles and two shoulders. Subjective and objective evaluations were carried out grouping the results in good, fair and poor categories according to patient satisfaction, presence of synovitis, pain, range of motion and limitation of activities of daily living. Subjective results included 19 good, 12 fair and four poor results. The objective evaluation showed 22 good, nine fair and four poor results at an average follow-up of 1.5 years. The use of intra-articular dexamethasone is an alternative in the short- to medium-term for treatment of advanced chronic haemophilic arthropathy with pain and limitation of function before resorting to surgical reconstruction.

2) Chemical synoviorthesis

The most commonly used chemicals have been osmic acid and rifampicin. In fact, they have been utilized as an alternative to radioactive agents because of lack of availability or fear of radiation as a potential source of malignancy.

In 1973, Menkes et al. reported their experience with the use of intra-articular osmic acid¹⁵. Their results were mixed and this procedure never achieved wide popularity.

Caruso, in the 1980's was one of the first to use rifampicin as a chemical agent for the treatment of synovitis associated with rheumatoid arthritis⁴. Rifampicin was chosen for its proteolytic and fibrinolytic properties. Despite encouraging early results there was, however, a high failure rate.

Salis et al.¹⁶ retrospectively reviewed their experience with non-surgical synovectomy in the treatment of recurrent haemarthrosis with arthropathy in patients with von Willebrand's disease, which is the most common inherited bleeding disorder, with an overall prevalence in the general population of 0.8-1.3%. Haemarthrosis occurs mainly in the most severe forms of the disease (type 3), with a frequency of 3.5-11%, and can cause severe arthropathy similar to that seen in haemophilia. Four of six patients had type 3 disease and the remaining two had type 2 disease. The age range was 13-63 years. The frequency of haemarthrosis prior to synovectomy was 1-4 per month. One (« = 2) or both (n = 1) knees were treated in four cases, one (n = 1) or both (n = 1) ankles in three cases and an elbow in one case. ⁹⁰Y was used in a dose of 5 millicuries (mCi) (or 185 mega becquerels (MBq)) for one knee, ¹⁸⁶Re in a dose of 2 mCi (or 74 MBq) for two ankles and the elbow and osmic acid for two knees and one ankle. Clinical and radiological results were evaluated 6 months after synovectomy using the World Federation of Haemophilia score. Radiological lesions remained stable and clinical manifestations improved in every case (P < 0.05). Five patients achieved a complete remission. Safety was satisfactory and there were no complications. The clinical efficacy of synovectomy, using radiocolloids or osmic acid in arthropathy caused by von Willebrand's disease, seems similar to that in haemophilia.

Caviglia et al.¹⁷ reported that, for many years, rifampicin has been used empirically for the treatment of chronic haemophilic synovitis with encouraging results. A clinical study was performed on 48 haemophilic patients (48 joints). Seventeen elbows, eight knees and 23 ankles were treated. The mean age of the patients was 6 years (range 4-23 years) and the mean follow-up was 29 months (range 24-53 months). Overall, 40 excellent and eight good results were obtained. The average number of weekly injections of rifampicin was 3.06 (range 1-10 injections). Eight patients experienced pain on the first injection, which subsided gradually with the subsequent procedures. Synoviorthesis with rifampicin seems to be a good method for the treatment of haemophilic synovitis, especially in small joints (elbows and ankles) and in younger children.

Caviglia et al.¹⁸ reported on the experience of three Latin American centres with rifampicin and compared it to radioactive synoviorthesis results. Results indicated that chemical synoviorthesis with rifampicin is indicated in younger patients (< 15 years) and small joint (ankles and elbows).

Fernandez-Palazzi et al.¹⁹ also assessed the effectiveness of intra-articular rifampicin in haemophilic patients. Two hundred and fifty milligrams of rifampicin was injected into the elbow and ankle joints and 500 mg was injected into knee joints with 3-10 mL of lidocaine, depending on the joint size. The injections were repeated once a week for 7 weeks. Patients were only covered with antihaemophilic factor on the day of the injection at 30% above their coagulation level. The results were evaluated using subjective reports from the patient and objective assessment by the examiner. In the subjective reports the patient graded the results from their own perspective from 1 (poor) to 10 (excellent): 1-3 poor; 4-6 fair; 7-8 good; and 9-10 excellent. In the objective reports the grading was: excellent ('dry joint', full function, no haemarthrosis, no synovitis); good (clinical improvement, synovitis, reduction of haemarthroses, full function); fair synovitis (reduction of haemarthroses, no change in function); poor synovitis (persistent haemarthroses). This paper reports on the results of 38 patients with 39 joints with more than 3 years follow-up (mean 1.8 years). There were 22 knees, nine elbows and eight ankles. Subjectively, there were excellent results in 21 joints (11 knees, six elbows and four ankles), good results in 15 joints (eight knees, three elbows and four ankles), fair results in two knees and a poor result in one knee. Objectively, results obtained were excellent in 20 joints (11 knees, six elbows and three ankles); good in 17 (nine knees, three elbows and five ankles); fair in one knee and poor in one knee.

Radossi et al.²⁰ have used intra-articular injections of rifampicin. Among a large cohort of nearly 500 patients, they treated 28 patients during a 2-year period. The patients followed an on-demand replacement therapy programme and developed single or multiple joint chronic synovitis. The indications for synoviorthesis were symptoms of chronic synovitis referred by patients reported in a questionnaire.

In Radossi's series there were five patients with inhibitors to factor VIII. Their average age was 34 years.

Rifamycin (250 mg) was diluted in 10 ml of saline solution and 1–5 ml was then injected into the joint. The follow-up ranged from 6 to 24 months. Thirty-five joints were treated with 169 infiltrations in total. Rifamycin was injected once a week for 5 weeks, that is the patient had to come to hospital at weekly intervals. Twenty-four procedures were considered effective in 19 patients according to the evaluation scale, while six treatments were considered fair to poor. Five patients (six joints) with anti-factor VIII inhibitors were treated. In four joints the results were good, while in the two remaining joints the results were poor.

3) The use of D-penicillamine

Corrigan et al.²¹ have used oral D-penicillamine for the treatment of 16 patients. The drug was given as a single dose in the morning before breakfast. The dose was 5–10 mg/kg body weight, not to exceed 10 mg/kg in children or 750 mg/day in adults. The duration of treatment was 2 months to 1 year (median 3 months). Ten patients had an unequivocal response, three had a reduction in palpable synovium, and three had no response. Minor reversible drug side effects occurred in two patients (proteinuria in one and a rash in the second). The study of Corrigan et al. has two main limitations: the small number of patients, and the lack of use of ultrasound and/or magnetic resonance imaging (MRI) for diagnostic purposes. It is also important to emphasize two potential side effects of D-penicillamine: aplastic anaemia and renal disease. To minimize the possibility of side effects, Corrigan and co-workers have suggested that the drug be used on a short-term basis (3–6 months).

4) Radiosynovectomy

Radioactive synoviorthesis is indicated in patients in grade I and II, and exceptionally in some early cases in grade III in the grading system developed by Fernandez-Palazzi and Caviglia. In grade I cases, synoviorthesis is indicated as a preventive treatment if there are more than two episodes of hemarthrosis in 6 months.²²

Ahlberg²³ reported the use of intra-articular radioactive gold (¹⁹⁸Au) in the haemophilia population in 1971, and many centres in the world have implemented programmes of intra-articular synovial control using yttrium-90 (⁹⁰Y) and phosphorus-32 (³²P), ¹⁸⁶Re (rhenium), ¹⁶⁹Er (erbium) or ¹⁶⁶Ho-Ferric Hydroxide.

Fernandez-Palazzi et al.²⁴ reported that radioactive synoviorthesis with ¹⁹⁸Au, ⁹⁰Y, Rhenium-186 (¹⁸⁶Re) or ³²P would be appropriate treatment for recurrent haemarthroses in haemophilia. The clinical results, obtained by different centres, show a definite diminution of haemarthroses in 88% of cases [3]. The advantages of radioactive synoviorthesis compared with surgical synovectomy are: equivalent or better results; the requirement of substantially reduced antihaemophilic factor; the possibility of performing the procedure on multiple joints concurrently on an ambulatory basis; much less discomfort for the patient; no loss in joint range of motion; and the low cost of the procedure. In cases of failure, the procedure can be repeated after 6 months, and as many as three times on the same joint. Studies performed on the chromosomal changes that could be attributed to the radioactive material show the disappearance of these

alterations a few years after treatment. Despite over 40 years experience, there have been no reports documenting an increased incidence of neoplasia following radiosynoviorthesis.

This is contradicted by the study of Bossard et al.²⁵, which shows that few long-term safety issues have been reported to date. Radioactive synovectomy does not seem to induce cartilage or bone toxicity, and the risk of cancer does not seem to be increased. However in a recent review of published studies, five reports of malignancy associated with radioactive synovectomy were identified (four associated with ¹⁹⁸Au and one with ⁹⁰Y), all cases occurred in patients treated for rheumatoid arthritis.²⁶ Two cases of acute lymphocytic leukaemia have been reported in paediatric patients following ³²P intra-articular injection. There are no published reports of malignancy associated with the use of ¹⁸⁶Re.

Selection of the radioisotope should consider the half-life, because the intensity of the inflammatory reaction is directly related to the rate of exposure; and the size of the radiocolloid, the larger the size the less tendency for the material to leak from the joint space. The material should be a pure beta-emitting radioisotope, thereby minimizing the whole body exposure from gamma radiation. Taking into account the high cost and limited supply of these materials, it is best to schedule groups of 6–8 patients to perform radiation synovectomy. This will require some patients to wait upwards of 3–6 months until the whole group is scheduled for the procedure. If possible, patients should be maintained on continuous prophylaxis and therapeutic exercises while waiting for the procedure.

Synoviorthesis can be performed at any age in haemophilia patients. Performing an intra-articular injection in a very young child does pose the problem of patient co-operation which may require conscious sedation or even general anaesthesia. The potential of radiation-induced cellular damage or chromosomal abnormalities remain a concern, particularly in the child.

One possible, although rare, minor complication is a cutaneous burn if the radioactive material leaks out of the joint. These burns are small and superficial, healing in about 2 weeks without residual scar. This problem can be prevented by flushing the needle and needle tract with a mixture of Xylocaine and a depositing steroid solution as the needle through which the radiocolloid was injected and then applying pressure to the injection site. Another potential complication is an inflammatory reaction after injection, which can be managed with rest and non-steroidal anti-inflammatory drugs (NSAIDs). These reactions are less likely with longer half-life agents. Image intensifier or ultrasound-guided articular puncture is commonly used to avoid extra-articular injection of the radioactive material.²⁶

It is possible to perform multiple synoviorthesis in a single session. It is probably best to carry out no more than two injections at the same time to reduce the risk should any of the material escape. If two joints are to be injected, consider injecting two joints on the same side (i.e. an elbow and knee, elbow and ankle, knee and an ankle)(Table 2)²⁷

Table 2 - Clinical indications of the radioactive isotopes most frequently used for radiosynoviorthesis.²⁷

Isotope	Joint
⁹⁰ Y	Large-sized joints: knees
¹⁸⁶ Re	Middle-sized joints: shoulder, hip, and tarsus
¹⁶⁹ Er	Small-sized joints: interdigitals, elbow, wrist, ankle

Molho et al.²⁸ reported on 116 chemical and 90 radioactive synovectomies performed between 1970 and 1994 on 107 patients with severe haemophilia and two with type 3 von Willebrand's disease. The products used were osmic acid in 100 cases, ⁹⁰Y in 35 cases, ¹⁸⁶Re in 48, erbium-169 (¹⁶⁹Er) in two, hexacetonide triamcinolone in 16 and ¹⁹⁸Au in five cases. The use of radioactive colloids is not allowed in France in patients under 15 years of age. Twenty-nine patients had more than one synovectomy in the same joint. All patients were evaluated for 6 months postsynovectomy, using both a clinical and a radiological score. Six months after synovectomy, a good or excellent result was obtained in 81% of the joints treated with isotopes, compared with 44% of those treated with osteoarthritis. This superiority of isotopes over osmic acid was still observed after 6 months for the 89 joints that were re-evaluated, with follow-up ranging from 1 to 9 years. A radiological score was calculated in 84 cases. The best results were from joints with the lowest scores presynovectomy (< 7). No correlation could be established between the clinical and the radiological scores, because of the small size of the sample. Molho et al. concluded that chemical and radioactive synovectomy are simple and safe procedures for haemophilic arthropathy. In their series, the efficacy of isotopic synovectomy was greater than that of chemical synovectomy, and this benefit seems to persist after 6 months, and up to 9 years in the group of patients with longer-term follow-up.

Nuss et al.²⁹ studied the clinical, plain X-ray and MRI findings in 13 haemophilic joints previously treated with radiosynoviorthesis. ³²P had been injected into the joints in an attempt to halt recurrent haemorrhage. Prior to ³²P injection, the majority of joints demonstrated bone damage evident on plain X-ray, secondary to recurrent haemorrhage. At the follow-up evaluation they found plain X-rays were adequate to identify cysts, erosions and cartilage loss in these very damaged joints. MRI was superior to clinical examination and plain X-ray in identifying synovial hyperplasia and effusions. However, the persistence of synovial thickening did not correlate with the bleeding frequency and clinical result.

Mathew et al.³⁰ presented their experience beginning in 1993 with 11 paediatric patients who underwent 17 ³²P isotopic synovectomies for chronic haemophilic arthropathy. ³²P was injected into the joint per protocol, approved by the institutional review board. All patients were male. Nine were factor VIII- and two were factor IX-deficient. The following joints were treated: ankle (n = 10 procedures), elbow (n = 5) and knee (n = 2). The first procedure was performed in December 1993. Mean age at the first procedure was 10.8 years (range 5.2-15.2 years). Mean pretreatment joint clinical scores using the World Federation of Haemophilia guidelines for the ankle was 5.5

(SD + 2.3), elbow 4.2 (+ 2.5) and knee 5.5 (± 3.5); the corresponding post-treatment scores were 2.6 (+2.0), 1.4 (+0.5) and 2.5 (+ 3.5), respectively. Presynovectomy mean radiological scores using the Pettersson method were: ankle 1.8, elbow 1.8 and knee 1.5. A scoring system used by the authors for evaluating joints using MRI gave the following mean pretreatment scores: ankle 9.5, elbow 8.4 and knee 5.0. A marked decrease (80-100%) in bleeding was seen in 13 of 17 procedures, and a moderate decrease (51-79%) in two procedures, accounting for 85% reduction in bleeding into the target joints. The procedure was well tolerated and no untoward side-effects were noted as of May 1999, with a median follow-up of 40 months (range 19-65 months). None had any clinical evidence of cancer. Three patients had their joints retreated [elbow (one), ankle (two)]. These procedures were also well tolerated. Matthew et al. concluded that isotopic synovectomy using ³²P appears to be feasible, safe and efficacious in the treatment of haemophilic arthropathy in paediatric patients who have been followed for a median of 40 months. As previously shown, MRI appears to give more detailed information about synovial hyperplasia and joint arthropathy than plain radiographs.

There is always the question about the cost of treatment in haemophilia, so Siegel et al.³¹ made a comparative analysis of surgical synovectomy vs. radiosynoviorthesis with ³²P. The cost analysis was done comparing radiation and surgical synovectomy using Medicare billing records. Surgical synovectomy requires large quantities of factor, and cost ranges from \$50,000 to more than \$100,000. In addition, the patient's stay in the hospital, including professional fees, operating room costs, and physical therapy costs, is approximately \$50,000. Radiosynovectomy requires only one or two doses of clotting factor in most patients and does not require physical therapy or a stay in the hospital. Currently, P-32 chromic phosphate is available only in 10-mCi quantities (1 mCi = 37 mBq) from the manufacturer, and the minimum quantity that can be ordered costs more than \$2000. However, when several patients are scheduled for treatment in a day, and the local radiopharmacy divides this quantity into unit doses. This practice markedly reduces the cost of one dose. The radiopharmaceutical costs range from \$250 to \$300, and the cost of a dose of clotting factor ranges

from \$1000 to \$1500. The World Federation of Hemophilia has estimated that there are 350,000 patients with hemophilia in the world and 28,000 in the United States. At the Orthopaedic Hospital of Los Angeles Hemophilia Center, designated as an international training center for the World Federation of Hemophilia, an estimated 25% of patients with hemophilia are potential candidates for a synovectomy. Thus, if each of these potential candidates in the United States had a radiosynovectomy, rather than a

surgical synovectomy (7000 × \$150,000 surgical compared with 7000 × \$4000 radiation), it would result in a savings of more than \$1 billion in national health care.³¹

Heim et al.³² injected radioactive ⁹⁰Y into 163 joints. Of these patients 115 were haemophiliacs with recurrent haemarthroses. The age at the time of the initial procedure was between 11 and 15 years and the median follow-up period was 11 years. Over 80% of the patients with haemophilia reported a decrease in the number of haemarthroses and 15% stopped bleeding altogether in the treated joint.

Between 1994 and 1999, Rodriguez-Merchan et al.³³ performed 66 ⁹⁰Y synoviortheses on 44 persons with haemophilia (45 knees, 12 elbows, nine ankles). At the time of injection 23 patients were HIV-positive and two had inhibitors. The average age was 21.1 years (range 9-39 years). Five mCi (185 MBq) of ⁹⁰Y were injected into the knees, and 3 mCi (111 MBq) into the elbows and ankles. The average follow-up was 3.5 years (range 1-6 years). Of the 45 knees, there were eight excellent, 10 good, 15 fair and 12 poor results. Of the 12 elbows there were three excellent results, five good, three fair and two poor. Of the nine ankles there were no excellent results, four good, three fair and one poor. The elbows had better results than the knees and ankles. The best results were obtained in the youngest patients, and in those with a moderate degree of synovitis, regardless of their HIV status and the presence of inhibitors. ⁹⁰Y synoviorthesis should be performed early, in patients when the amount of synovium is still moderate and there is minimal joint damage. Usually, these patients are in the first decade of life. Once the degree of synovitis has become severe and the joint surface is significantly eroded, the results of radioactive synoviorthesis are worse.

Silva et al. reported the experience of Luck and Siegel³⁴ who performed 170 radiosynovectomies using ³²P chromic phosphate between 1988 and 2000. Results of 130 procedures (115 primary procedures and 15 repeat procedures), in 97 haemophilic patients (88 of them type A and nine type B), were analysed. Patients in this study group had a bleeding frequency of at least three episodes per month in a target joint and failed conservative treatment, which included a combination of clotting factor concentrate and physical therapy. The 115 primary procedures, including 50 knees, 44 elbows, 14 ankles, five shoulders and two subtalar joints, were followed for an average of 3 years (range 0.5-11.6 years). The 15 repeat procedures, including seven knees, six elbows and two ankles, were followed for an average of 2.7 years (range 0.5-7.2 years). The average postprocedure bleeding frequency reduction, including primary and repeat procedures, was 70%. For primary procedures, excellent and good results (haemarthrosis reduction from 75 to 100%) were obtained in 79.2% of cases at 6 months to 8 years. For repeat procedures a combination of excellent and good results were obtained in 62.4% of cases at 6 months to 3 years. Regression analysis showed no correlation between results in terms of bleeding reduction, and age or degree of arthropathy. Radiation was well contained within the joint and there were no observed or identified complications. The authors concluded that the

procedure is effective, safe and highly cost-effective in comparison to open surgical or arthroscopic synovectomy.

Lofqvist et al.³⁵ reported on nine patients with haemophilia and clotting factor inhibitors (six with haemophilia A, three with haemophilia B). Nineteen joints were treated with radioactive synoviorthesis using ¹⁹⁸Au. Ages ranged from 3 to 40 years. Synoviorthesis was performed when the antibody titre was low (< 10 Bethesda units), thus making haemostasis possible by factor administration for 2-4 days. On five occasions, radioactive synoviorthesis was performed simultaneously with tolerance induction according to the Malmo protocol. A bleeding-free interval of more than 6 months was obtained in 11 joints, six of which remained haemarthrosis-free for more than 1 year. At long-term follow-up (range 18-182 months) five joints were rated good, one joint was fair and 11 joints were poor. Although the results were inferior to those for patients with haemophilia without inhibitor, radioactive synoviorthesis should be considered because of its ease of performance and the definite decrease in joint bleeding frequency that it brings about. This is of particular interest in patients with haemophilia caused by factor inhibitor who otherwise are difficult to treat.

Falcon de Vargas and Fernandez-Palazzi³⁶ assessed chromosomal structural changes (CSCs) studied by conventional lymphocyte cultures and banding techniques in 79 haemophilic patients with haemarthrosis treated with radioactive synoviorthesis, 31 haemophilic patients with haemarthrosis not treated by this procedure and 110 non-haemophilic patients matched by age and sex (control group). In 14 patients treated with ¹⁹⁸Au (group A), premalignant CSCs and non-specific CSCs were found in 1.69 and 17.23% of metaphases, respectively. The former disappeared, but 1.7% of the non-specific changes persisted 2 years after injection. In 31 patients treated with ¹⁸⁶Rh (group B), CSCs were not found previous to radioactive synoviorthesis but were present as non-specific changes in 1.25% of metaphases 6 months later; they disappeared 1 year after injection. In 34 patients treated with ⁹⁰Y (group C), CSCs were not found previous to radioactive synoviorthesis but were present as non-specific changes in 0.89% of meta-phases 6 months later; they disappeared 1 year after injection. Only non-specific CSCs were found in 0.79% of metaphases in haemophilia patients not treated with radioactive synoviorthesis (group D). CSCs were not present in control subjects. The authors concluded that in some haemophilic patients with haemarthrosis treated with radioactive synoviorthesis using ¹⁹⁸Au, ¹⁸⁶Rh or ⁹⁰Y, reversible premalignant or non-specific CSCs could be present; non-specific CSCs may persist in a low proportion of metaphases up to 2 years after injection when ¹⁹⁸Au is used as the radioactive agent. ¹⁹⁸Au is both a beta and gamma emitter. Radioactive synoviorthesis with a pure beta emitter seems to be, from a cytogenetic point of view, a safe alternative for these patients.

There is always a concern about the use of radiosynovectomy and the effects on joint cartilage and the incidence of cancer after this kind of treatment. Jahangier et al.³⁷ have found that radiation synovectomy with ⁹⁰Y for

persisting arthritis has harmful effects in vitro on human cartilage that cannot be prevented by co-administration of glucocorticoids. These results urge for a more detailed in vivo evaluation of cartilage changes after radiosynovectomy. Dunn et al.³⁸ reported about two patients which developed acute lymphocytic leukemia (ALL), one T-cell ALL and one precursor B-cell ALL, within one year of radioactive synovectomy with ³²P.

There are also new radiocolloids tested. Calegaro et al.³⁹ reported of the results in the treatment of chronic haemophilic arthropathy with ¹⁵³Samarium hydroxyapatite (¹⁵³Sm-HA) in 31 patients with haemophilia.

5) Alternatives to synoviorthesis

Rodriguez-Merchan et al.⁴⁰ reported a prospective study carried out from 1974 to 1996 to determine optimal treatment for chronic haemophilic synovitis of the knee and synovitis of the elbow. Sixty-five patients with synovitis affecting 65 knee joints and 40 patients who had synovitis of the elbow (44 elbows), despite a 3-month trial of prophylactic substitution therapy, were treated by synovectomy. Radiation synovectomies (¹⁹⁸Au synoviorthesis) were performed on 38 knees, open surgical synovectomy on 18 and nine had an arthroscopic procedure. Radioactive gold synoviorthesis was performed on 29 elbows, and 15 had a resection of the radial head and partial open synovectomy. Synovectomy (by any method) significantly reduced bleeding episodes, but did not halt the radiographical deterioration of the joints. It is thought that radiation synovectomy is the best choice for patients with persistent synovitis of the knee and elbow unresponsive to a 3-month trial of prophylactic factor replacement. If two to three consecutive synoviortheses with 3-6 months intervals had been ineffective, or when the radiographical score is more than two points, a surgical synovectomy is indicated.

When chronic synovitis is allowed to persist, the membrane can hypertrophy to the point where it cannot be adequately ablated by a pure beta-emitting radiocolloid, which only penetrates about 5 mm. In these cases as well as those in which repeated radiosynoviorthesis has failed, arthroscopic synovectomy is often effective.⁴

Conclusions

Synoviorthesis is a highly effective procedure that decreases both the frequency and the intensity of recurrent intra-articular bleeds related to joint synovitis. The procedure should be performed as soon as possible to minimize the degree of articular cartilage damage, which, based on many studies, is irreversible.

It can also be used in patients with inhibitors with minimal risk of complications. On average, synoviorthesis has a 75-80% satisfactory outcome in the long term. From the clinical standpoint, such efficacy can be measured by the decrease in the number of haemarthroses, with complete cessation for several years in some cases.

Synoviorthesis of any kind is a highly cost-effective method compared to open or arthroscopic synovectomy.

One should bear in mind that in 20-25% of cases, synoviorthesis fails to control haemarthroses. In such cases, it can be repeated.

⁹⁰Y should be used in large joints (knees) and ¹⁸⁶Re in small joints (interdigitals, elbow, wrist, ankle). Global results of treatment with chemical synovectomy (osmic acid and rifampicin) seems to be less favourable than with radionuclides (⁹⁰Y, ³²P, ¹⁸⁶Re), except for small joints, where the results are comparable.

In cases where the synovium is thicker than 5-10 mm, and haemarthroses persist following synoviorthesis, arthroscopic synovectomy is indicated.

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