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# Synovectomy with $^{153}\text{Samarium}$ Hydroxyapatite in Haemophilic Arthropathy

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## Abstract

There are two main types of haemophilia, classified according to deficiency: type A, caused by factor VIII deficiency; and type B, which is rarer and the result of a deficiency in factor IX. Haemarthroses account for 80% of bleeding in haemophilic patients, with half of these exhibiting deformities. Repeated joint effusion leads to a local inflammatory response, with the formation of hyperplastic and hypertrophic cells and subsequent buildup of haemosiderin. Fibroblasts proliferate and produce collagenases and proteinases that act on the synovium, cartilage and bone, with a decrease in the joint space. Another mechanism involved is the damage caused by direct action of red blood cells on the cartilaginous surface of the joint lining.  $^{153}\text{samarium}$  was obtained in research reactor by neutron irradiation of  $^{152}\text{Sm}_2\text{O}_3$  (99.4%) in the nitrate form,  $^{152}\text{Sm}(n,p)^{153}\text{Sm}$ , for 30–36 h. The labelling process was performed with 40 mg of hydroxyapatite, according to Barboza et al. Radiochemical purity, particle size, microbiological tests for sterility and pyrogen were the tests applied to obtain an useful material. The introduction of  $^{153}\text{Sm}$ -HA for the treatment of haemophilic arthropathy in large and medium joints was a safe, cost-effective, minimally invasive and effective procedure in controlling bleeding and pain.

**Keywords:** haemophilic arthropathy, radiosynovectomy,  $^{153}\text{samarium}$ -hydroxyapatite

## 1. Introduction

The treatment of joints using radioactive material began in the 1950s, more specifically in 1952, with chromic phosphate P32 [10]. It was initially aimed at joint involvement caused by rheumatoid arthritis and, to a lesser degree, pigmented villonodular synovitis, ankylosing spondylitis, collagenosis and psoriatic arthritis in the years that followed [24]. With the advent of longer follow-up studies, it has also benefitted rheumatic diseases and

haemophilic arthropathy, which exhibit a similar sequence of events including repetitive intra-articular haemorrhages causing synovitis, joint pain, limited mobility and posterior muscular atrophy. Recurrent synovitis results in cartilage destruction, progressive loss of movement, joint deformities, bone damage and ultimately total ankylosis. The treatment procedure was originally denominated synovectomy (from the Greek ‘ectomía’ meaning ‘to cut out’) and later synoviorthesis (from the Greek word ‘orthesis’ meaning ‘restoration’) via radionuclides [8].

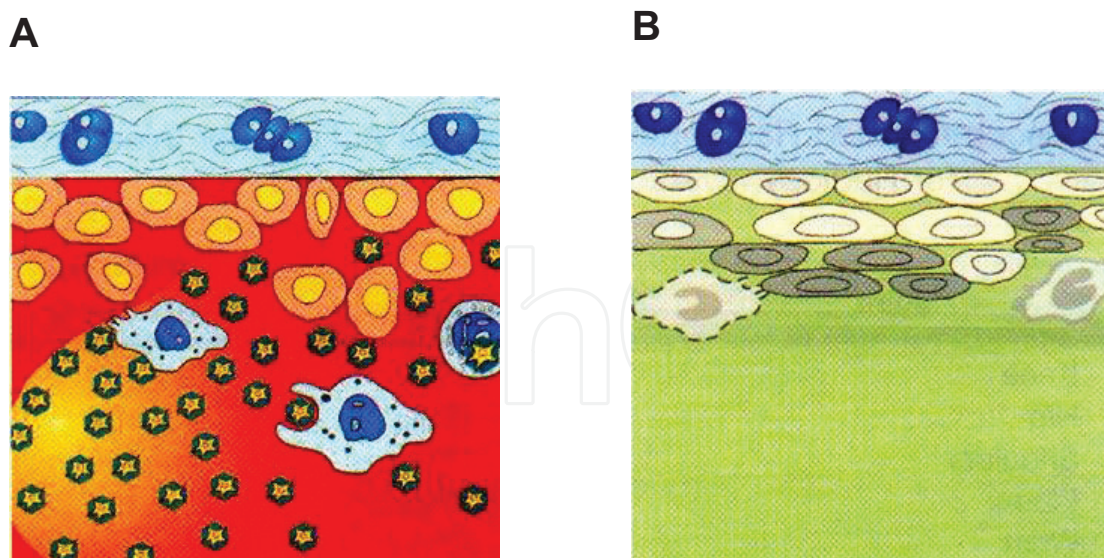
Different radioactive materials have been used to eradicate synovitis, some emitting only beta radiation and others beta and gamma radiation. Synovectomy in haemophilia using radioactive material began in 1971 [1]. Since then, a variety of materials have been used, including P32, colloidal 198Au, 186Re, 90Y, 165Dy, 166Ho, and 169Er. **Table 1** shows the characteristics of the materials used [1, 12, 16–18, 21, 28].

Irradiation occurs via the intra-articular retention of the radioactive material. However, it should be noted that the radioactive material is bound to larger particles, known as carriers, which undergo phagocytosis by the macrophages in the inflammatory process, favouring greater retention in the joint space. These macrophages migrate through the interstice of synovial cell layers, resulting in more homogeneous action by the ionising radiation. This behaviour was highlighted in autoradiographic studies [7], which more clearly indicate the location of samarium-153 particulate at different synovial tissue depths than other materials used, such as 186Re. This is also reported by Schneider et al. [23] (shown in **Figure 1**), in addition to direct irradiation by the intra-articular radionuclide. As such, average penetration is ascertained by the range of the  $\beta$  particle and maximum penetration by macrophage permeation into synovial cell layers.

Radioisotopes	Half-life (days)	Max. beta energy (MeV)	Gamma energy (KeV)	Penetration (mm)		Particle size ( $\mu$ m)	Leakage (%)
				Max.	Av.		
Colloidal 198Au	2.7	0.96	110	3.6	1.2	0.02–0.04	20–35
P32 (chromic phosphate)	14.0	1.7	–	7.9	2.6	0.05–0.1	2–4
186Re (sulphide colloid)	3.75	1.07	140	3.6	1.2	0.05–0.1	2
Colloidal 90Y	2.7	2.2	–	10.8	3.8	1.5–3.5	3
166Ho (FHMA)	1.2	1.85	81	8.7	2.2	1.82–12	1
165Dy (FHMA)	0.095	1.3	95	5.6	1.4	0.8–12	1
169Er (citrate)	9.4	0.34	–	1.0	0.3	0.1–10	1
153Sm (HA)	1.95	0.80	100	3.1	0.8	1–10	0.1

FHMA = ferric hydroxide macroaggregates.

**Table 1.** Characteristics of the radioisotopes used in synovectomy.



**Figure 1.** (A)  $\beta$ -Emitting colloidal particles (yellow stars) phagocytised by inflamed hypertrophic synovial lining with proliferating synoviocytes (pink). The cartilage layer remains unaffected. (B) Subsequent cell damage and sclerosis of synovial membrane.

Another noteworthy aspect is that radionuclide leakage from the joint is inversely proportional to particle size. This is clearly evident in the last two columns of **Table 1**. The presence of gamma radiation allows synovectomy to be monitored over several days via scintigraphy.

## 2. Haemophilic arthropathy

Haemophilia is a congenital bleeding disorder linked to the X chromosome of the human genome, with the two most common types being haemophilia A, a lack of blood clotting factor VIII, and haemophilia B, caused by missing or defective factor IX. Joint bleeding associated with muscle bleeding represents 90% of bleeding episodes in haemophilia patients, while haemarthrosis alone accounts for 70–80% of these episodes. In 80% of cases, haemarthrosis occurs in the knees, elbows and ankles [22], producing inflammatory changes in the synovial membrane. Recurrence of this inflammation over time triggers a chain of events that lead to joint ankylosis, including the direct damage of blood on the articular cartilage [15].

In cases of arthropathy mediated by reactive synovitis, synovectomy with radioactive material is an alternative to intra-articular injection of glucocorticoids and other chemical agents (osmic acid, collagenase, rifocin and thiotepa) or surgery. Furthermore, radiosynovectomy, introduced by Ahlberg in the 1970s, has been proposed as a first-line treatment option for haemophilic arthropathy [22, 23].

### 3. <sup>153</sup>Samarium-hydroxyapatite

<sup>153</sup>-samarium was obtained in an IEA-R1 research reactor (IPEN-CNEN, São Paulo, Brazil) by neutron irradiation of <sup>152</sup>Sm<sub>2</sub>O<sub>3</sub> (99.4%) in the nitrate form, <sup>152</sup>Sm(n,p)<sup>153</sup>Sm, for 30–36 h. The labelling process was performed with 40 mg of hydroxyapatite, using appropriately sized particles (20 µm), according to Barboza et al. [2]. Percentage bound activity or labelling efficiency was determined by centrifugation, measuring the activity of the precipitate (<sup>153</sup>Sm-HA) and supernatant (<sup>153</sup>Sm-free) using a dose calibrator, and was always >90%. Radiochemical purity was higher than 98%, measured using Whatman 3MM paper chromatography (from GE, Milwaukee, WI, USA) in 0.9% saline, remaining stable for 24 h. Particle size was determined by laser scattering and filtration in a filter system of known sizes (1–15 µm), with a mean of 10 µm (range: 3–12 µm). Microbiological tests for sterility and pyrogen were always negative in all samples.

### 4. Patient selection

Participants were haemophilic patients with chronic synovitis, monitored at the Department of Haematology – Hospital de Apoio in the Federal District (DF), and the Orthopaedics and Nuclear Medicine Service of the Hospital de Base (DF), between 2002 and 2011.

Patients were assessed by clinical history and a physical examination, paying special attention to the compromised joint. Particular emphasis should be given to haematology tests in order to characterise the type and severity of haemophilia, as well as the absence of coagulation inhibition factors. Imaging (radiology) tests make it possible to determine the degree of arthropathy, with the Pettersson score being widely used. Three-phase whole-body scans are used to identify any other joints involved and more accurately characterise the synovial inflammatory process. Other procedures used for this purpose include ultrasound or magnetic resonance imaging (particularly for the knees).

Inclusion criteria were the following: chronic synovitis when occurs repetitive effusions (minimum: once a month), pain on joint palpation and absence of other joint disease, like the rheumatologic or orthopaedic nature. Exclusion criteria were ruptured Baker's cyst, major effusions, signs of acute synovitis or presence of an articular or periarticular infectious process.

### 5. Procedure

Synovectomy of the radioactive material was made by an orthopaedist with previous use of the deficient clotting factor, applying topical anaesthesia in accordance with the asepsis and antisepsis performances used for invasive intra-articular orthopaedic procedures. The use of ultrasound to guide the punctures was not necessary, as these were assured by the aspiration of synovial fluid before administration of the radionuclide (**Figure 2**). Fixed doses of 5 mCi (185 MBq) or 20 mCi (740 MBq) of <sup>153</sup>Sm-hydroxyapatite were used, with only one injection





**Figure 2.** Injection of the knee.

administered per patient. The maximum volume of radioactive material was 0.5 mL; material adhered to the puncture site was washed away with saline, at fractions of 0.5 mL, without exceeding the final volume of 1.5–2.0 mL.

The reflux and homogeneity (or lack thereof) of the intra-articular material and its escape from the joint were monitored by a scintigraphic study in a gamma camera, with a wide field of vision detector and low-energy collimator. Imaging was made using a 128-pixel matrix and the spectrometer window was centred at 100 keV, using precocious, 1 and 2 h, and later times, 3–7 days, after <sup>153</sup>Sm-HA injection. A summary of this protocol is shown in **Table 2**.

1	Use a coagulation factor before the procedure;
2	Local asepsis;
3	Use local anaesthetic;
4	Joint puncture using a 21G needle;
5	Aspirate synovial fluid;
6	Inject 5 mCi of <sup>153</sup> Sm-HA into the intermediate joints and 20 mCi into the knees;
7	Wash the puncture site with a total of 2.0 mL of saline without using corticosteroids;
8	Compression bandaging using crepe bandage;
9	Monitor the material used in the puncture;
10	Functionally permissible joint mobility;
11	Immediate (1–2 hours after synovectomy) and later (3–7 days) scintigraphy image

**Table 2.** Protocol for synovectomy with <sup>153</sup>Sm-hydroxyapatite.

## 6. Side effects

Reactive synovitis may occur in the days following application of the radiopharmaceutical agent, which was treated using conservative measure such as joint rest, local application of ice and a non-steroid anti-inflammatory agent. The cases observed in our study were mild and occurred in 4–8% of joints.

Radionecrosis may occur if the material leaks from the administration route. This complication did not occur in the cases we treated because the material was only administered after correct injection and the puncture site was washed with saline to prevent leakage.

Immobilisation of the affected limb will ultimately result in thrombosis; however, this was prevented by the protocol used.

There is no concern about possible carcinogenic effects of this procedure. Systemic irradiation can result from fluid leakage or the gamma component of  $^{153}\text{Sm}$ . Studies on chromosomal abnormalities in circulating lymphocytes related to samarium [19] have shown no definitive changes, but rather transient and reversible ones. It is important to note that this irradiation is smaller than in diagnosis by conventional bone scintigraphy or whole-body scanning with  $^{67}\text{Ga}$ . Considering the local effect at joint level, several studies with long follow-up times have shown no occurrence of tumours [14, 26, 27], indicating that this possibility has not yet been characterised.

## 7. Synovectomy

The first study was conducted to evaluate the efficiency of treatment with  $^{153}\text{-samarium}$  hydroxyapatite ( $^{153}\text{-Sm-HA}$ ) in haemophilic arthropathy. Thirty-one patients (30 males) between 8 and 34 years old (medium age = 20.6 years) were treated with a fixed intra-articular dose of 5 mCi (185 MBq) and divided into two groups: paediatric (13 patients aged up to 18 years, with a medium age of 12.7 years and arthropathy evolution of 7.8 years); and adults (18 patients over 18 years old, with an average age of 24 years and arthropathy evolution of 18.7 years). Clinical assessment before and 1 year after synoviorthesis used the following criteria: subjective (pain according to the visual analogue scale, joint inspection), objective (joint movement through flexion level, pain to palpation and leakage through joint circumference), reduced use of the coagulation factor, number of haemarthroses, and the occurrence of adverse effects. The results were classified as: 1, good (symptom remission of 70–100%); 2, moderate (symptom remission between 40 and 69%); and 3, poor (0–39% symptom remission). Seventy-eight joints were tested: 15 knees, 36 elbows, 24 ankles, 1 shoulder and 2 hips. Early (1–2 h) and late phase scintigraphic imaging (24–72 h) was made after synovectomy. No significant inter-group difference in synovectomy results was observed. The results obtained were good for 75% of elbows, 87.5% of ankles and 40% of knees; reduction in effusions and use of the coagulation factor were, respectively, 78% and 80% for elbows, 82% and 85% for ankles, and 30% and 35% for knees. Four cases of reactive synovitis were observed in the 78 joints tested. Scintigraphy showed homogeneous distribution of the material with no leakage.

The introduction of  $^{153}\text{Sm}$ -HA in the treatment of the haemophilic arthropathy is effective for intermediate joints (elbows and ankles), but less so for knees. Moreover, this treatment offers excellent safety and is affordable [3].

The penetration of beta energy from  $^{153}\text{Sm}$  ( $^{153}\text{Sm}$ ) (0.8 MeV) is not only suitable for synoviorthesis of intermediate joints, but can improve the radionecrosis effect using higher radioactivity levels. The next study assessed the efficacy of 5 mCi (185 MBq) and 20 mCi (740 MBq) of  $^{153}\text{Sm}$  hydroxyapatite ( $^{153}\text{Sm}$ -HA) in the knees of haemophilic patients. Thirty-one patients (36 knees, 30 males) were divided into two groups without corticosteroid co-injection: 1 – 14 patients (17 knees) treated with an intra-articular dose of 5 mCi of  $^{153}\text{Sm}$ -HA, medium age 23 years; 2 – 17 patients (19 knees), administering 20 mCi of  $^{153}\text{Sm}$ -HA, medium age 21.3 years. Evaluation before and 1 year after synoviorthesis used the following points: reduction in the number of effusions and use of the coagulation factor, and increment in joint mobility. The occurrence of side effects was also considered. Early and late-phase scintillations studies were made after synovectomy and no articular immobilisation was recommended. Reduction in effusions and use of the coagulation factor, respectively, were: group 1 – 31.3% and 25%; group 2 – 81.5% and 79%, with  $p < 0.001$ . No significant increment in knee mobility was observed in either group. Four cases of mild reactive synovitis were observed in each group. Scintigraphy showed homogenous distribution of the radioactive material with no leakage; the material was considered safe by its retention in the joint. A significant increment was observed in the synoviorthesis of haemophilic knees with 20 mCi of  $^{153}\text{Sm}$ -HA; the lower penetration of its beta radiation was offset by the improved radiobiological effect when higher radioactivity is used [4].

Another study compared the use of 20 mCi (740 MBq) of  $^{153}\text{Sm}$  and 5 mCi (185 MBq) of  $^{90}\text{Y}$ , both labelling hydroxyapatite (HA), for knee synoviorthesis in haemophilic patients, 1 year after the procedure. Thirty-three men (36 knees) were studied, divided into two groups: a – injection of 740 MBq of  $^{153}\text{Sm}$ -HA: 20 knees of 18 patients, with an average age of  $21.4 \pm 13.3$  years (range: 7–56 years) and medium Pettersson score of 5.3; b – injection of 185 MBq of  $^{90}\text{Y}$ -HA: 16 knees of 15 patients, with an average age of  $26.3 \pm 10.3$  (range: 7–51 years) and medium Pettersson score of 6.3. Episodes of haemarthrosis, use of clotting factors and pain intensity were evaluated before and after treatment, as well as improved joint mobility. The occurrence of side effects in the treatment was also considered. The chi-squared, Wilcoxon and Mann–Whitney tests were applied, with a significance level of  $p \leq 0.05$ . The occurrence of effusions decreased by 65.7% with the use of  $^{153}\text{Sm}$ -HA and 82.6% for  $^{90}\text{Y}$ -HA, without statistical significance between the groups ( $p = 0.632$ ); pain reduction was 42.5% in group a and 30.7% in group b, again without statistical significance ( $p = 0.637$ ). Increment in joint mobility was not significant for either group. Two cases of mild reactive synovitis were observed in group a and one in group b, which had resolution without medical intervention. Although the beta energy from  $^{90}\text{Y}$  is the more appropriate for knee synoviorthesis, the higher radioactivity levels of  $^{153}\text{Sm}$  is an alternative in locations that only produce this material [5].

## 8. Follow-up

This study aimed to evaluate synovectomy with  $^{153}\text{Sm}$ -hydroxyapatite ( $^{153}\text{Sm}$ -HA) in synovitis of the elbows and ankles of haemophilic patients. Synovectomy was performed using



185 MBq of  $^{153}\text{Sm}$ -HA in 166 joints (63 ankles and 84 elbows) of 82 haemophilic patients (average age 24.4 years) with follow-up of 12 and 42 months. Arthropathy was characterised by recurrent joint bleeding. Episodes of haemarthrosis, use of clotting factors and pain intensity were evaluated before and after treatment. Scintigraphic analyses and adverse effects were also considered. Statistics used  $p \leq 0.05$ . The results indicated: (a) reduction in haemarthrosis was 78% and 68%, in elbows and 82% and 72% in ankles; (b) use of clotting factors was 80% and 70% for elbows, and 85% and 75% for ankles; (c) pain intensity was 37% and 34% in elbows, and 61% and 57% in ankles, after 12 and 42 months, respectively. Among the 166 joints studied, three cases of mild reactive synovitis were observed in ankles and four in elbows, with no leakage in any of the cases. In conclusion, the use of  $^{153}\text{Sm}$ -HA in elbows and ankles was effective, very safe, minimally invasive and the results showed consistency at follow-up [6].

Another interesting aspect to consider is treatment repetition. We recommend this be done after 1 year, but a minimum interval of 6 months is permitted.

## 9. Final considerations

The radioactive material ( $^{153}\text{Sm}$ ) was aggregated with hydroxyapatite particles to ensure longer intra-articular retention without arterial-venous or peri-articular lymphatic leakage. When the two are separated, the advantage of the compound is that the carrier (hydroxyapatite) enters the body's metabolism because it is part of the bone matrix.

No escape (lymphatic or vascular) was detected with  $^{153}\text{Sm}$  because when it separates from the carrier (hydroxyapatite), it forms insoluble compounds with the synovial fluid that precipitate in the articulation; this permanence was confirmed by other previous studies [20] and by our controls (see **Figure 3**).

Scintigraphic images obtained after early and late-phase injection showed appropriate intra-articular distribution, as well as the absence of leakage to regional lymph nodes or other organs, or urinary elimination. The ability to obtain good-quality scintigraphic images is an advantage of  $^{153}\text{Sm}$  since gamma emission occurs in the energy amplitude of 100 keV. Another possible advantage is the mild reactive synovitis observed in all the studies, resolved without invasive medical intervention, possibly due to low beta energy penetration.

These studies are among the few that evaluate only the therapeutic effect of intra-articular radioactive material, since it is often administered in conjunction with corticosteroids. This creates bias in result analysis because corticosteroids are also used for the same purpose in the treatment of haemophilic arthropathy [11]. This combination has been called into question [13] and is one of the reasons why we chose not to use it when beginning treatment [3], in addition to the lack of information in the literature characterising the nature of its effect as competitive, additive or synergistic.



**Figure 3.** Knee scintigraphy showing good joint distribution and no leakage.

The reduction in haemarthrosis for ankles (82%), elbows (78%) and knees (65.7%) was similar to values recorded in other studies of haemophilic patients with different types of radioactive material. A German revision pointed nine studies between 1982 and 1991 with good and excellent results for radiosynovectomy in 60–80% of the haemophilic arthropathy [9]. The findings presented in our studies also corroborate those summarised by Siegel et al. [25] regarding the benefits of radiosynoviorthesis, with an approximate 75% decrease in effusions, few adverse effects and better quality of life in 75% of the cases. This can be extended to shoulders and hips, which exhibited similar results to intermediate joints. Finally, it can be concluded that  $^{153}\text{samarium}$  labelled with hydroxyapatite is a useful tool in the treatment of chronic synovitis in haemophilic patients.

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