

ORIGINAL ARTICLE *Musculoskeletal*The use of 185 MBq and 740 MBq of <sup>153</sup>Samarium hydroxyapatite for knee synovectomy in haemophiliaJ. U. M. CALEGARO,\* J. MACHADO,† R. G. FURTADO,\* J. S. C. DE ALMEIDA,‡  
A. V. P. DE VASCONCELOS,† M. F. DE BARBOZA§ and A. P. DE PAULA¶

\*Grupo Núcleos of Nuclear Medicine; †Orthopedic Service Hospital de Base; ‡International Hemophilia Training Center, Brasília, DF; §Radiopharmaceutical Center - IPEN/CNEN, São Paulo, SP; and ¶Secretaria de Estado de Saúde do DF, Brasília, DF, Brazil

**Summary.** The penetration of beta energy of <sup>153</sup>Samarium (<sup>153</sup>Sm) (0.8 MeV) is not only appropriate for synovectomy of median articulations but is possible to improve the radiobiological effect using increased activities. The aim of this study was to assess the effectiveness of 185 MBq and 740 MBq of <sup>153</sup>Samarium hydroxyapatite (<sup>153</sup>Sm-HA) in knees of haemophilic patients. Thirty-one patients – 36 knees, 30 males, were divided into two groups without coinjection of corticosteroid: A – 14 patients (17 knees) treated with intra-articular dose of 185 MBq of <sup>153</sup>Sm-HA, average age 23 years; B – 17 patients (19 knees) with 740 MBq of <sup>153</sup>Sm-HA, average age 21.3 years. The evaluation before and after 1 year of synovectomy used the following criteria: reduction in the number of haemarthroses and use of the coagulation factor and improvement in articular motility. Adverse-effects occurrence was considered too. Early and late scintigraphic studies were

performed after synoviorthesis and no joint immobilization was recommended. The reduction in haemarthrosis and use of coagulation factor were: group 1 – 31.3% and 25%; group 2 – 81.5% and 79% with  $P < 0.001$  respectively; no significant improvement in knees motility was noted for both groups. Four cases of mild reactional synovitis were observed in each group. The scintigraphic control showed homogenous distribution of the radiopharmaceuticals with no articular escape; the material was considered safe by its permanence in the articulation. We have significant improvement in the synovectomy of haemophilic knees with 740 MBq of <sup>153</sup>Sm-HA; the less penetration of its beta radiation was compensated by the increased biological effect with the higher used activity.

**Keywords:** comparison between different activities, haemophilia, knees arthropathy, samarium-153

## Introduction

Haemophilia is a congenital bleeding disorder linked to the X chromosome of the human genome, represented mainly by two types: haemophilia A – deficiency of factor VIII (most frequent) and haemophilia B – deficiency of factor IX. Joint bleeding associated with muscle bleeding represents 90% of bleeding episodes in haemophilia patients, but alone, haemarthrosis corresponds to 70–80% of these episodes [1]. The haemarthrosis occurs in 80% of the time in knees, elbows and ankles [2]. These haemarthroses produce inflammatory changes in the synovial membrane; the

repetition of which over time promotes a chain of events that will result in joint ankylosis, including the direct damage of blood on the articular cartilage [3].

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. Moreover, radiosynovectomy was introduced by Ahlberg in the 1970s and has been proposed as the first option for the treatment of haemophilic arthropathy [1,4,5] and since then, various materials such as <sup>32</sup>P, <sup>186</sup>Re, <sup>90</sup>Y, <sup>165</sup>Dy, <sup>169</sup>Er have been used, with variable beta energy and half-lives.

In other research, we used <sup>153</sup>Samarium (<sup>153</sup>Sm) labelling the hydroxyapatite (HA) to control synovitis caused by haemophilic arthropathy, with fixed activity of 185 MBq and good results were obtained for intermediate-sized joints such as elbows and ankles, but

Correspondence: José U. M. Calegari, AOS 06 - Bloco D – Ap. 604, 70660-064 Brasília, Brazil.

Tel.: +55 61 81528444; fax: +55 61 33644252;

e-mail: jcalegari@uol.com.br

Accepted after revision 16 October 2013

poor results for knees [6]. This was attributed to the beta energy of 0.8 MeV of the material that has penetration in average range of 0.8 mm and maximum of 3.1 mm in soft tissues. However, in another study we showed that the use of  $^{153}\text{Sm}$  with higher activities provide better results [7]. The aim of this study was to compare the effect of 185 and 740 MBq of  $^{153}\text{Sm}$ -HA in the knees of haemophilic patients.

## Patients and methods

This prospective study evaluated haemophilic patients with chronic knee synovitis, followed by the Department of Hematology – *Hospital de Apoio*, Federal District and by the Orthopedics and Nuclear Medicine Services, *Hospital de Base*, Federal District, between 2004 and 2008.

Inclusion criteria were: activity in haemophilic arthropathy characterized by recurrent joint bleeding (at least one per month). Exclusion criteria were: haemophilic patients without knee arthropathy, other osteoarticular diseases, articular or periarticular infectious process or ruptured Baker's cyst.

Thirty-one patients (30 men) and 36 knees were treated as outpatients and divided into two groups: A – 14 patients (17 knees) received activity of 185 MBq of  $^{153}\text{Sm}$ -HA, mean age of  $23 \pm 7.9$  (range: 9–42) year, arthropathy evolution of 10.4 years and radiological Pettersson score = 5.9, B – 17 patients (19 knees) with activity of 740 MBq of  $^{153}\text{Sm}$ -HA, mean age of  $21.3 \pm 7.2$  (range: 6–31) years, arthropathy evolution of 10 years and Pettersson score = 5.2. No patient had inhibitors to coagulation factors. In the first group, 12 patients had haemophilia A (six severe and six moderate) and 2 type B (one severe and one moderate); in the second group, 13 patients had haemophilia A (five severe and eight moderate) and 4 type B (one severe and three moderate).

$^{153}\text{Sm}$  was obtained in research reactor (IEA-R1, from IPEN-CNEN, São Paulo, Brazil) 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 HA, using particles of appropriate size (20  $\mu\text{m}$ ), according to Couto *et al.* [8]. The percentage of bound activity or labelled efficiency was determined by centrifugation, by measuring the activity of the precipitate ( $^{153}\text{Sm}$ -HA) and supernatant ( $^{153}\text{Sm}$ -free) using a dose calibrator, was always >80%. Radiochemical purity was determined by Whatman 3MM paper chromatography (from GE, Milwaukee, WI, USA) in saline 0.9%, being higher than 98%, with stability of 24 h after. The particle size was measured by laser scattering and by filtration in a filter system of known sizes (1–15  $\mu\text{m}$ ). The mean obtained was 10  $\mu\text{m}$  (range: 3–12  $\mu\text{m}$ ). Microbiological tests for sterility and pyrogen were always negative in all samples.

The articular puncture, preceded by the use of the coagulation factor, was performed by an orthopaedist according to principles of invasive procedures, with 21 g needle, and was confirmed through aspiration of at least 2 mL of synovial fluid, followed by injection of 0.5 mL of  $^{153}\text{Sm}$ -HA (185 MBq or 740 MBq). The system was washed with fractions of 0.5 mL of saline solution, not exceeding the final volume of 2.0 mL, without coinjection of corticosteroids. If the joint had larger effusion a proper aspiration was performed. No injection for anaesthesia was made to minimize trauma to the patient: only topical anaesthetic was used. The material of the puncture was monitored by Geiger–Müller monitor (SE International, Summertown, TN, USA). No subsequent joint immobilization was recommended and the movement was limited by existing functional restriction.

Whole-body scintigraphy was performed immediately (1–2 h after) and later (3–7 days after) to ensure that the puncture was performed properly and to evaluate the homogeneity of the intra-articular distribution and systemic escape of the material. A gamma camera with detector of large field of view (Millennium, GE), low-energy collimator, high resolution, with a photo peak centred at 100 keV and 15% window was used. Whole-body images were obtained with a matrix of  $128 \times 128$  pixels.

Clinical evaluation of joints was performed before and 1 year after synovectomy according to the following criteria: decreased number of joint bleedings and use of the clotting factor and improvement in joint mobility, as measured by goniometry. One year, despite the revisions made each 3 months was chosen to compare some data with the initial work published [6]. The response was classified as: (i) good (full or partial reduction in manifestations: 100–70%), (ii) moderate (significant reduction: 69–40%) and (iii) poor (no reduction or discrete reduction: 39–0%). The occurrence of side effects was another aspect considered.

The statistical analysis considered significance of 95% ( $P \geq 0.05$ ), using the chi-squared bi-causal or Fisher tests. This study was approved by the Ethics Committee of the Department of Health, Federal District, and participants or their legal guardians signed the consent form.

## Results

Thirty-six knees were treated and divided into two groups: A – 17 knees received intra-articular activity of 185 MBq (5 mCi), B – 19 knees received 740 MBq (20 mCi) of  $^{153}\text{Sm}$ -HA. The number of haemarthroses per month before and 1 year after the synovectomy was respectively: A =  $2.7 \pm 2.3$  (range: 1–10) and  $1.85 \pm 0.5$  (range: 0–10); B =  $2.8 \pm 2.2$  (range: 1–15) and  $0.52 \pm 0.4$  (range: 0–10).

The use of the clotting factor had the same frequency of haemarthrosis before the synovectomy: A =  $2.7 \pm 2.3$  (range: 1–10); B =  $2.8 \pm 2.2$  but 1 year later decreased by 25% in the group A and by 79% in the group B.

The improvement in joint mobility measured by goniometry was little without statistical significance for both groups.

Group A showed poor response to treatment in all evaluated parameters and group B showed a good response in reducing haemarthrosis and the use of clotting factor.

There were four cases of mild reactive synovitis in each group that evolved well, without intervention measures, improving with joint rest, local application of ice and use of non-steroid anti-inflammatory drug. It should be remembered that no immobilization was performed in any joint.

The analysis of the residual radioactivity in the puncture material with Geiger–Müller counter showed low levels of radiation in all cases, ensuring good quality of the procedure. The early and late scintigraphic controls showed material always in the joint space, confirming that joint escape did not occur and ratifying synovial irradiation without detectable systemic circulation of  $^{153}\text{Sm-HA}$ . Figure 1 illustrates this type of control.

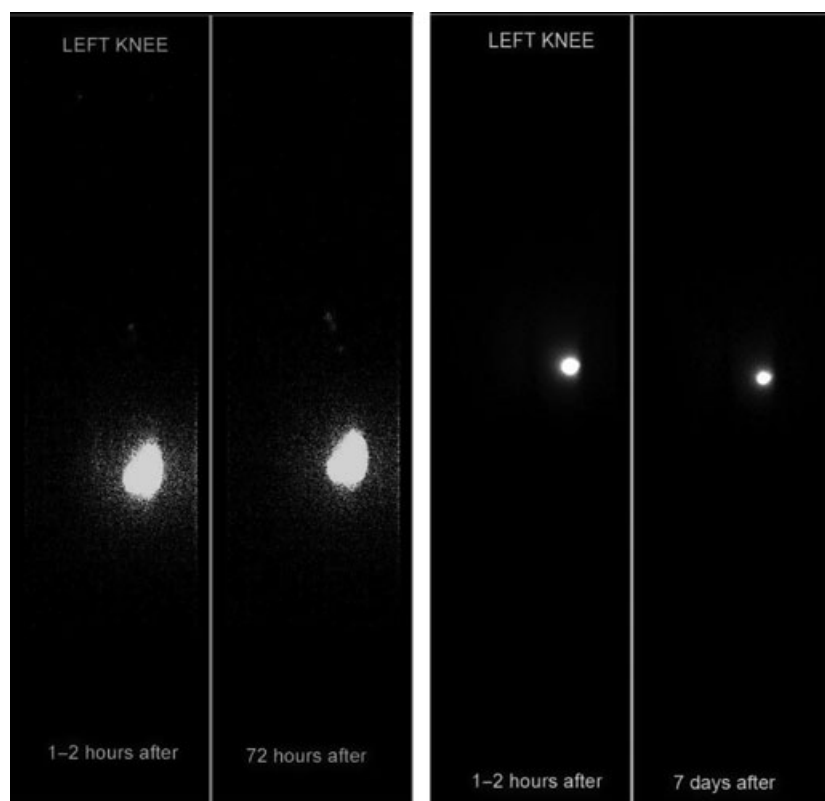
## Discussion

It is known by radiobiology principles concerning other materials with therapeutic purposes such as  $^{131}\text{I}$  or even those usually employed in radioisotope synovectomy that higher activities provide more pronounced biological effects [9]. In this context, the results of this study show a significant difference using higher activities (740 MBq or 20 mCi) in knees with  $^{153}\text{Sm-HA}$  than the lower doses (185 MBq or 5 mCi). The reduction in joint effusions using higher activities, shown in Table 1 after 1 year of treatment, can be superimposed to the 60–80% in the revision of Schneider when the effect of various radioactive materials were analysed [10] or to the 78–84% in the haemophilic arthropathy of knees treated with  $^{32}\text{P}$  [11]. And this value (81.5%)

**Table 1.** Synovectomy results 1 year after the use of 185 MBq and 740 MBq of  $^{153}\text{Sm-HA}$ .

	Haemarthrosis reduction (%)	↓ Use of coagulation factor (%)
185 MBq $^{153}\text{Sm-HA}$ (17 knees)	31.3	25
740 MBq $^{153}\text{Sm-HA}$ (19 knees)	81.5	79

All results have  $P > 0.001$  by Fisher test.  
 $^{153}\text{Sm-HA}$ ,  $^{153}$ -samarium hydroxyapatite.



**Fig. 1.** Examples of immediate and late scintigraphic controls utilized.

is similar to those obtained for elbows (78%) and ankles (82%) using lower doses (185 MBq) [6].

The decreased use of the clotting factor showed similar proportion and is another important aspect because it means lower costs in the treatment of haemophilic patients [12]. The values were not the same compared to haemarthrosis because bleeding may occur in other sites of the patient: its reduction is slightly less.

The improvement in the joint mobility was the same for both groups (3–4 degrees by goniometry, Saehan, São Paulo, Brazil), i.e. small range without statistical significance. This is reasonable because studies with nuclear magnetic resonance have shown a reduction in synovial thickness either with  $^{153}\text{Sm}$  or other materials [13,14], but not in bone arthropathy already present. It should be noted that the patients of this study have arthropathy evolution of at least 10 years.

The scintigraphic control with images obtained after early and late injection showed appropriate intra-articular distribution, as well as absence of escape to regional lymph nodes, other organs or urinary elimination. The possibility of performing good quality scintigraphic images is one advantage of  $^{153}\text{Sm}$  by having gamma emission in the energy amplitude of 100 keV. Another possible advantage is the mild degree of reactive synovitis observed in both groups, solved without invasive medical intervention, possibly related to low penetration of its beta energy. According to Clunie [15], co-administration of corticosteroids is used in 60% of European services, and published works that do not use it are scarce [16], claiming that it has a washing effect on the injection orifice to prevent joint escape or reactive synovitis installed after the use of radioactive material [10–12]. We do not use this procedure because the washing effect on the injection site is made with saline flushing during puncture; the number of reactive synovitis is small and of low intensity, usually resolved with conservative measures. Corticosteroids could be used later if there is any case to justify this procedure. We agree with Gedik [17] that this procedure may not be necessary because this material has been used to treat haemophilic arthropathy [18,19] and constitutes a bias in the evaluation of results. There are works with corticosteroids for other reactive arthropathy [20,21], especially in rheumatoid arthritis, in groups of patient with and without  $^{153}\text{Sm}$ -HA: this limits the analysis of results from our point of view because they are drugs with similar objectives and used variable activities of the radioactive material (between

185 and 740 MBq). Moreover, these works have no information if corticosteroid coinjection made competitive, additive or synergic effect in the synovectomy.

The joint escape depends mainly on the size of the particles added to the radioactive material to prevent them from being drained by the synovial or lymphatic bloodstream of the periarticular region. These particles facilitate phagocytosis by macrophages present in the inflammatory process, constituting one of the main mechanisms of radiation; the other is the very permanence of the radioactive material within the joint. All works referenced in this article recommend joint immobilization as a key measure for limiting the escape. This process was not recommended in this study and the late scintigraphy (3–7 days) show intra-articular retention in all knees. We agree with Chinol [22], who reported that the biological behaviour of  $^{153}\text{Sm}$  plays a key role: while aggregating with the carrier (HA), there is no escape due to the size of the particles, after its dissociation, it forms compounds that are insoluble with the synovial fluid, which is facilitated by the acid pH resulting from the inflammatory process, precipitating in the joint. In clinical terms, this has been already reported by Clunie [23]. Possibly, it is the only radionuclide with this behaviour, giving the material an excellent retention profile.

There is no concern about possible carcinogenic effects of this procedure. Systemic irradiation can result from articular escape or from the gamma component of the  $^{153}\text{Sm}$ : studies on chromosomal abnormalities in circulating lymphocytes related to samarium [24] or to other radioactive materials [25] have not shown definitive changes, but transient and reversible ones. It should be observed that this irradiation is less than a diagnostic procedure of conventional bone scintigraphy or whole-body study with  $^{67}\text{Ga}$ . If the local effect is considered at the joint level, there are several studies with long follow-up times showing no occurrence of tumour [10,26–28]. Therefore, this possibility has not yet been characterized.

It could be inferred that the biological effect of  $^{153}\text{Sm}$ -hydroxyapatite in the activity of 740 MBq (20 mCi) is significantly higher than that of 185 MBq (5 mCi), considering only the action of the radioactive material. The material distribution is diffuse through the synovial membrane, as assessed by histological studies [20]; thus, the effect of this beta emitter with little penetration in soft tissues may be effective in larger joints such as knees.

## References

- 1 Luck JV Jr, Kasper CKL. General orthopedics: a tribute to J. Vernon Luck. Symposium: Surgical management of advanced hemophilic arthropathy: an overview of 20 years' experience. *Clin Orthop* 1989; 242: 60.
- 2 Rodriguez-Merchan EC, Jimenez-Yuste V, Aznar JA *et al.* Joint protection in haemophilia. *Haemophilia* 2011; 17(Suppl. 2): 1–23.
- 3 Jansen NW, Roosendaal G, Bijlisma JW *et al.* Degenerated and healthy cartilage are equally vulnerable to blood-induced damage. *Ann Rheum Dis* 2008; 67: 1468–73.
- 4 Ahlberg A. Radioactive gold in the treatment of chronic synovial effusion on

- hemophilia. In: Ana F, Denson KWE eds. Proc VII Congress World Federation of Hemophilia. Amsterdam, Holland: Teherat Excerpta Medica, 1971: 212–5.
- 5 Ahlberg A, Pettersson H. Synoviorthesis with radioactive gold in hemophiliacs. Clinical and radiological follow-up. *Acta Orthop Scand* 1979; 50: 513–27.
  - 6 Calegario JUM, Machado J, de Paula JC, de Almeida JSC, Casulari LA. Clinical evaluation after one year of samarium-153 hydroxyapatite synovectomy in patients with hemophilic arthropathy. *Haemophilia* 2009; 15: 240–6.
  - 7 Calegario JUM, Sayago M, Landa DC *et al.* Sinovectomia com crescentes atividades de 153-samário hidroxiapatita em joelhos de pacientes hemofílicos. *Radiol Bras* 2008; 41(Suppl. 1): 102–3.
  - 8 Couto RM, Araújo EB, Souza AA, Mengatti J, Barboza MF. Preparation of hydroxyapatite ( $^{90}\text{Y}$ -HA) for synovectomy. *Radiol Bras* 2006; 39(Suppl. 1): 95.
  - 9 Kassis AL, Adelstein SJ. Radiobiological principles in radionuclide therapy. *J Nucl Med* 2005; 46(Suppl. 1): 4s–12s.
  - 10 Schneider P, Farahati J, Reiners C. Radiosynovectomy in rheumatology, orthopedics, and hemophilia. *J Nucl Med* 2005; 46(Suppl. 1): 48s–54s.
  - 11 Siegel HJ, Luck JV Jr, Siegel ME, Quines C, Anderson E. Hemarthrosis and synovitis associated with hemophilia: clinical use of P-32 chromic phosphate synoviorthesis for treatment. *Radiology* 1994; 190: 257–61.
  - 12 Siegel ME, Siegel HJ, Luck JV Jr. Radiosynovectomy's clinical applications and cost effectiveness: a review. *Semin Nucl Med* 1997; 27: 364–71.
  - 13 Clunie GPR, Wilkinson LD, Lui D *et al.* Changes in articular synovial lining volume measured by magnetic resonance in a randomized, double-blind, controlled trial of intra-articular samarium-153 particulate hydroxyapatite for chronic knee synovitis. *Rheumatology* 1999; 38: 113–7.
  - 14 Pirich C, Schwameis E, Bernecker P *et al.* Influence of radiation synovectomy on articular cartilage, synovial thickness and enhancement as evidenced by MRI in patients with chronic synovitis. *J Nucl Med* 1999; 40: 1277–84.
  - 15 Clunie G, Ell PJ. A survey of radiation synovectomy in Europe, 1991–1993. *Eur J Nucl Med* 1995; 22: 970–6.
  - 16 Kavakli K, Aydogdu S, Taner M *et al.* Radioisotope synovectomy with rhenium<sup>186</sup> in haemophilic synovitis for elbows, ankles and shoulders. *Haemophilia* 2008; 14: 518–23.
  - 17 Gedik GK, Ugur O, Atilla B, Dundar S. Is corticosteroid coinjection necessary in radiosynovectomy of patients with hemophilia? *Clin Nucl Med* 2004; 29: 538–41.
  - 18 Shupak R, Teitel J, Garvey MB, Freedman J. Intraarticular methylprednisolone therapy in hemophilic arthropathy. *Am J Hematol* 1988; 23: 26–9.
  - 19 Fernandez-Palazzi F, Caviglia HA, Salazar JR, López J, Aoun R. Intraarticular dexamethasone in advanced chronic synovitis in hemophilia. *Clin Orthop Relat Res* 1997; 343: 25–9.
  - 20 O'Duffy EK, Clunie GPR, Lui D, Edwards JCW, Ell PJ. Double blind glucocorticoid controlled trial of samarium-153 particulate hydroxyapatite radiation synovectomy for chronic knee synovitis. *Ann Rheum Dis* 1999; 58: 554–8.
  - 21 Dos Santos MF, Furtado RNV, Konai MS, Castiglioni MLV, Marchetti RS, Natour J. Effectiveness of radiation synovectomy with samarium-153 particulate hydroxyapatite in rheumatoid arthritis patients with knee synovitis: a controlled randomized double-blind trial. *Clinics (São Paulo)* 2009; 64: 1187–93.
  - 22 Chinol M, Vallabhajosula S, Goldsmith SJ *et al.* Chemistry and biological behavior of samarium-153 and rhenium-186-labeled hydroxyapatite particles: potential radiopharmaceuticals for radiation synovectomy. *J Nucl Med* 1993; 34: 1536–42.
  - 23 Clunie G, Lui D, Cullum I, Edwards JCW, Ell PJ. Samarium-153-particulate hydroxyapatite radiation synovectomy: biodistribution data for chronic knee synovitis. *J Nucl Med* 1995; 36: 51–7.
  - 24 O'Duffy EK, Oliver FJ, Chatters SJ *et al.* Chromosomal analysis of peripheral lymphocytes of patients before and after radiation synovectomy with samarium-153 particulate hydroxyapatite. *Rheumatology* 1999; 38: 316–20.
  - 25 Klett R, Lange U, Haas H, Voth M, Pinkert J. Radiosynoviorthesis of medium-sized joints with rhenium-186-sulphide colloid: a review of the literature. *Rheumatology* 2007; 46: 1531–7.
  - 26 Teigland JC, Tjonnfjord GE, Evensen SA, Charania B. Synovectomy for hemophilic arthropathy: 6–21 years of follow-up in 16 patients. *J Intern Med* 1994; 235:139–243.
  - 27 Heim M, Tiktinski R, Amit Y, Martinowitz U. Yttrium synoviorthesis of the elbow in persons with haemophilia. *Haemophilia* 2004; 10: 590–2.
  - 28 Vuorela J, Sokka T, Pukkala E, Hannonen P. Does yttrium radiosynovectomy increase the risk of cancer in patients with rheumatoid arthritis? *Ann Rheum Dis* 2003; 62: 251–3.