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ORIGINAL ARTICLE

Knee radiosynovectomy with ^{153}Sm-hydroxyapatite compared to ^{90}Y-hydroxyapatite: initial results of a prospective trial

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Abstract

Introduction Radiosynovectomy (RS) with ^{90}Y-hydroxyapatite (^{90}Y-HyA) aims to control knee hemarthrosis in hemophiliac patients to prevent secondary arthropathy. However, knee RS using ^{153}Sm-hydroxyapatite (^{153}Sm-HyA) is considered less suitable due to the lower average soft tissue range and energy of ^{153}Sm for large joints, such as the knees.

Purpose The objective of this investigation was to assess the efficacy and safety of knee RS with ^{153}Sm-HyA, compared to ^{90}Y-HyA.

Methods Forty patients were prospectively assigned to undergo knee RS with ^{153}Sm-HyA ($n=19$) or with ^{90}Y-HyA ($n=21$). The frequency of hemarthrosis episodes before and after treatment were compared.

Results After six months of knee RS, ^{153}Sm-HyA and ^{90}Y-HyA promoted a similar reduction of hemarthrosis episodes (50% and 66.7%, respectively). However, after 12 months of knee RS, the reduction of hemarthrosis episodes was significantly ($p=0.037$) higher using ^{153}Sm-HyA (87.5%) compared to ^{90}Y-HyA (50.0%). This discrepancy was more pronounced ($p=0.002$) for ^{153}Sm-HyA compared to ^{90}Y-HyA in adults/adolescents.

Conclusion Knee radiosynovectomy with ^{153}Sm-HyA is safe, reduces hemarthrosis episodes after 12 months of treatments, especially in adults/adolescents and even with grades III/IV arthropathy, similar to ^{90}Y-HyA. ^{90}Y-HyA seems to promote better hemarthrosis control in small children.

Keywords Radiosynovectomy · Knee · Hemarthrosis · ^{90}Y-hydroxyapatite · Samarium-153 · ^{153}Sm-hydroxyapatite

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Introduction

Hemophilia is an X-linked inherited bleeding disorder resulting from a deficiency of factor VIII (hemophilia A) in 80% of the cases or from factor IX (hemophilia B). The estimated prevalence is approximately 1/10.000 births for hemophilia A and 1/40.000 births for hemophilia B [1]. The most common clinical presentation in hemophilia consists of bleeding of the joints (80%), muscle (10–20%), tissues or cavities (5–10%), and brain (< 5%) [1]. The consequences are economic, physical, and psychological, with a significant impact on the quality of life of the patient [2].

Hemarthrosis, i.e., the presence of blood in the joint cavity, triggers an inflammatory process, with iron accumulation in the synovial cells mediated by cytokines. The inflammatory cells release pro-angiogenic factors, leading to synovial thickening with villi proliferation. The synovial

proliferation is the initial stage of the hemophilic arthropathy; the villi proliferation is friable and predisposes to more bleeding with more joint damage, thus perpetuating a vicious cycle of progressive and irreversible joint destruction (chronic hemophilic arthropathy). Therefore, successive hemarthroses lead to chronic synovitis, which, if not adequately treated, will lead to a loss of function [3].

Treatment aims to control hemarthroses and prevent secondary arthropathy, and several approaches exist, depending on the stage of the disease: rest, replacement of coagulation factors, immobilization, systemic or intra-articular injections of steroids [1, 4]. If the synovitis is refractory to these treatments, then synovectomy is warranted [5, 6].

Even though primary prophylaxis with the regular use of clotting factors concentrates is the most effective treatment for patients with hemophilia and may prevent joint destruction [7], unfortunately, this therapy is not available for the entire population of patients with hemophilia in low and middle-income countries, and approximately 54% of patients do not adhere to the treatment [8]. Even in developed countries in which adherence is better due to superior socioeconomic conditions, it is still a problem [9]. Furthermore, prophylaxis with clotting factors is not curative, may lead to hemophilic arthropathy and joint dysfunction, and bears an extremely high cost for the country's health care system. Although corticosteroids intra-articular injection is useful in chronic and refractory pain, it is a palliative therapy aimed at alleviating symptoms, does not prevent the progression of the disease, and may have complications, such as tendon rupture, osteonecrosis, septic arthritis and systemic effects of corticosteroids [1, 3].

Radiosynovectomy (RS) is regarded as the first-line therapy in hemophilia patients with a high risk of joint bleeding, to prevent joint destruction and reduce episodes of hemarthrosis refractory to prophylaxis by replacement of coagulation factors. RS is indicated in patients with three or more of hemarthrosis episodes in a specific joint (target joint) for six months [10]. RS consists of the intra-articular radioisotope injection of colloid or hydroxyapatite crystals (particles 2–10 μm) that are not absorbed by the blood/lymphatic vessels. The colloid/hydroxyapatite crystals suffer phagocytosis, are incorporated in the inflamed synovial space within the joint, and the ionizing beta radiation cause direct and indirect cytotoxic effects, leading to fibrosis of the synovial lining.

Yttrium-90 (^{90}Y) is the main radioisotope utilized for RS in large joints (ex. knees) where the synovial is thicker because of its high penetration (mean 3.6 mm) and energy (maximum β energy emission = 2.25 meV) while for medium-sized joints (ex. elbows), rhenium-186 (^{186}Re) is customarily used. There are also differences in the pharmaceutical linked to the isotope. A radiolabeled colloid is more widely used with robust consolidated studies in the literature [6, 10, 11], while hydroxyapatite is less used [12–14].

Although RS is efficient, safe, and with excellent cost-effectiveness, in low/middle-income countries, this treatment is underused, as ^{90}Y-hydroxyapatite (^{90}Y-HyA) maybe not as widely available and may be much more expensive in some countries when compared to samarium-153 labeled hydroxyapatite (^{153}Sm-HyA). ^{153}Sm-HyA can be used for knee RS, with low penetration (mean 0.7 mm) and energy (maximum β energy emission = 0.29 meV).

Furthermore, when evaluating the potential complications of radiotracer leakage, ^{90}Y-HyA bears higher risk than ^{153}Sm-HyA, especially in small children (i.e. below 12 years old) due to the higher tissue penetration range and beta-energy of ^{90}Y.

The purpose of this investigation was to assess the efficacy and safety of knee RS with ^{153}Sm-HyA in comparison to knee RS with ^{90}Y-HyA.

Materials and methods

Hemophiliac patients with a diagnosis of chronic knee synovitis due to repeated episodes of hemarthrosis for knee radiosynovectomy (RS) treatment were prospectively enrolled. The patients were assigned to receive ^{153}Sm-hydroxyapatite (^{153}Sm-HyA) or ^{90}Y-hydroxyapatite (^{90}Y-HyA) according to the availability of the radiotracer at the time of enrollment.

The Ethics Committee of the local Institution (CAAE: 08934112.2.0000.5404) approved this study. All patients signed a written informed consent before the procedures.

The inclusion criteria consisted of patients with three or more years of age, hemophilic knee arthropathy, and presence of target joint, defined as three or more episodes of hemarthrosis in the same knee within six months [15].

Exclusion criteria consisted of children with inherited conditions that predispose to cancer (ex. Fanconi's anemia; Bloom's syndrome); prior history of malignancy or chemotherapy or radiotherapy; fever or a known infection seven days before knee RS; signs of infection on the injection site in the skin or the joint; signs and symptoms of acute hemarthrosis on the day of the procedure.

Clinical, laboratory and radiologic assessments

Clinical parameters evaluated included age (adults/adolescents *vs.* small children (i.e. below 12 years old), type (A or B) and severity of hemophilia (severe or moderate) and the presence (or absence) of factor VIII or IX inhibitory antibodies (inhibitor).

The degree of arthropathy was classified according to radiographic images as no/mild arthropathy: Grades I–II; moderate/severe arthropathy: Grades III–V [16].

Three months before knee RS, laboratory evaluation was undertaken in all patients for the presence (or absence) of inhibitors to factors VIII or IX.

Knee RS procedure

The patient preparation was performed by administering immediately before knee RS, factors VIII or IX concentrates to increase these factor levels by 80%, followed by two doses to increase the factor level by 30% every 24 h for three days. Additionally, a single dose of an anti-fibrinolytic agent, epsilon aminocaproic acid (50 mg/kg) was injected intravenously. Inhibitor patients received bypassing agents, either activated prothrombin complex (aPCC) (Feiba®, Takeda Deerfield, IL, USA) (75–100 IU/kg per day for three days) or recombinant activated factor VIIa (NovoSeven®, Novo Nordisk, Denmark) (90–120 mcg/kg every 2–3 h, three doses in total), with the first dose administered 10 min before the procedure.

The preparation of the injection site was performed in all patients by a highly trained experienced orthopedic surgeon (R.P.) and, in equivocal cases, also by a radiologist specialized in ultrasound musculoskeletal imaging (E.T.S.) as a safety measure to confirm the position of the needle for a secure injection. Before radiotracer injection, the injection site was disinfected and anesthetized with lidocaine at 1% without a vasoconstrictor. Aspirate of synovial fluid and blood indicated that the needle was adequately placed in the joint space.

Radiotracer injection in the diseased knee joint was carried out with hydroxyapatite either labeled with yttrium (^{90}Y-HyA) or labeled with samarium-153 (^{153}Sm-HyA). The Nuclear and Energy Research Institute (IPEN/CNEN, Brazil) provided ^{153}Sm-HyA and ^{90}Y-HyA. Required radiochemical purity was higher than 95%. Doses were determined according to the age of the patient. ^{90}Y-HyA doses were 185 MBq (5 mCi) in adults/adolescents and 74–111 MBq (2–3 mCi) in small children. ^{153}Sm-HyA doses were 740 MBq (20 mCi) in adults/adolescents and 296–444 MBq (8–12 mCi) in small children. The syringe was flushed twice with 1–3 mL of saline solution to reduce the radiopharmaceutical particle adherence to the syringe wall.

After radiotracer injection, a dose of 1 mL of Diprospan ® (1 mL ampoule = 5 mg of betamethasone and 2 mg of disodium phosphate) was administered. The skin was compressed to avoid leakage of radioactive material. Subsequently, a radioactivity detector was applied to evaluate eventual skin leakage of radioactive material. In case of leakage, thorough decontamination was undertaken until no radioactivity was detected. This step was crucial to avoid radiation necrosis of the skin in the event of leakage. A splint immobilization (semi-rigid Robert Jones) was applied for 48 h after the procedure, and anti-inflammatory medication was prescribed for seven days. Replacement treatment with factor VIII or IX concentrate or bypassing agent was prescribed for at least 24 h to 72 h after the knee RS to avoid a new hemarthrosis and edema.

Determination of the procedure efficiency

The procedure efficiency was determined by comparing the reduction of hemarthrosis episodes before and after knee RS—in all patients and stratified by adults/adolescents and small children and according to the degree of arthropathy (Grades I–II vs. Grades II–IV), as follows:

- ^{153}Sm-HyA (only) after six months of knee RS
- ^{90}Y-HyA (only) after six months of knee RS
- ^{153}Sm-HyA vs. ^{90}Y-HyA after six months of knee RS
- ^{153}Sm-HyA (only) after 12 months of knee RS
- ^{90}Y-HyA (only) after 12 months of knee RS
- ^{153}Sm-HyA vs. ^{90}Y-HyA after 12 months of knee RS.

The percentage of reduction of bleeding episodes was calculated for each radiopharmaceutical by subtracting the number of bleeding episodes (NB) at six or 12 months after radiosynovectomy from the NB in the same period of time (6 or 12 months) just before treatment, divided by the NB before treatment, according to the following equation:

$$\%\ \text{reduction of bleeding} = \frac{(\text{NB before}) - (\text{NB after})}{\text{NB before treatment}} \times 100$$

Procedure efficiency was also evaluated by counting the residual syringe radioactivity. The residual syringe radioactivity was measured by placing the syringe (with needle) used to inject the radiopharmaceutical in the dose calibrator. To avoid geometry interference with calculation of residual radioactivity, the same dose calibrator was used to measure the activity prior to and after injection. Therefore, the residual syringe radioactivity was a product of the radioactivity measured prior to and after injection. The residual syringe radioactivity after intra-articular injection was correlated to the percent reduction of hemarthrosis for each radiotracer.

Determination of the procedure safety

Post-treatment whole-body and static Images after 24 h of knee RS were performed on a scintillation camera for both ^{153}Sm-HyA and ^{90}Y-HyA. Additionally, PET images were also acquired for patients submitted to knee RS with ^{90}Y-HyA. The purpose of obtaining whole-body images after 24 h of radiotracer injection was to determine the safety of knee RS by identifying extra-articular radiopharmaceutical leakage.

Statistical analyses

The Wilcoxon's test was applied to compare the results between the two groups submitted to knee RS (^{153}Sm-HyA and ^{90}Y-HyA).

p values ≤ 0.05 were considered significant.

The R-version 3.6.1 (The R Foundation for Statistical Computing Platform: x86_64-w64-mingw32/x64 (64-bit)) was used for analysis.

The ROC curve was generated to determine the optimal to determine the cutoff point related to the maximum acceptable percentage of radioactivity retained in a syringe that will still allow a reduction of 50% of the bleeding episodes after one year of knee RS [17].

Results

Forty patients were enrolled in the study, with ages ranging from 4–65 years old (mean = 16.7 years), and among them, 14 (35%) were small children (below 12 years). All patients were male, mean age in child group was 7.9 years and in adult group was 21.4 years. There were 35 (87.5%) patients with hemophilia A and 5 (12.5%) with hemophilia B. Five hemophilia A patients had inhibitor (12.5%). The degree of arthropathy was as follows: Grades I – II in 20 patients (50%), Grades III–IV in 20 (50%) patients and no patients were Grade V. Table 1 displays the demographic data and stratifies according to the two types of radiotracers used for knee RS.

Efficacy

Table 2 displays the clinical response to knee RS stratified according to the two types of radiotracers used for all patients after 6 and 12 months of RS. All patients were injected and treated; none were excluded.

Table 2 Percentage of reduction of knee joint bleeding episodes after radiosynovectomy (RS) and according to the radiotracer after 6 and 12 months of RS in all 40 patients and stratified by age

		% reduction bleeding after 6 months of RS		% reduction bleeding after 12 months of RS	
Radiotracer		^{90}Y-HA	^{153}Sm-HA	^{90}Y-HA	^{153}Sm-HA
$N = 40$ (all patients)	Median	66.7%	50%	50%	87.5%
	Min	0%	0%	0%	0%
	Max	100%	100%	100%	100%
	N	21	19	21	19
	p value	0.842		**0.037**	
$N = 26$ (adults)	Median	66.7%	50%	46.7%	100%
	Min	14.3%	0%	2.9%	0%
	Max	86.8%	100%	61.9%	100%
	N	11	15	11	15
	p value	0.854		**0.003**	
$N = 14$ (children)	Median	64.6%	20%	55.2%	20%
	Min	0%	0%	0%	0%
	Max	100%	100%	100%	100%
	N	10	4	10	4
	p value	0.498		0.357	

Bold values denote statistical significance at the $p < 0.05$ level

N Number of patients

After six months of knee RS, there was a significant reduction of hemarthrosis episodes in patients submitted to ^{153}Sm-HyA ($p \leq 0.001$) and ^{90}Y-HyA ($p \leq 0.001$). The percentage of reduction of bleeding episodes was similar ($p = 0.842$) when comparing ^{153}Sm-HyA to ^{90}Y-HyA (50% vs. 66.7%, respectively). After 12 months of knee RS, there was a significant persistent reduction of hemarthrosis episodes in patients submitted to ^{153}Sm-HyA ($p \leq 0.001$) and ^{90}Y-HyA ($p \leq 0.001$). However, the percentage of reduction of bleeding episodes maintained high for ^{153}Sm-HyA

Table 1 Demographic data of patients submitted to radiosynovectomy

Variables		All		90Y-HA*		153Sm-HA*	
		N	(%)	N	(%)	N	(%)
Age group	Adult	26	65.0%	11	52.0%	15	79%
	Child	14	35.0%	10	47.0%	4	21%
Hemophilia	A	35	87.5%	20	95.2%	15	78.9%
	B	5	12.5%	1	4.8%	4	21.1%
Factor VIII inhibitor	Positive	5	12.5%	0	0.0%	5	26.3%
	Negative	35	87.5%	21	100.0%	14	73.7%
Degree of arthropathy	I–II	20	50.0%	13	61.9%	7	36.8%
	III–IV	20	50.0%	8	38.1%	12	63.2%
Side	Right	17	42.5%	6	28.6%	11	57.9%
	Left	23	57.5%	15	65.2%	8	42.1%

*^{90}Y-HA ^{90}Y-hydroxiapatite, ^{153}Sm-HA ^{1542}Sm-hydroxyapatite

(87.5%) but not for ^{90}Y-HyA (50.0%). This discrepancy among radiotracers was significant ($p=0.037$).

In adults/adolescents only ($n=26$), after six months of knee RS, there was a significant reduction of hemarthrosis episodes in patients submitted to ^{153}Sm-HyA ($p=0.001$) and ^{90}Y-HyA ($p=0.004$). However, the percentage of reduction of bleeding episodes was similar (not significant—$p=0.854$) with ^{153}Sm-HyA and ^{90}Y-HyA (50% vs. 66.7%, respectively). After 12 months of knee RS, a significant and persistent reduction of hemarthrosis episodes occurred in both procedures, with ^{153}Sm-HyA ($p=0.001$) and ^{90}Y-HyA ($p=0.004$). Additionally, the percentage of reduction of bleeding episodes maintained significantly ($p=0.003$) higher for ^{153}Sm-HyA (100%) compared to ^{90}Y-HyA (46.7%).

In small children only ($n=14$), knee RS with ^{90}Y-HyA controlled hemarthrosis better than with ^{153}Sm-HyA. After six months of treatment, there was a non-significant reduction of hemarthrosis episodes in patients submitted to ^{153}Sm-HyA ($p=0.5$), while a significant reduction of bleeding episodes occurred in patients submitted to ^{90}Y-HyA ($p=0.006$). However, the reduction of bleeding episodes in small children using ^{90}Y-HyA was not significant ($p=0.498$), compared to ^{153}Sm-HyA (64.6% vs. 20%, respectively). After 12 months of knee RS, the maintenance of reduced episodes of hemarthrosis was not significant for small children submitted to ^{153}Sm-HyA ($p=0.5$) but was significant using treatment with ^{90}Y-HyA ($p=0.009$). However, the percentage reduction of bleeding episodes was not significant ($p=0.357$) among radiotracers: ^{153}Sm-HyA (20%) and ^{90}Y-HyA (55.2%).

Correlation to imaging

Table 3 displays the clinical response to knee RS according to the two types of radiotracers applied according to the degree of arthropathy (Grades I–II vs. Grades III–IV). Both ^{153}Sm-HyA and ^{90}Y-HyA performed equally well in reducing episodes of hemarthrosis at 6 and 12 months post RS with no significant difference according to the degree of knee arthropathy. However, there was a tendency ($p=0.064$) of ^{153}Sm-HyA to have promoted a higher reduction of hemarthrosis episodes after 12 months (100%) compared to ^{90}Y-HyA (47.7%) in Grade III–IV patients.

Safety

The percentage of residual radioactivity in the syringe to promote and guarantee a 50% reduction in hemarthrosis episodes maintained after one year of RS was established. A maximum of 38% of residual radioactivity of ^{153}Sm-HyA retained in the syringe will promote 50% reduction in hemarthrosis episodes after one year of RS with an 85.7% specificity (odds ratio (OR) = 7.69; 95% confidence interval (CI) = 0.54–159). For ^{90}Y-HyA, the maximum retention of 48% will promote the same reduction in hemarthrosis episodes after one year of RS, with a specificity of 82% (OR = 2.84; CI = 0.29–41.1) (Fig. 1).

Table 3 Percentage of reduction of knee joint bleeding episodes after radiosynovectomy (RS) and according to the radiotracer after 6 and 12 months of RS in all 40 patients stratified according to the degree of arthropathy

Degree of arthropathy		% reduction bleeding after 6 months of RS		% reduction bleeding after 12 months of RS	
Radiotracer		^{90}Y-HA	^{153}Sm-HA	^{90}Y-HA	^{153}Sm-HA
$N=20$ GI–GII	Median	66.7%	50%	52.6%	66.7%
	Min	0%	0%	9.1%	0%
	Max	100%	100%	100%	100%
	N	13	7	13	7
	p value	0.780		0.383	
$N=20$ GIII–GIV	Median	57.1%	50%	47.7%	100%
	Min	33.3%	0%	0%	0%
	Max	86.7%	100%	76.9%	100%
	N	8	11*	8	12
	p value	0.967		*0.064*	

N Number of patients; *1 missing

A successful intra-articular injection occurred in all patients. Extra-articular radiotracer leakage occurred in 3 patients in the ^{153}Sm-HyA group and none in the ^{90}Y-HyA group. Among the three patients with extra-articular radiotracer leakage, two patients had inguinal lymph nodes uptake, and one patient had lung, liver, and spleen uptake (Fig. 2) but with a low calculated absorbed dose (3.76 mGy) [18, 19]. None of the patients from any of the groups presented side effects of radiation-induced synovitis, skin necrosis, nor infection. Furthermore, the potential contamination of ^{153}Sm by the presence of the long-lived ^{154}Eu is negligible and not a limitation unlike the injection of high doses of ^{153}Sm-EDTMP for metastatic bone pain palliation [20–22].

The qualitative analysis of images did not reveal differences among patients that received total radioactive dose and reduced dose caused by residual syringe radioactivity. Furthermore, there was no difference between the percentage of the reduction of bleeding and percentage of residual syringe radioactivity with ^{153}Sm-HyA ($\rho=0.24$; p value = 0.322) nor ^{90}Y-HyA ($\rho=0.078$; p value = 0.737).

Discussion

Our preliminary investigation demonstrated that knee radiosynovectomy (RS) with ^{153}Sm-hydroxyapatite (^{153}Sm-HyA) reduced knee hemarthrosis, similar to RS with ^{90}Y-hydroxyapatite (^{90}Y-HyA).

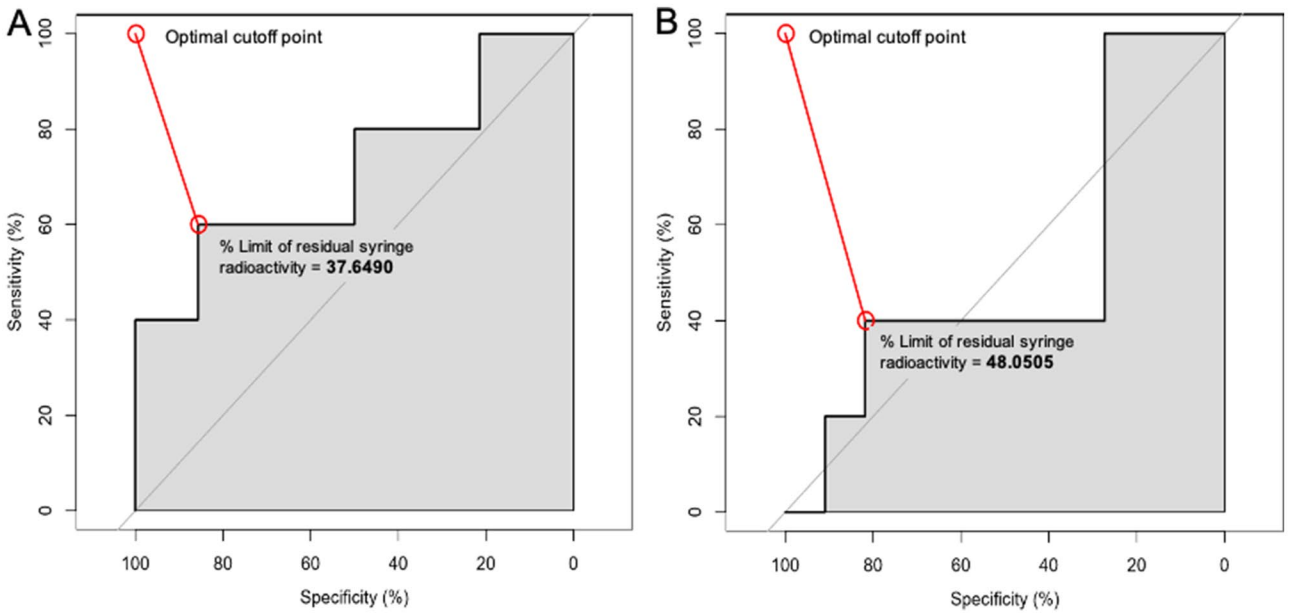

Fig. 1 ROC curve to determine the optimal cutoff point related to the maximum acceptable percentage of residual syringe radioactivity that will still allow a reduction of 50% of the bleeding episodes after one year of radiosynovectomy. **a** The ^{153}Sm-HyA maximum accepted %radioactivity retained is 38%. **b** The ^{90}Y-HyA maximum accepted %radioactivity retained 48%

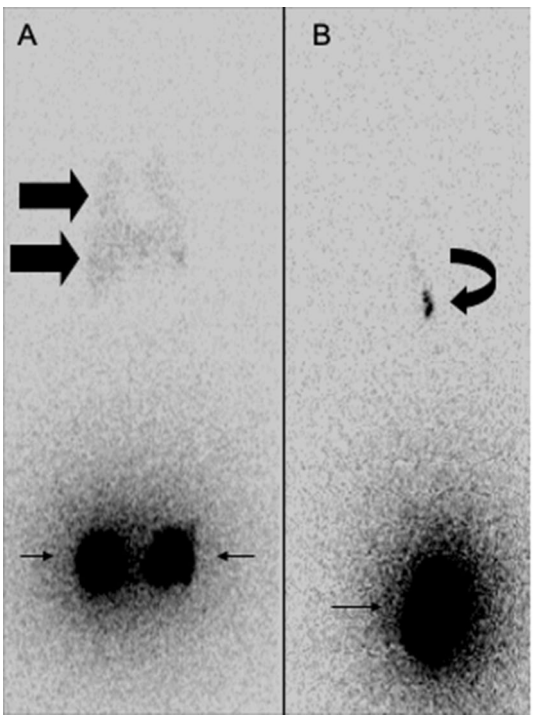

Fig. 2 Extra-articular radiopharmaceutical leakage. **a** There is an uptake in the lungs, liver, and spleen (thick arrows) after bilateral knee radiosynovectomy (arrows). **b** Uptake noted in a left inguinal lymph node (curved arrow) after left knee radiosynovectomy (arrow)

Interestingly, even though the number of episodes of bleeding reduced relatively equally after six months of knee RS using both ^{153}Sm-HyA and ^{90}Y-HyA (50% vs. 66.7%, respectively), after one year of treatment, there was quite a discrepancy. There was a significant benefit in the maintenance of reduction of knee bleeding episodes after 12 months using RS with ^{153}Sm-HyA (87.5%) compared to ^{90}Y-HyA (50%).

The better performance in hemarthrosis control with ^{153}Sm-HyA could be due to the higher injected doses of ^{153}Sm-HyA, guaranteeing effective treatments for more extended periods, contrary to the low doses applied with ^{90}Y-HyA. The ^{90}Y doses are necessarily lower than ^{153}Sm doses due to the higher toxicity of ^{90}Y in the normal bone because of the higher range of beta particles and also longer half-life compared to ^{153}Sm, which is why the doses of ^{90}Y-HyA were lower than ^{153}Sm-HyA. Furthermore, even though remote, ^{90}Y doses are lower because of the possibility of extravasation of the radiotracer, which could enter the bloodstream and irradiate the lungs and liver. Importantly, the dose applied seems to alter the clinical outcome entirely.

Calegaro et al. [13] performed ^{153}Sm-HyA RS in 31 hemophiliac small children ($n = 13$) and adults/adolescent ($n = 18$) patients with fixed low doses (185 MBq—5 mCi) and showed a reduction of hemarthrosis episodes that was mild in the knees (30%) but better in the elbows (78%) and ankles (82%). However, the discrepancies in hemarthrosis control efficiency rates in the knees may be due to the low doses initially used by Calegaro et al. [13], which are four

times lower than the doses applied to the current patient population. Higher ^{153}Sm-HyA doses (740 MBq—20 mCi) were delivered in the current study because dosimetry investigations demonstrated that ^{153}Sm activities 5.5 times higher than ^{90}Y activity are necessary to provide the same absorbed dose in the joint. Our findings agree with Calegaro et al. [12] subsequent publication that performed knee RS with ^{153}Sm-HyA using different doses (185 MBq vs. 740 MBq). They found a significantly higher reduction in hemarthrosis in patients injected with 740 MBq compared to 185 MBq (81.5% vs. 31.3%, respectively). Likewise, a study compared knee RS with 740 MBq of ^{153}Sm-HyA to 185 MBq of ^{90}Y-HyA and found a similar reduction of bleeding episodes for both radiotracers [23]. Radiolabeled hydroxyapatite was safe and performed equally well compared to colloid compounds, as has been demonstrated by Thomas et al. [24] that treated 221 joints of hemophiliac patients with either ^{90}Y-HyA or ^{90}Y-colloid. The authors found a similar reduction in hemarthrosis, regardless of joint type, age, gender, degree of arthropathy, and presence of inhibitors.

Specifically analyzing adults/adolescents, after one year of RS, the reduction of hemarthrosis episodes was significantly higher for ^{153}Sm-HyA compared to ^{90}Y-HyA (100% vs. 46.7%, respectively), similar to the retrospective analysis of Rodrigues-Merchan et al. [25], evaluating 500 RSs using either ^{90}Y-colloid or ^{186}Re-colloid. The authors reported a decrease of 64% in the number of hemarthroses. Kim et al. [26] found that the ^{90}Y-HyA retention time in the knee joint space ranged from 77% ± 5% after four days of injection and the clinical improvement increases as time go by with improvement ratios of 72% at six months after RS and 76% at 12 months after injection RS. Therefore, these findings demonstrate that the success of RS improves over time, although ^{153}Sm-HyA seems to control hemarthrosis better.

Evaluating exclusively the small children, however, ^{153}Sm-HyA RS performed worse in reducing hemarthrosis episodes compared to ^{90}Y-HyA RS after six months (20% vs. 64.6%, respectively) and 12 months (20% vs. 55.2%, respectively). This disparity could have been caused by the correction of the injected doses in small children according solely to age and weight and not to the volume of the knee hemarthrosis. The small children had similar knee volume with hemarthrosis as the adult/adolescent population. Therefore, it may be that, in small children, a dose adjustment according to the volume of the knee (instead of age and weight) would promote a better hemarthrosis control. Ideally, the evaluation of the synovial thickness by MRI before treatment would be a better strategy [11].

All patients had some degree of knee arthropathy, 50% were grades III and IV. Although hemarthrosis control with ^{153}Sm-HyA was just as effective as ^{90}Y-HyA after six months (50% vs. 57%, respectively), ^{153}Sm-HyA was slightly more effective after 12 months (100% vs. 48%, respectively). In patients with grades I–II arthropathy, ^{153}Sm-HyA RS and ^{90}Y-HyA RS were equally effective. Our findings using ^{153}Sm-HyA are similar to the study by Querol-Guiner et al. [27] that performed RS in 174 hemophiliac patients using ^{90}Y-colloid in the knees and ^{186}Re-colloid in the elbows, ankles, and shoulder joints. The authors found that RS provided adequate treatment for chronic hemophilic synovitis, was effective in all ages, regardless of the arthropathy grade.

The current study proposed establishing the optimal minimum accepted percentage of retention of radioactivity in the syringe after injection to promote, guarantee and maintain a 50% reduction in hemarthrosis episodes after one year of RS. The maximum accepted retention of radioactivity of 38% for ^{153}Sm-HyA (probably because of precipitation and dose adherence to the syringe and needle) would promote 7 times higher likelihood of reducing by 50% the hemarthrosis episodes after one year of RS, with a specificity of nearly 86%. For ^{190}Y-HyA, the maximum accepted retention of radioactivity was higher (48%) and would promote almost 3 times superior likelihood of reducing hemarthrosis episodes with a specificity of 82%. Based on these facts, if radioactivity retention in the syringe is above the thresholds discussed, performing an additional injection with the equivalent to the remainder radioactivity on the same day may guarantee a higher probability of success.

This study has some limitations, such as the small sample size. Furthermore, this study was non-randomized as ^{153}Sm-HyA in our country was introduced after ^{90}Y-HyA. Hence, occult inclusion biases cannot be entirely ruled out.

The major strength of this study was the possibility to demonstrate that ^{153}Sm-HyA could be an equal and adequate alternative to ^{90}Y-HyA when the latter is not available for knee radiosynovectomy, in patients with hemophilia. High activities of ^{153}Sm-HyA are safe and have similar or even better results compared to ^{90}Y-HyA.

It is also important to measure the residual activity in the syringe and to adjust radioactivity when necessary to ensure better clinical results.

To our knowledge, there are only a few studies [12, 23] that demonstrated the effectiveness of knee RS with ^{153}Sm-HyA with higher doses (740 MBq). Furthermore, radiotracer leakage with ^{153}Sm-HyA occurred only in three patients; therefore, the procedure remains safe. No leakage occurred with ^{90}Y-HyA and no radiation-induced complications (synovitis, skin necrosis or infection) occurred, similar to other publications [11, 13, 14]. The safety of ^{153}Sm-HyA relies on the fact that ^{153}Sm aggregates to HyA and escapes less frequently because of the particle size (different from colloids in which the particle size may vary) and because it forms an insoluble compound within the synovial fluid, facilitated by the acid pH resulting from the inflammatory process, precipitating in the joint [28]. ^{153}Sm-HyA is most

likely the only radionuclide with this behavior, giving the material an excellent retention profile [28].

Our findings may also be useful in hemarthrosis of other joints, such as elbows, wrists, and ankles, allowing us to take the next step in performing studies using ^{153}Sm-HyA in such situations described above and compare to ^{90}Y-HyA.

Conclusion

Knee radiosynovectomy with ^{153}Sm-HyA is safe, significantly reduces hemarthrosis episodes after 12 months of treatments, especially in adults/adolescents and even with grades III/IV arthropathy, similar to ^{90}Y-HyA. ^{90}Y-HyA seems to promote better hemarthrosis control in small children than ^{153}Sm-HyA. In countries where ^{153}Sm-HyA is available and if the cost is lower than ^{90}Y-hydroxyapatite, ^{153}Sm-hydroxyapatite may be a better alternative.

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Author contribution All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by AOS, JBSR, RP, MMNM, ESB, ETS, EBA, SQB, EMB, MEST and RZ. The first draft of the manuscript was written by AOS and LFMP. The final draft by AOS, MCO and ECSCE. All authors read and approved the final manuscript.

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Compliance with ethical standards

Conflict of interest None to declare.

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