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ORIGINAL ARTICLE *Musculoskeletal*

Radioactive synovectomy with Yttrium^{90} citrate in haemophilic synovitis: Brazilian experience

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Summary. Recurrent haemarthroses leading to chronic synovitis and arthropathy remain a major cause of morbidity in patients with haemophilia. Radioactive synovectomy (RS) is considered the first choice of treatment for chronic haemophilic synovitis. The aim of this study was to evaluate the effect of RS with Yttrium^{90} citrate (C-Y^{90}) in the joints of patients with chronic haemophilic synovitis. From 2003 to 2007, 245 joints (118 knees, 76 elbows, 49 ankles and two shoulders) of 190 patients with haemophilia or von Willebrand disease were submitted to RS with C-Y^{90} at Hemocentro de Mato Grosso, Brazil. Forty joints had radiographic Pettersson scores above 8. There were 36 joints of 22 patients with inhibitors to factor VIII. The procedure was safe with low occurrence of adverse events. The main effect was the overall reduction in joint bleeding frequency, from 19.8 to 2.6 per year post-RS. Similar results were obtained in cases with high radiographic scores and in inhibitor patients. Pain reduction was observed in most cases. Average range of motion was maintained or increased 1 year post-RS in most joints. Extension was stable or increased in 88.2% of the knees and 86.5% of the elbows. Ankle plantarflexion was stable or increased in 90.9%, whereas dorsiflexion was maintained or increased in 87.9%. Worsening of the range of motion, when present, ranged from 14 to 17 degrees. We concluded that RS with C-Y^{90} represents an important resource for the treatment of chronic haemophilic synovitis, markedly reducing joint bleeding frequency and pain, irrespective of the radiographic stage and inhibitor status.

Keywords: haemophilia, inhibitors, radioactive synovectomy, synovitis, von Willebrand disease, Yttrium

Introduction

Haemarthroses are responsible for nearly 80% of all bleeding episodes in patients with severe haemophilia; when recurrent, they can lead to chronic synovitis and progressive arthropathy [1–3]. Severe types of von Willebrand disease (VWD) may present with haemarthroses and synovitis [4].

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Despite the research studies that support the success of primary prophylaxis with factor concentrates for the prevention of haemophilic arthropathy, this treatment is currently accessible to fewer than 10% of the global population [5]. Prophylactic treatment is still not made widely available to Brazilian population with haemophilia (8172 registered patients) the third largest in the world [6]. Hence, musculoskeletal problems, especially chronic synovitis are frequent complications [7] that need to be addressed.

Radioactive synovectomy (RS) has a long record of safety and efficacy in haemophilic synovitis, mainly through the decrease in haemarthroses frequency. It has similar results to those achieved with arthroscopy, being additionally less invasive and less costly [8–20]. Radioactive synovectomy is therefore the preferred method for the treatment of haemophilic synovitis, according to many authors [8–10, 20].

The present work studied the effects of RS with Yttrium^{90} citrate (C-Y^{90}) in a cohort of 245 joints of 190 patients with chronic synovitis and haemophilia or VWD. It was accessed the initial radiographic joint stage as well as bleeding frequency, joint pain and range of motion (ROM) before and after the first 2 years of treatment. Furthermore, eventual side effects were tracked during follow-up. The same variables were evaluated in the group presenting advanced radiographic stages of arthropathy and in patients with inhibitors to FVIII.

Patients and methods

Between April 2003 and June 2007, RS with C-Y^{90} was performed in 245 joints of 190 patients with haemophilia (n = 185) and VWD (n = 5) at Hemocentro de Mato Grosso, Brazil. Patients were referred from 21 haemophilia centres in Brazil.

Inclusion criteria to enter the study were diagnosis of haemophilia or VWD; presence of ≥3 haemarthroses in the same joint within 6 months and clinical diagnosis of synovitis by experienced haematologist and orthopaedic surgeon. Ultrasound imaging (US) [21,22], magnetic resonance imaging (MRI) [23] and three-phase bone scintigraphy [23,24] were performed to obtain an objective diagnosis of synovitis and to rule out surgical indication. The following criteria were used to perform the diagnostic imaging tests: (i) US: all patients; (ii) MRI: children with <5 years of age and patients presenting advanced arthropathy on clinical examination; (iii) scintigraphy: patients presenting normal clinical examination and patients presenting advanced arthropathy.

Three individuals were previously excluded from the cohort of 190, two because of an acute bacterial infection on the day of RS and one because of the history of oncological condition [19] (eosinophilic granuloma). All individuals gave prior informed consent, approved by the institutional ethical committee.

The history of haemarthroses, pain scores [25], ROM [26] and radiographic Pettersson scores [27] were evaluated before RS. Information about the number of haemarthroses was obtained from the patients log books, which included the total number of bleeds in the joint treated within the previous 12 months and after the subsequent 1 and 2 years after treatment. The evaluation of pain was based on the World Federation of Hemophilia scores as described by Gilbert [25]: 0 = No pain, no functional deficit, no analgesic use (except with acute haemarthrosis); 1 = Mild pain, does not interfere with occupation nor with activities of daily living (ADL), may require occasional non-narcotic analgesic; 2 = Moderate pain, partial or occasional interference with occupation or ADL, use of non-narcotic medications, may require occasional narcotics; and 3 = Severe pain, interferes with occupation or ADL, requires frequent non-narcotics and narcotics medications. Plain radiographs were performed and Pettersson scale was used to score the severity of joint damage of each treated joint. Score intervals considered were: 0, 1–4, 5–8 and above 8.

All patients were infused with factor concentrates according to the type of bleeding disorder. The doses were sufficient to raise the patient's factor level to 50% and 30% respectively before and 24 h after RS. Inhibitor patients received either activated prothrombin complex concentrate (75 IU kg^{-1} pre- and 24 h post-RS) or recombinant FVIIa (90 μg kg^{-1} pre and 2 h post-RS).

Doses of C-Y^{90} (CIS BIO International, France) were [20] 5 mCi (185 mBq) for knees, 3 mCi (111 mBq) for elbows and ankles and 4 mCi (148 mBq) for shoulders. Half of these doses were used in patients weighing <20 kg. Children who presented extremely large knees were treated with 5 mCi.

A 23G needle was used to reach joint space and to inject lidocaine 2%; synovial fluid was aspirated, C-Y^{90} injected, followed by triamcinolone hexacetonide. Local compression was performed with sterile gauze pad, which was then scanned, using a Geiger–Müller counter; if any trace of radiation was detected on the gauze, skin was cleaned until the counter could not detect radiation. Robert Jones bandage was used to immobilize the limb for 48 h after RS. Partial weigh bearing with crutches was allowed after the 3rd day of RS. Whole body and local scintigraphy were obtained to check for C-Y^{90} leakage to non-target organs.

During the follow-up period, information of the number of haemarthroses per year, pain and ROM, 1 and 2 years post-RS was recorded. All patients were evaluated for acute adverse events, such as postinjection bleeding or infection, skin lesion due to leakage of radioactive material and actinic synovitis. All patients were encouraged to undergo a post-RS rehabilitation programme for 6 months [26].

Data analysis was performed using the SPSS program (SPSS version 13.0, Chicago, IL, USA). Non-parametric statistics was used for analysis with Wilcoxon signed-rank test. Distribution of data from the patients lost to follow-up was evaluated with chi-squared test. Differences were considered statistically significant if P-value ≤0.05.

Results

The characteristics of the study population are summarized in Table 1. The data lost to follow-up were not uniform among the outcomes. Data concerning the number of haemarthroses in 30 joints (12.2%) were lost, while those concerning pain in 77/245 (31.4%) of the joints were lost. We have observed a differential loss (P = 0.05) in the second year among

Table 1. Distribution of patients and joints according to gender, age, joints (knees, elbows, ankles and shoulders), number of procedures per joint, type of bleeding disorder and severity, presence of inhibitors and Pettersson scores (0, 1–3, 4–7 and 8–13) at the time of treatment.

	N	%
Gender		
Male	187	98.4
Female	3	1.6
Age (years)		
0–5	7	3.7
6–10	55	28.9
11–15	55	28.9
16–20	39	20.5
21–25	20	10.2
26–30	7	4.1
≥31	7	3.7
(Minimum 3; Maximum 45; Mean 14.59; SD 7.19)		
Number of joints treated		
Knees	118	48.2
Elbows	76	31.0
Ankles	49	20.0
Shoulders	2	0.8
Type of bleeding disorder		
Severe haemophilia A	132	69.5
Moderate haemophilia A	36	19.0
Severe haemophilia B	9	4.7
Moderate haemophilia B	8	4.2
von Willebrand disease	5	2.6
Presence of inhibitor	24	12.6
Pettersson score at the time of RS		
0	17	6.9
1–3	58	23.7
4–7	122	49.8
8–13	40	16.3
Total number of treated joints	245	
Total number of patients	190	

RS, radioactive synovectomy.

individuals with moderate haemophilia B and VWD, in contrast to those with more severe phenotypes, whereas patients with advanced radiological scores remained in the study in higher proportion in the 2nd year ($P = 0.003$).

There were 22 patients (11.58%) with inhibitors to FVIII, totalling 36 joints (36/245); two knees were lost to follow-up in this group.

There were no cases of lesion caused by leakage of C-Y^{90}. No patient presented postinjection acute bleeding or infection due to the treatment. Three joints (two elbows and one ankle) presented mild actinic synovitis within the first week of RS. The symptoms subsided after 1–3 weeks, without further lesion.

The average number of haemarthroses (Fig. 1a) per year was reduced from 19.8 pre-RS to 2.6 and 2.2 in the 1st and 2nd years post-RS respectively. Bleeding frequency in knees decreased from 20.9 to 3.3 and 2.7 respectively in the 1st year and 2nd year (Fig. 1b); in ankles, from 19.3 to 2.3 and 2.6 respectively in the 1st year and 2nd year (Fig. 1d), and in elbows from 19.3 to 1.9 and 1.4 respectively in the 1st year and 2nd year (Fig. 1c). The two shoulders with respectively 30 and 24 haemarthroses per year before RS had no further haemarthrosis 2 years post-RS.

We found a significant reduction in joint bleeding in patients with inhibitors who reached 1 year of follow-up ($n = 34$), from 15.8 (2–36) bleeds per year pre-RS to 2.15 (0–11) within 1 year post-RS in all joints.

Evaluating the possibility of a negative impact of high Pettersson scores on bleeding frequency, we found a statistically significant reduction in bleeds during 1 year post-RS in all groups, irrespective of the radiographic status (Fig. 1e).

There was a significant reduction in pain in all joints. As shown in Table 2, 74.8% of all patients referred pain before treatment, in contrast to 28% and 26% who were pain-free respectively 1 and 2 years post-RS. Of the percentage of patients who referred the worst pain score pre-RS (26.5%), only 1.8% and 0.9% remained with severe pain respectively after the 1st year and 2nd year post-RS. Similar results were seen in the group with Pettersson scores above 8, from 15% without pain to 65.2% 1 year post-RS. We found similar results in patients with inhibitors, from 29.2% without pain to 62.5% 1 year post-RS. The results were maintained in the 2nd year post-RS in all groups.

Range of motion maintained or improved from 7 to 9 degrees of motion 1 year post-RS in most joints. As shown in Table 3, extension remained stable or improved in 88.2% of the knees and 86.5% of the elbows. Ankle plantarflexion maintained or improved in 90.9% and dorsiflexion maintained or improved in 87.9% of the cases. However, there was loss of the 14 to 17 degrees of ROM in the remaining cases.

Discussion

Brazil has 8.172 registered patients with haemophilia [6]. Prophylaxis with coagulation factors is not offered to the Brazilian population [7], which is consequently exposed to haemophilic arthropathy. The present study describes a large cohort of patients with chronic synovitis treated with RS, some already presenting advanced stages of joint disease (Table 1).

The finding of a differential loss of follow-up data among individuals with moderate haemophilia B and VWD, in contrast to the patients with advanced radiographic joint scores, might have a negative effect on our study, because it could have favoured the cases with worse prognosis. Nevertheless, the present work was able to demonstrate significant effects of RS in haemophilic synovitis in all groups (Table S1).

Concerning our choice of radioisotope, there is a lack of well-designed comparative studies between different radiopharmaceuticals for intra-articular use in different joints and many authors reported good results using Yttrium in knees, elbows and ankles 9,12,17,28–30] According to the European Association of Nuclear Medicine, $Yttrium^{90}$ is the radioisotope recommended for RS in knees, whereas $Rhenium^{186}$ is recommended

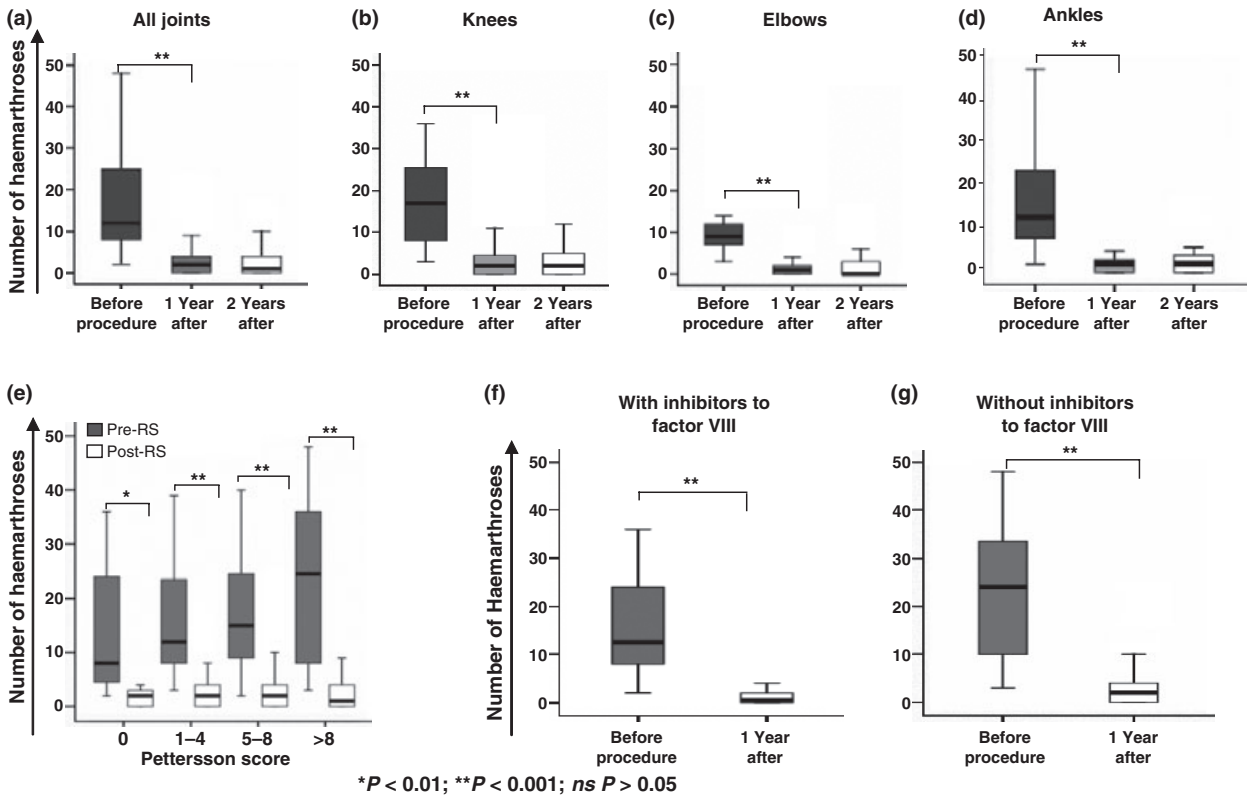

Fig. 1. Distribution in box-plots of the mean number of haemarthroses/year, 1 year pre-RS and, 1 and 2 years post-RS. (a) All joints (knees, elbows, ankles). (b), (c) and (d) respectively are knees, elbows and ankles. (e) Mean no. haemarthroses 1 year post-RS, according to four ranges of Pettersson scores, in all joints. Pettersson score intervals considered were 0, 1–4, 5–8 and >8. (f) Mean no. of haemarthroses/year 1 year pre and 1 year post-RS in joints from patients with inhibitors and (g) without inhibitors.

Table 2. Distribution of pain scores evaluated immediately before RS and after 1 and 2 years post-RS; joints included in all the Pettersson scores, compared to the joints presenting Pettersson score >8.

Pain score	Set of joints	Before RS n = 245 (%)	1 year after RS n = 168 (%)	2 years after RS n = 108 (%)
0	All joints	25.2	72	74
	Pettersson score >8	15	65.2	64.7
1	All joints	20.7	19.6	16.7
	Pettersson score >8	17.5	26.1	17.6
2	All joints	27.7	6.5	8.3
	Pettersson score >8	20	4.3	11.8
3	All joints	26.4	1.8	0.9
	Pettersson score >8	47.5	4.3	5.9

RS, radioactive synovectomy; Pettersson score >8, included only joints with Pettersson scores higher than 8; n, total number joints evaluated in each period; %, percentage of joints evaluated, comparing Pettersson scores to pain scores.

Table 3. Distribution of the range of motion (ROM) measured in degrees in knees, elbows and ankles, immediately before and 1 year after RS, mean values, standard deviation and P values.

	Knees (%)		Elbows (%)		Ankles (%)	
ROM	≥	<	≥	<	≥	<
Extension	88.2	11.8	86.5	13.5		
Flexion	84.2	15.8	86.5	13.5		
Dorsiflexion					87.9	12.1
Plantarflexion					90.9	9.1
N. joints evaluated	76		25		33	

RS, radioactive synovectomy; ROM, range of motion.
≥: Percentage of joints that maintained or increased ROM.
<: Percentage of joints that lost ROM.

for hips, shoulders, elbows, wrists, ankles and subtalar joints [31]. Yttrium colloids are non-toxic, pure beta-emitters being safe for the use in children, our main population, hence Yttrium was chosen based on its safety and efficacy. We decided not to choose Rhenium^{186} because it emits gamma radiation besides beta.

We described a marked decrease in the number of haemarthroses after treatment, independently of the type of joint as well as an important reduction in joint pain in most patients, similar to the results obtained by other authors [4,8–18,28–30]. The two shoulders had complete cessation of haemarthroses and pain in 2 years of follow-up, in agreement with previous studies [8–18,20].

Most patients maintained or increased ROM, although 9.1–15.8% lost ROM. This side effect has been previously reported by Heim *et al.*, [32] regarding elbows. Other authors observed that ROM is the parameter less likely to improve after RS with various radioisotopes [19]. One possible explanation for the worsening of the ROM in knees, as well as in ankles and

elbows, in our study is that most joints (93.1%) already presented some change in plain radiographs, hence the aggravation of the arthropathy could be part of the natural history of the disease [23,27]. Moreover, the importance of a rehabilitation and physiotherapy programme for the success of RS with Yttrium has been demonstrated [26], but unfortunately, only 47% of the patients included in this study had access to specialized physiotherapy facilities. We compared the changes in ROM in the patients with and without access to physiotherapy (odds ratio: 2.09, with confidence interval: 0.7–6). The lack of statistical significance could be explained by the small number of joints which have lost ROM.

Despite current advances, haemophilic arthropathy remains a burden for a great number of patients [5,20,28,33] and the ideal early treatment of the synovitis is still challenging [10]. While some studies did not find benefit of performing RS in joints presenting radiographic changes, or question this indication [9,12,19], others suggest that it can still be used with some level of success [8,33]. We found an elevated number of joints with advanced radiographic scores (40/245). Considering that these joints showed signs of synovitis, they were considered eligible for RS. Pain reduction and safety were not different in this group. We found no correlation between radiographic scores and bleeding outcome, in agreement with that reported by other authors [30,33].

Good outcomes were found in inhibitors patients, similar to that reported by other authors [34–36]. Although the incidence of haemarthroses in patients with and without inhibitors is usually similar [35,36], the burden of orthopaedic problems is known to be more severe in the individuals with inhibitors [36]. We found a higher number of haemarthroses pre-RS in the non-inhibitor group (mean 21.39) than in the inhibitors (mean 16.2), independent of age or radiological status. One possible explanation for this finding is the priority that we gave to the inhibitor patients to receive RS, thus a faster access might prevent the increase in the number of haemarthroses.

We concluded that RS with C-Y^{90} represents an important resource for the treatment of chronic synovitis, reducing bleeding frequency and pain, irrespective of the type of joint, radiographic stage or the presence of inhibitors.

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Disclosures

The authors stated that they had no interests which might be perceived as posing a conflict or bias.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Evaluation of the distribution of patients and joints lost to follow-up hemarthroses frequency.

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