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Original article

Yttrium-90 radiosynovectomy in knees and ankles (25 joints in 22 hemophilic patients). Short-term results

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ABSTRACT

Introduction: The radiosynovectomy (RS) is one treatment option for recurrent hemarthrosis in patients with hemophilia (PWH). A prospective cohort study was designed to evaluate the effects of the RS on the synovial membrane volume in the ankles and knees of PWH and patient characteristics related to the RS outcome.

Methods: In a one-year follow-up, 25 joints of 22 PWH who presented 3 bleeds or more in the same joint over the last 6 months (target joints) were subjected to the RS. Two groups were compared: those who retained target joints following the RS and those who did not (less than 3 bleeds/6 months after the RS). The groups were analyzed according to age, hemophilia type/severity, joint, body mass index (BMI), inhibitor and Hemophilia Joint Health Score 2.1 (HJHS). The magnetic resonance images (MRI) of six ankles and six knees were acquired prior to, and 6 months after, the RS. The synovial membrane volume and arthropathy MRI scale were accessed and volumes were compared and correlated with the Yttrium-90 dose injected.

Results: Patients with a mean age of 12 years and a mean HJHS of 6.7 ($p < 0.05$) retained target joints after the RS. The inhibitor, joint, type/severity of disease and BMI showed no significant differences between groups. The synovial membrane volume had a significant reduction after the RS ($p = 0.03$), but no correlation with the Yttrium-90 dose. In proportion to the synovial membrane volume, doses injected to the ankles were larger than those injected to the knees.

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Conclusion: The synovial membrane volume is reduced after the RS, regardless of the effective 90Y dose.

Introduction

Hemarthroses are common in patients with hemophilia (PWH), which is a deficiency in coagulation factors VIII or IX. The origin of the intra-articular bleeding is the synovial membrane, more specifically, the sub-synovial vascular plexus. After several episodes of hemarthrosis, the synovium becomes highly hypertrophied, and in more advanced cases of hemophilic synovitis, the synovium appears villous and significantly enlarged.[1] The hypertrophied synovium becomes resistant to clinical treatment and surgical excision may be necessary, despite the high degree of surgical difficulty and complications, such as postoperative bleeding, capsular adherence and joint rigidity.[2]

Radiosynovectomy (RS), also known as radioactive synovectomy, has been shown to be an effective and minimally invasive treatment for chronic hemophilic synovitis whenever the prophylactic clotting factor replacement therapy fails, or when patients develop inhibitors (neutralizing antibodies). Other options of therapy are: chemical synovectomy, arthroscopic or open synovectomy and arthrodesis or prosthesis.[2,3]

Among other factors, the success of RS depends on the therapeutic dose effectively delivered to the target tissue. Hypertrophy of the synovium should be considered when calculating the proper volume injected and the radioactive dose to achieve appropriate distribution and obtain the expected therapeutic response. Several radioisotopes can be used for RS. However, the ideal radioisotope is a pure beta emitter, with a limited range of penetration through tissues and a moderate physical half-life. The most commonly applied radioisotopes are Yttrium-90 (90Y) citrate colloid and rhenium-186 (186Re) sulphide colloid, used in Europe, or Yttrium-90 hydroxyapatite colloid and samarium-153 (153Sm) particulate hydroxyapatite, used in Brazil.[4–6] Improvements following RS seem to be independent of the patient and joint characteristics; however, to our knowledge, the dose has not been the subject of investigation.[7]

Studies with 3D magnetic resonance images (MRI) have demonstrated that features, such as the degree of reduction in the synovial membrane volume and thickness in the knees of the PWH could be considered as a guide to aid and select the most suitable radionuclide and respective dose.[8] However, there have been no similar studies for the ankle joint.

The present study was designed to analyze whether any correlation exists between changes in the volume of the synovial membrane and radiopharmaceutical dose injected in the knee and ankle of the PWH. In addition, other variables, such as age, hemophilia type, affected joint, body mass index (BMI), inhibitor presence and Hemophilia Joint Health Score 2.1 (HJHS) were explored.

Methods

This was a cohort study, carried out with the PWH, from October 2015 to November 2017, at a major regional hemotherapy center associated with a university hospital. The study was approved by the Ethics Committee of the hospital and an informed consent form was signed by all patients prior to their enrollment. All procedures were performed in accordance with the principles of the Declaration of Helsinki of the World Medical Association.

The inclusion criteria was at least three bleeding episodes over the previous 6-month period in the same joint, henceforth referred to as a target joint,[9] according to patient-provided information, despite prophylactic factor replacement. The exclusion criteria were the occurrence of local or systemic acute infection or prior neoplasm. A group of 22 PWH presenting with target joints were subjected to RS. A total of 25 joints were treated, including eighteen knees and seven ankles.

Clinical evaluation

An expert physiotherapist performed clinical evaluations before the RS by applying a measurement and classification instrument known as the HJHS 2.1, which was developed by the International Prophylaxis Study Group (IPSG) and is recommended by the World Federation of Hemophilia (WFH).[10] Twelve patients with a target joint (six knees and six ankles) also had an MRI performed both before RS and six months after it.

Isotope injection

The intra-articular injection of Yttrium-90 hydroxyapatite colloid was carried out on an outpatient basis, under local anesthesia. In all cases, the RS was administered under appropriate hemostatic replacement, with the clotting factors being administered 30 min. prior to intra-articular injection of the radioisotope. The RS was performed in a similar manner to that performed for joint fluid aspiration (arthrocentesis),[11] with a 21-gauge needle being introduced into the medial compartment of the knee, or lateral recess of the ankle. The injections were performed blind with no ultrasound control by an experienced orthopedic surgeon. Triamcinolone was injected before the needle was withdrawn to avoid isotopic burns.

The following clinical variables were recorded for patients at the time of the RS: age; hemophilia type and severity; presence of a circulating inhibitor, and; BMI. The isotope was supplied by the Nuclear and Energy Research Institute, a governmental agency that manages applications of radiation and

radioisotopes, and a specialist at the Nuclear Medicine Sector of the institution was responsible for preparing the correct 90Y hydroxyapatite colloid doses.[12]

The isotope data were also recorded, including the administered radioactive doses and residues present in the syringe and three-way system immediately after the injection, similar to the prescribed radiation protocol established by Thomas et al.[8] According to those authors, the activity of an administered 90Y hydroxiapatite colloid should be adjusted, depending on the physical examination and joint evaluation by MRI. In our study, when the patient knee circumference was 30% higher than the opposite one, it received from 6 to 10 milliCurie (mCi), corresponding to 222–370 mega Becquerel (MBq), of radioactivity of 90Y; when the knee was smaller than this, it received 5 mCi or 148 MBq of radioactivity. For the ankles, doses ranged from 1 to 2 mCi radioactivity, or 37–74 MBq (1 mCi = 37 MBq).[13]

The Magnetic Resonance Imaging Protocol: routine 2D MRI exams were obtained from 12 PWH, using a 1.5- Tesla MRI system (Philips Achieva 1.5-T MRI System, Philips Medical Systems, Best, The Netherlands), totaling six knees and six ankles. The remaining patients were not examined owing to a series of logistic difficulties. Images were obtained before the RS, and 6 months after the procedure (Fig. 1).

The 20-step additive scale[14] developed by the International Prophylactic Study Group (IPSG), derived from the original progressive Denver[15] and additive European MRI scales,[16] was applied. The synovial membrane volume was measured, using free, open-source software (ITK SNAP).[17]

The synovial membrane of each sagittal T2-weighted SPIR (Spectral Pre-saturation with Inversion Recovery) slice was outlined, cluster values of the synovium were obtained from multiple regions of interest, enhanced pixels on a segmented image were counted and the relevant areas were automatically calculated. Synovial membrane volume measured in milliliters (mL) was obtained by summing the values measured for each sliced area. The T2 sequence enhances the signals of joint effusion and tissues that contain water. Other tissues, such as hyaline cartilage, bone marrow lesions, synovial cysts and synovial membranes, impregnated with hemosiderin, appear black. Consequently, a manual correction using the Paint Effects and Erase Label tools was required to eliminate blemishes. The image assessments and segmentation pre- and post-RS were performed by the same author (AFM) during the follow up and repeated one year later.

Statistical analysis was performed, using the R software (2016), a language and environment for statistical computing (R Foundation for Statistical Computing, Vienna, Austria).

Descriptive measures (clinical characteristics of patients) were presented as continuous variables. The 95% confidence intervals of the estimated differences between groups and the *p*-values, based on the Student's t-test for independent samples, were calculated. For categorical variables, contingency tables were constructed and *p*-values based on the Fisher's exact test were calculated. A *p*-value of 0.05 was considered significant.

Descriptive measures of the synovial membrane volume and MRI scores were presented for the 12 patients. The differences in the synovium volume pre- and post-RS were evaluated using *p*-values, Student's t-test paired samples and 95% confidence intervals, according to the outcome (presence or absence of target joints, post-RS).

The reproducibility of the quantification of volume was evaluated. Intra-observer variation was expressed as the mean percentage, average absolute variation and Pearson's correlation coefficient.

Results

The mean age was 22.3 years (7–39 range). Eighteen patients presented severe hemophilia A (81.8%); three, moderate hemophilia A (13.6%) and one, moderate hemophilia B. Four patients (18.2%) developed inhibitors. The mean BMI was 23.06, whereas the mean HJHS was 26.94, despite six missing values.

The occurrence of new bleeding episodes after the RS was significantly higher ($p = 0.001$) in patients with a mean age of 12 years and those with a mean HJHS score of 6.7 ($p = 0.0034$). The BMI ($p = 0.556$), hemophilia type and severity ($p = 0.63$), presence of inhibitor ($p = 0.527$) and affected joint ($p = 0.618$) showed no differences between groups (Tables 1 and 2).

The effectiveness of treatment was 80.9 %, meaning that 21 joints reduced the number of post-RS bleeds to less than 2 episodes in six months and 4 joints had three or more episodes of post-RS bleeds. MRI group: The mean overall MRI additive scale score was 12.4, with 15.2 being observed for the knee 9.83, for the ankle. The mean joint volume before injection of the isotope was 105.9 mL for the knee and 9.04 mL for the ankle, decreasing to 69.2 mL and 6.78 mL in the post-RS. This represented a 26.16% and 26.09% reduction, respectively, at 6 months after injection. The mean Yttrium-90 dose injected was 6.05 mCi for the knee and 1.66 mCi for the ankle.

Differences between joint volumes pre-RS and post-RS were significant, with $p = 0.03$ for the knee and $p = 0.031$ for the ankle (Table 3).

Correlations between the percentage volume reduction and 90Y dose were not observed for the knee ($r = 0.022$) or ankle ($r = -0.427$).

High intra-observer reproducibility was demonstrated. The absolute intra-class correlation coefficient for volume quantification prior to the RS was 96.8% and post-RS, 90.1%; the corresponding Pearson correlation coefficients were 0.966 and 0.893, respectively.

Discussion

In this study, the average age of the patients was 22.3 years, reflecting the prevalence of recurrent hemarthrosis in a relatively young population. Most of the target joints were observed in patients with severe hemophilia A, which is consistent with the epidemiological and phenotypical characteristics of the disease.

Inhibitory antibodies were observed in 16% of the patients. The overall prevalence of inhibitors in unselected hemophiliac populations is reportedly 5–7%.[18] The comparatively high prevalence found in our group was expected because inhibitors render treatment with replacement factor concentrates difficult; thus, patients with inhibitors generally have more orthopedic complications than those without.[19]

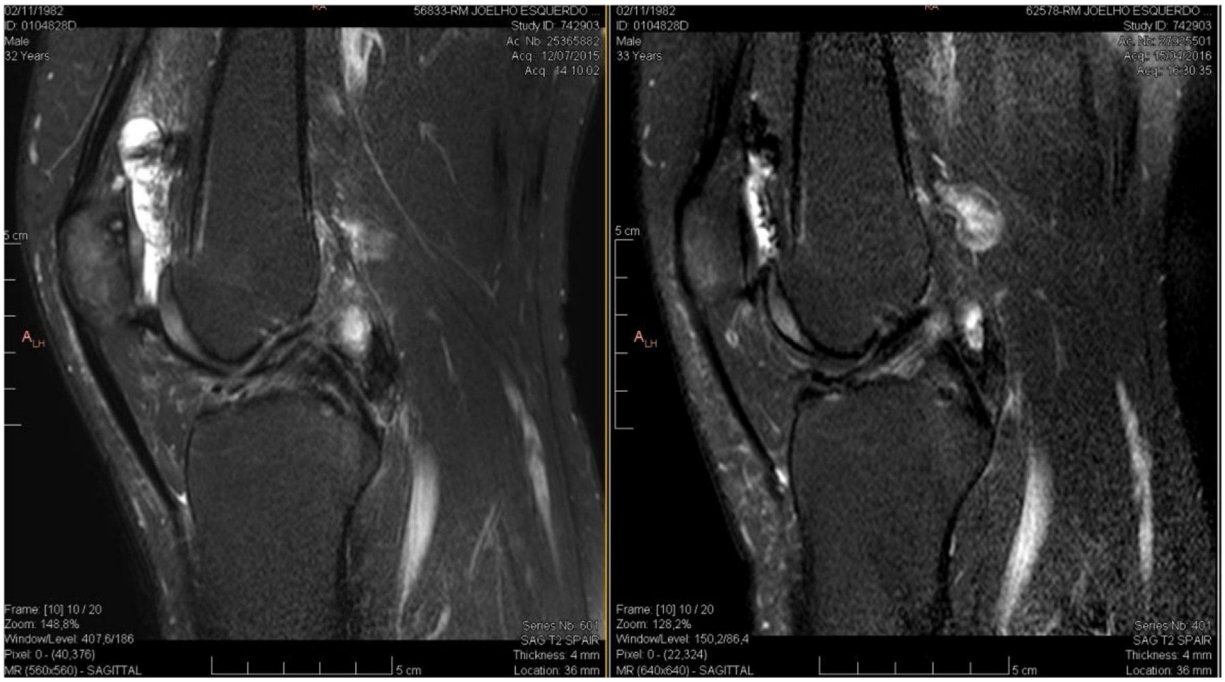

Fig. 1 – Magnetic resonance imaging of a 33-year-old patient with haemophilic arthropathy of the knee. The T2-weighted SPIR (Spectral Presaturation with Inversion Recovery) image shows highly enhanced joint effusion. The hypertrophic synovium with black hemosiderin deposits is irregular with variable composition and different thicknesses along the articular surface (arrows). Adjacent soft tissues appear light grey (left). Magnetic resonance imaging obtained six months after treatment shows that the size of the synovium (arrow) and extent of joint effusion have both been reduced (right).

Table 1 – Analysis of outcome with respect to continuous variables.

Variable	N	T.J.	Min.	First quartile	Mean	Mean	Third quartile	Max.	SD	95% CI(*p*-value)
BMI	21	Absent	16.20	19.95	22.10	23.34	25.45	37.80	5.59	−4.35; 7.88
BMI	4	Present	16.00	17.3	22.5	21.57	24.92	25.30	4.08	(0.556)
Age	21	Absent	11.00	21.25	24.00	24.23	29.50	39.00	7.35	6.51;18.06
Age	4	Present	7.00	8.00	13.00	12.00	15.00	15.00	3.83	(0.001)
HJHS	16	Absent	16	23	31	30.75	33	65	11.77	12.08;36.08
HJHS	3	Present	3.00	3.00	3.00	6.67	8.50	14.00	6.35	(0.0034)

N: number; T.J.: target joint; Min.: minimum; Max.: maximum; CI: confidence interval; HJHS: Hemophilia Joint Health Score; BMI: bone mass index.

Table 2 – Analysis of outcome with respect to categorical variables.

Variable	Target joint				*p*-Value
	Absent N = 21		Present N = 4		
	Number	%	Number	%	
Type of hemophilia A severe	18	81.8	4	100	0.651
A moderate	3	13.6	0	0	
B moderate	1	4.5	0	0	
Presence of inhibitor	18	81.8	3	75	0.6
Absence	4	18.2	1	25	
Joint	14	63.6	3	60	0.528
Knee					
Ankle	7	31.8	1	20	

Target joints - Present - 3–6 bleeds/6 months after RS; absent - less than 3–6 bleeds/6 months after RS.

Table 3 – Paired sample *t*-test data obtained before, and 6 months after, RS.

ID	Joint	Volume Pre-RS	Volume Post-RS	Mean (SD)	95% CI (*p*-value)
9	Ankle	10.71	5.63	Volume pre-RS	0.34; 4.9
12	Ankle	11.2	5.73	10.57 (5.86)	(0.031)
8	Ankle	9.36	8.29		
11	Ankle	5.94	5.15	Volume post-RS	
10	Ankle	7.07	6.4	6.78 (2.50)	
7	Ankle	9.97	7.23		
1	Knee	44.27	30.89	Volume pre-RS	14.01; 38.86
4	Knee	125.55	103.47	99.23 (32.73)	(0.03)
3	Knee	75.52	59.26		
2	Knee	72.35	44.84	Volume post-RS	
5	Knee	154.09	119.59	69.20 (18.13)	
6	Knee	163.50	118.58		

ID: identification; SD: standard deviation; CI: confidence interval; RS: radiosynovectomy.

The mean bone mass index was 23.06, which is considered normal. This means that this variable was not a predisposing factor for joint overload and secondary bleedings. The mean global HJHS was 26.94. However, due to various constraints, such as lack of transport to the city, only 16 patients were submitted to the evaluation. The global HJHS joint evaluation was used to indirectly infer global mobility and functionality status of our patients. This relatively high HJHS value indicates the existence of joint damage in a population that did not have access to primary prophylaxis. As prophylactic treatment for severe hemophilia A was only recently established in Brazil, many patients have deteriorated joint status.[20] In contrast, boys with severe hemophilia A from two European and three North American treatment centers, who were treated intensively, showed near optimal joint health and functional ability.[21]

The recurrence of bleeding episodes after the RS was significantly higher in patients with a mean aged of 12 years and a mean HJHS score of 6.7, suggesting that the patients with more preserved joints were in fact more prone to bleeding episodes after treatment. As the current HJHS 2.1 scale correlates well with overall global physical assessments of joint health, the bleeding episodes may be related to higher levels of physical activity and joint trauma to which younger and healthier boys are typically exposed. Thus, a more rigorous follow-up and intensive treatment is needed in this group, in order to prevent arthropathy.

The BMI, severity and hemophilia type, presence of inhibitor antibody and affected joint showed no significant differences between groups. According to Querol-Giner et al., the RS provides effective treatment for chronic hemophilic synovitis and is effective in all patient groups, independently of the presence of circulating inhibitory antibodies, type of joint involved, degree of synovial membrane hypertrophy and presence of radiographic findings of joint degeneration (arthropathy).[22] Thus, other factors are likely associated with the response to the RS, given the presence of some degree of secondary or traumatic inflammatory activity in the joint.[23]

No significant differences were noted between the percentage reduction in the synovial membrane volume and radiopharmaceutical dose administered to knees and ankles. As proposed by Barbara M et al., combined with a Monte Carlo simulation, the quantification of synovial joint features using the MRI can be used to develop a treatment plan for the RS.[24]

However, in the present study, synovial membrane volumes were significantly reduced following exposure to radiation. The MRI-based estimates of the synovial membrane volume have been previously correlated with clinical, laboratory, imaging and histological measures of inflammation, predict erosive progression and indicate rapid changes following various types of treatment in the patient with rheumatoid arthritis.[25] One relevant fact is that, although the percentage volume reduction was similar in the knees and ankles, the mean dose of 90Y injected was 68% larger in the ankles. One patient developed a full-thickness skin necrosis around the injection site on the ankle three months after the RS, despite corticoids wash-out, necessitating surgical debridement and secondary wound closure. Other authors have reported persistent cutaneous ulcers after the RS with 90Y.[26] This might suggest that the doses of yttrium injected into the ankles were excessive, in comparison to the synovial membrane volume before the RS.

The present study has some drawbacks, as for instance the occurrence of intermittent reactive synovitis that was reported by the patient as hemarthrosis. This fact most likely leads to an overestimation of bleedings. Other limitations include the relatively small number of patients and short duration of the follow-up.

Conclusion

The synovial membrane volume was reduced after the RS; however, no correlation with the effective 90Y dose was noted. The volume of 90Y administered to the ankles, in proportion to that administered to the synovial membrane, was higher than that injected to the knees. The patients with an average age of 12 years and an average HJHS score of 6.7 retained target joints after the RS, suggesting the need for an intensive hemostatic and orthopedic treatment.

Conflicts of interest

The authors declare no conflicts of interest.

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