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Original Article

Radiosynovectomy of the ankle in hemophilic arthropathy: effectiveness of samarium-153 and yttrium-90

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Abstract

Objective: Evaluate the effect of radiosynovectomy of the ankle with samarium-153 and yttrium-90 in hemophilic arthropathy through the possible reduction of hemarthrosis, analyzing complications, adverse effects, and the need for complementary therapies.

Methods: Radiosynovectomy of the ankle in 15 hemophilic patients was analyzed retrospectively and followed between January 2008 and December 2021. The analysis was performed through patients' medical records and diaries to quantify hemarthrosis that occurred six months before and six months after the procedure. Clinical follow-up and evaluation of outcomes were also analyzed.

Results: Eighteen radiosynovectomies of the ankle were performed in 15 patients with a mean follow-up of 124 months. A reduction in episodes of haemarthrosis has been demonstrated within six months ($p<0.001$). There were no adverse effects or complications in the short and long term. Approximately 61.1% of the patients did not require complementary therapies afterward.

Conclusion: The study demonstrated that radiosynovectomy of the ankle with samarium-153 and yttrium-90 in hemophilic patients is effective and safe. There was a decreased frequency of hemarthrosis, less need for complementary procedures, and no complications and adverse effects.

Level of Evidence IV, Case Series.

Keywords: Ankle; Arthropathy; Hemophilia; Synovectomy; Radioisotopes.

Introduction

Hemophilia is an inherited bleeding disorder related to the X chromosome, characterized by deficiency or abnormality of coagulation proteins factor VIII (hemophilia A) or factor IX (hemophilia B). Hemophilia A is more common than hemophilia B, with a prevalence of 1 in 5,000 male births compared to 1 in 30,000, respectively[(1)]. Depending on coagulation deficiency, hemophilia can be classified as mild, moderate, or severe. Joint hemorrhage (hemarthrosis) is the finding more characteristic in hemophilia, affecting mainly the ankle, knee, and elbow[(2)]. The ankle has the earliest involvement and the greatest risk of progressing to terminal arthropathy in younger patients[(3)].

Repeated episodes of hemarthrosis lead to joint remodeling and subsequent hemophilic arthropathy. Iron deposition generates a local inflammatory response characterized by synovitis, lysosomal enzymes, and pro-inflammatory cytokines. The articular surface is progressively damaged,

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evolving with permanent damage and bone weakness[4]. Thus, hemophilic arthropathy is the most frequent and limiting sequelae in patients with hemophilia, determined by joint destruction, chronic pain, deformity, loss of range of motion, and disability. The patients most at risk for developing this condition are those in which the occurrence of target joint is observed, that is, three or more episodes of bleeding in six months[5].

Minimally invasive treatment with radiosynovectomy can transform a highly vascularized synovium into sclerotic tissue. The procedure delays the cartilaginous damage that intra-articular blood tends to produce in the long term. Radiosynovectomy is the first-line treatment for chronic synovitis and recurrent ankle hemarthrosis[6,7]. Studies indicate that radiosynovectomy is an efficient procedure whose success rate ranges from 76 to 80% and can be performed in any age group on an outpatient basis[8].

Most studies evaluating radiosynovectomy's effect on arthropathies are mainly based on the knee joint[9]. Even today, few studies demonstrate the use of different radiosynovectomy of the ankle in hemophilic arthropathy. In this context, the objective of this study is to evaluate the effect of radiosynovectomy of the ankle with samarium-153 and yttrium-90 in hemophilic arthropathy through the possible reduction of hemarthrosis, analyzing complications, adverse effects, and the need for complementary therapies.

Methods

The study was approved by the institution's ethics committee and performed in a university hospital. Radiosynovectomy of the ankle in 15 hemophilic patients was analyzed retrospectively and followed between January 2008 and December 2021. The analysis was performed through patients' medical records and diaries to quantify hemarthrosis that occurred six months before and six months after the procedure. Clinical follow-up and evaluation of outcomes were also analyzed.

The inclusion criteria for radiosynovectomy were: patients diagnosed with hemophilia, recurrent ankle hemarthrosis considered as target joint, limiting clinical status, with signs of joint damage on radiography and in tertiary prophylaxis, that is, using coagulation factor continuously and regularly after diagnosis of joint involvement by physical examination and imaging. Exclusion criteria were the occurrence of acute local or systemic infection, pregnant women, and previous neoplasia.

The protocol was divided into three stages: pre-procedure, procedure, and post-procedure. In the pre-procedure phase, the patients were submitted to clinical, radiographic, and scintigraphic evaluation. In the procedure phase, under an aseptic technique and local anesthesia, the coagulation factor was administered to prevent hemarthrosis caused by the procedure, and the radiopharmaceutical (yttrium-90 hydroxyapatite (90-Y-HA) or samarium-153 hydroxyapatite(153-Sm-HA)) was injected into the ankle joint using the ultrasound-guided anteromedial approach, followed by intra-articular corticosteroids injection. Before the patient's release, radioactivity in the skin at the puncture site was monitored using a swab with gauze, monitored by portable radiation meters such as the Geiger Müller counter model MIR 7026. After the procedure, the patients received pain relievers and anti-inflammatory drugs, coagulation factors, immobilization of the tibiotarsal joint, and periodic outpatient evaluations. In addition, patients underwent scintigraphy to evaluate the radiopharmaceutical distribution and joint leakage within 72 hours. All procedures were performed by the same orthopedics, nuclear medicine, and radiology professionals. The follow-up occurred jointly between the orthopedics and hematology teams.

Eighteen radiosynovectomies of the ankle were performed in 15 patients, and three were bilateral. All patients were using tertiary prophylaxis with coagulation factor previously. Only one patient had a high response inhibitor, inhibitory alloantibodies against the infused coagulation factor. The general characteristics of the sampling are shown in table 1. The mean follow-up was 10.3 years (7.9-13.4). The mean age at the time of radiosynovectomy was 17.8 (6-42).

The number of joint bleeds six months before and six months after radiosynovectomy was considered, also pain complaints, functional limitations, and complementary procedures in the outpatient follow-up of these patients.

The patients filled out a diary with notes referring to episodes of hemarthrosis, pain, and the need for pain relievers. These diaries were reviewed monthly in the blood centers where these patients have follow-ups. Nine patients are followed-up in the blood center of our institution, and the others in other services.

Table 1. General characteristics

Characteristic	General
Sex	
General	15
Male	15 (100%)
Female	0 (0%)
Hemophilia	
A moderate	3 (20%)
A severe	11 (73.3%)
B severe	1 (6.7%)
Laterality	
Bilateral	3 (20%)
Right	8 (53.33%)
Left	4 (26.67%)
High response inhibitor	
Present	1 (6.67%)
Not Present	14 (93.33%)
Radionuclides	
Samarium-153	13 (72.2%)
Yttrium-90	5 (27.7)

The results were compared according to the Wilcoxon-signed-rank test for dependent samples when it cannot be assumed that the population is normally distributed. The Real Statistics extension program of Microsoft Excel® 2010 (Microsoft Corporation, Redmond, Washington, USA) was used for data analysis, considering $p<0.05$ significant. In addition, a boxplot diagram was performed to compare the data variation through position measurements.

Results

Among the 18 procedures, 13 were performed with 153-Sm-HA and five with 90-Y-HA. The administration of 153-Sm-HA ranged from 4.2mCi to 20.2mCi, and 90-Y-HA ranged from 2.5mCi to 5.2mCi. None of the groups had an adverse effect. The administration varied according to age, weight, or volume of the patient's joint and the radioactive waste that remained retained in the syringe after administration of the tracer.

The total bleeds in the study group were 138 during the six months pre-procedure and 34 within six months post-procedure. An absolute reduction of ankle hemarthrosis by 75% has been demonstrated. The minimum and maximum number of bleeds per patient: two and 15 pre-procedure; 0 and 6 post-procedure (Table 2). Median and interquartile range in the studied group: seven (5.5) pre-procedure; two (3.0) post-procedure ($p<0.001$) (Figure 1).

During the follow-up, between 2008 and 2021, 11 of the 18 procedures performed did not require complementary therapies after radiosynovectomy. Only three patients were submitted to corticosteroid infiltration in the tibiotarsal joint, two underwent ultrasound-guided viscosupplementation, and one underwent ankle cyst curettage with grafting associated with arthroscopic synovectomy. In addition, one patient was submitted to supramalleolar variant osteotomy, evolving with moderate chronic pain (Table 3). No patient required ankle arthrodesis.

The patients who did not require complementary therapy reported a significant reduction in episodes of ankle hemarthrosis and pain improvement, which previously limited their daily activities. The number of hemarthroses was analyzed in the follow-up returns and recorded in the medical records.

Four of the 15 patients monitored through regular and daily consultations maintained moderate limitations to impact exercises associated with mild chronic pain. The other patients reported pain improvement and mild limitations to exercise.

Discussion

This study demonstrated that radiosynovectomy of the ankle with samarium-153 and yttrium-90 in hemophilic arthro-

Table 2. Number of joint bleeds in each patient before and after radiosynovectomy

Patient	Ankle	Pre-procedure	Post-procedure
1	Left	7	2
1	Right	8	2
2	Left	12	0
3	Left	10	2
4	Right	2	0
5	Right	9	2
6	Right	7	3
7	Right	15	6
8	Right	5	1
9	Right	12	4
10	Right	3	0
11	Left	6	0
12	Right	6	1
13	Left	5	3
14	Left	15	4
14	Right	7	2
15	Right	5	2
15	Left	4	0
Total bleeds	-	138	34
Mean	-	7.67	1.88
Median	-	7	2

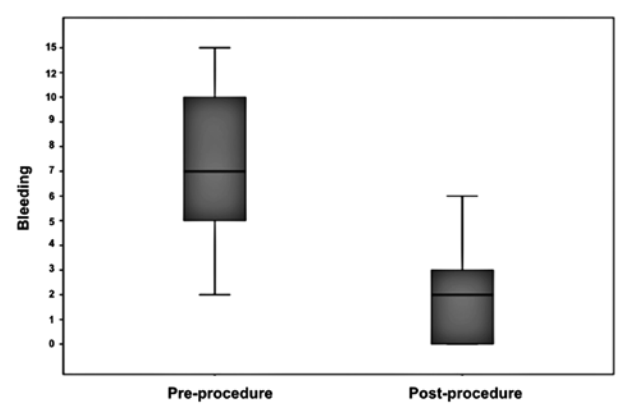

Figure 1. Comparison of joint bleeds before and after radiosynovectomy.

Table 3. Statistical relationship of complementary therapies at follow-up

Complementary therapies at follow-up	
Did not need	11 (61.1)
Corticosteroid infiltration	3 (16.7)
Viscosupplementation	2 (11.1%)
Curettage	1 (5.5%)
Osteotomy	1 (5.5%)

pathy is an effective procedure to decrease the hemarthrosis rate. In addition, there was a 75% decrease in the frequency of bleeding during the study period. This result is comparable to previous studies involving other joints, with a success rate ranging from 75% to 90% after radiosynovectomy with yttrium-90, rhenium-186, and other radionuclides in patients with hemophilic arthropathy[10].

In addition, no adverse effects and complications associated with a lower need for complementary therapies during follow-up make this technique safe and validated as a therapeutic tool for hemophilic ankle arthropathy. Despite the small sample, it was observed that there was no superiority between the two radionuclides, so both groups presented favorable outcomes.

Immediately after the injection, the radiopharmaceutical particles are phagocyted by synovial macrophages, forming elements large enough not to reach the bloodstream[11]. As a result, the beta radiation emitted has low tissue penetration power, most of which is absorbed by the synovium, cartilage, and joint capsule. Therefore, radiosynovectomy is a safe procedure, sparing subchondral bone and adjacent structures[10].

Das[12] states, in a study published in 2007, that radiosynovectomy complications are rare compared to intra-articular corticosteroid injections, the most common being joint infection (1: 35,000 procedures). During the study, no infectious process was observed in any patient.

Secondary skin necrosis to radiopharmaceutical leakage and arthritis are other complications related to radiosynovectomy cited in the literature[13]. The ultrasound-guided procedure was used to ensure the presence of the radiopharmaceutical in the joint space. The absence of leakage and the radiopharmaceutical distribution in the joint was confirmed by scintigraphy within 72 hours after the procedure. Thus, it was observed that there were no significant changes in clinical and imaging findings suggestive of leakage.

The absence of skin complications in our patients contrasts with the study by Bickels et al.[13] that described unacceptable complications of radiosynovectomy of the ankle using 15 mCi of yttrium-90 citrate colloidal with fluoroscopic-guided injection, treatment of pigmented villonodular synovitis. The high incidence of complications is probably related to the increased activity of injected yttrium-90, much higher than that usually administered in larger joints such as the knee. In our study, only five of the 18 procedures were performed with yttrium-90 and activities approximately 3-6 times lower, adjusted according to age, weight, and joint volume. In addition, most procedures were performed with samarium-153, a radionuclide with lower tissue penetration power and which emits lower energy radiation when compared to yttrium-90.

The ideal radionuclide should be a pure beta-emitter to promote synovial ablation, moderate half-life, of uniform joint distribution to not lead to an exacerbated inflammatory response[14,15]. The radiopharmaceutical selection was based mainly on the availability in the local radiopharmaceutical market and on the current Brazilian sanitary regulations. However, there is still no consensus in the literature on the best option due to the insufficient comparative studies between different radiopharmaceuticals[16]. Nevertheless, previous studies suggest a better use of yttrium in joints with high synovial volume, such as knees, and samarium for medium joints with lower synovial volume, such as elbows and ankles, because it is a radiopharmaceutical that emits radiation with lower tissue penetration than yttrium[17].

With the advent of prophylactic coagulation factors, episodes of hemarthrosis were reduced, bringing a better quality of life to patients and a lower rate of interventions in the tibiotarsal joint. However, services whose prophylaxis is not widely available, patients with chronic synovitis, hemarthrosis refractory to prophylactic treatment, difficult-to-manage hemarthrosis, and patients with high titer inhibitors may still benefit from radiosynovectomy.

It is also worth noting that the reduction in episodes of hemarthrosis results in a potential decrease in the use of the coagulation factor. From a financial point of view, this directly impacts the reduction of treatment costs for patients with hemophilia and corroborates the procedure's benefits.

Finally, the relevance of this study is the contribution to the scientific literature since there is a shortage of studies on radiosynovectomy of the ankle in hemophilic arthropathy. Particularly, the use of Samarium-153 in the ankle is still little reported in this procedure, predominating radiopharmaceuticals such as yttrium-90, rhenium-186, and phosphorus-32[11]. However, this study has limitations such as retrospective design, the absence of a control group, the possibility of failure in the medical records, and the relatively small sample.

Conclusion

The radiosynovectomy of the ankle protocol adopted in this study is a minimally invasive procedure demonstrating that administered with samarium-153 and yttrium-90 in patients with hemophilic arthropathy is effective and safe. There was a decreased frequency of hemarthrosis, less need for complementary procedures, and no complications and adverse effects.

Authors' Contribution: Each author personally and significantly contributed towards the development of this article: HMR* (https://orcid.org/0000-0003-0401-2968) Conceived and planned the activities that led to the study, wrote the paper, interpreted the results of the study, statistical analysis, formatting of the article, participated in the reviewing process, bibliographic review, approved the final version; GSMDSPC *(https://orcid.org/0000-0002-8388-5849), and MSM*(https://orcid.org/0000-0002-0502-586X) Data collection, interpreted the results of the study, participated in the reviewing process. MCMD* (https://orcid.org/0000-0001-6572-1771) Interpreted the results of the study, participated in the reviewing process. GFAP *(https://orcid.org/0000-0001-7091-9918), and JBSR *(https://orcid.org/0000-0002-1822-0576) Data collection, participated in the reviewing process, approved the final version; ETIS *(https://orcid.org/0000-0002-5791-3295), and AOS*(https://orcid.org/0000-0002-9192-6946) Performed the radiosynovectomy, participated in the reviewing process, approved the final version; MCO* (https://orcid.org/0000-0001-5938-0675) Participated in the reviewing process, approved the final version. RGP* (https://orcid.org/0000-0002-6064-2027) Conceived and planned the activities that led to the study, formatting of the article, wrote the paper, participated in the reviewing process, approved the final version. All authors read and approved the final manuscript. *ORCID (Open Researcher and Contributor ID) iD.

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