Radiosynoviorthesis in hemophilic joints with yttrium-90 citrate and rhenium-186 sulfide and long term results

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Abstract

Repeated bleeding in the joint cavities is the most annoying symptom and often has disabling effects in patients with hemophilia (PWH). *Our aim was* to study the effect of radiosynovectomy (RSO) with beta particle-emitting radiocolloids in the treatment of hemorhagic arthropathy. *We have treated 22 joints from 18 patients* with hemophilia A, from April 2008 to February *2012*, 5 knees, 11 elbows and 6 ankles. Joints were divided into two Groups, those treated with yttrium-90-citrate (^{90}Y-C) (5 knees, 2 of them twice)-Group I and those with rhenium-186-sulfide (^{186}Re-S) (11 elbows, 1 of them treated twice and 6 ankles)-Group II. A total of 25 treatments. Follow-up period was 3 months, 1 year and 3 years. *Results* showed a favourable subjective and a better objective result in all 5 joints of Group I and in 15/17 joints of Group II, respectively. Follow-up after 3 months showed significant improvement in Hemophilia Join Health Score (HJHS) after 20 treatments and steady score after 5 treatments. After 1 year, 19 treated joints had improved for the first time, 3 remained steady and 2 were not examined. After 3 years, 9 treated joints were HJHS steady, while 16 were not examined. One year after treatment, 13/14 joints of patients, aged 6-23 years showed better HJHS score, while 9/11 joints of patients aged 26-51 years, showed better HJHS. Synovial membrane thickness as measured by MRI in 8 joints, before and 3 months after treatment was not related to prognosis. *In conclusion,* in a small group of hemophilic patients with hemorrhagic arthropathy treated with ^{90}Y-C and with ^{186}Re-S, our study showed good results irrespective of age in 22/25 treatments after 3 months or 1 year. The thickness of synovial membrane in the 8 joints studied was not related to prognosis.

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Introduction

In patients with hemophilia (PWH), hemorrhagic arthropathy is a very annoying symptom and often causes disability. Knees, ankles, elbows, hips and shoulders are most frequently affected. Symptoms are progressive and often surgical intervention is required to prevent total loss of joint motility. Radiosynovectomy (RSO) using beta particle-emitting radiocolloids has been quite effective in reducing the frequency of hemarthroses and the development of chronic synovitis [1]. Synovium is the primarly site of joint degeneration, which also processes to the joint cartilage. Repeated bleeding leads to synovial hypertrophy and to synovial bleeding [1]. Treatment by RSO applies the intraarticular injection of radiocolloids, bound to citrate, sulphide, ferric hydroxide or other carriers [2], with an efficacy from 76% to 80% [3-5].

The worldwide incidence of PWH A is approximately 1 case per 5000 male individuals. There are more than 33.000 PWH of A and of B type in Europe and 750 of them in the Czech Republic. We have studied PWH A patients because this is the most common type [http://www.ehc.eu/about-bleeding-disorders/about-haemophilia.html]. The aim of the present study was to describe our experience, during a long-term period of follow-up, on the effects of RSO on the rare group of hemophilic A patients, who usually suffer from hemophilic arthropathy.

Subjects and methods

Eighteen PWH A were enrolled in this study, from April 2008 to February 2012. Diagnosis of arthropathy was based on clinical findings and on the history of bleed-

Table 1. *Patients, hemophilia joint health score (HJHS) and magnetic resonance imaging (MRI) findings*

No. of patients	Age (years)	Localisation	HJHS pre-tr.	HJHS post-tr. 3 m	HJHS post-tr. 1 y	HJHS post-tr. 3 y	MRI synovial thickness pre-tr. (mm)	MRI synovial thickness 3 m post-tr. (mm)
Group I								
1	20	L knee	15	15	8	8	2	2
2	35	R »	15	10	9	8	2	2
3	20	L »	15	9	9	9	2	Not done
4	26	R »	15	10	10	Not done	2	»
5	20	L »	15	15	15	» »	1	»
6	20	» »	13	9	9	» »	1	»
7	21	» »	15	10	Not done	» »	1	»
Group II								
1	21	R elbow	15	9	9	9	1	1
2	23	» »	13	8	8	8	1	1
3	20	» »	15	13	8	8	1	1
4	20	» »	13	8	8	8	1	Not done
5	26	» »	14	10	9	10	2	2
6	13	» »	11	10	10	10	1	1
7	31	» »	15	10	10	Not done	2	2
8	26	» »	13	9	9	»	1	Not done
9	44	L »	17	17	17	»	1	»
10	14	» »	12	10	10	»	1	»
11	37	» »	12	8	8	»	1	»
12	19	» »	15	10	10	»	1	»
13	28	» ankle	13	9	9	»	1	»
14	53	» »	17	17	17	»	1	»
15	20	» »	12	9	9	»	1	»
16	37	R »	13	10	10	»	1	»
17	39	» »	14	8	Not done	»	1	»
18	6	L »	10	8	»	»	1	»

HJHS: Hemophilia joint health score, MRI: Magnetic resonance imaging, tr: treatment

ing episodes. The patients were divided into two groups according to the radiopharmaceutical used for treatment. Group I patients were aged 20-35 years (median 24 years) and Group II were 6-53 years (median 27 years). A total of 22 joints (5 knees, 11 elbows and 6 ankles) in 18 patients were treated. A second treatment was needed 3 times (in 2 knees and 1 elbow). A total of 25 treatments have been applied. The observation period was at 3 months, 1 year and 3 years. A written informed consent was obtained from every patient before treatment. Every patient was evaluated before the administration of radiocolloid by the Hemophilia Joint Health Score (HJHS) and 8 patients were examined by MRI (Table 1). No Baker´s cysts were present in any of the 5 treated knees. Patients were also classified according to the clinical findings of their arthropathies as described by Rodriguez-Merchan (Table 2). The HJH score was re-evaluated after 3 months, 1 and 3 years (Table 1). Each patient was asked to express his/her subjective opinion about the treatment procedure and if would wish to repeat it, if necessary (Table 3). We also assessed the objective effect of treatment (Table 4). Doses of the radiopharmaceutical used for each joint, the distribution of radiopharmaceutical at the injection site and its possible leakage are shown in Table 5. We classified as "good result"

Table 2. *Patients' classification according to their arthropathies*

Stage	Indications	No. of knees Group I	No. of ankles + elbows Group II
I. Transitory synovitis	With no post-bleeding sequel. RSO is indicated as preventive if there are more than two episodes in 6 months.	0	3 (1 ankle, 2 elbows)
II. Permanent synovitis	With persistent thickening of the synovial membrane and diminution of range of motion. RSO is mandatory.	5	12 (4 ankles, 8 elbows – one of them treated twice)
III. Chronic artropathy	As for stage II. plus muscular atrophy and axial deformities of the limb. RSO is helpful.	0	2 (1 ankle, 1 elbow)
IV. Fibrous or osseous ankylosis	RSO is contraindicated.	0	0

RSO: radiosynoviorthesis

when the frequency of bleeding episodes had decreased by 80%. If not, the result was classified as "fair" and treatment was repeated.

The dose of radioactivity injected is shown in Table 5. The joint was then immobilised for 72h in a plaster splint or brace. An individual rehabilitation programme followed for at least 3 weeks. The patients were controlled for clotting factors from the time of injection till the end of rehabilitation period. Only factor VIII was administered to the PWH.

We used Yttrium-90 citrate (^{90}Y-C) for the knees (Group I) and rhenium-186 sulphide (^{186}Re-S) for the elbows and an-

Table 3. *Subjective results of treatment in both Groups*

	Group I Yes	Group I No	Group II Yes	Group II No
Satisfied with the result	5	0	11	1
To be treated that way again	5	0	12	0

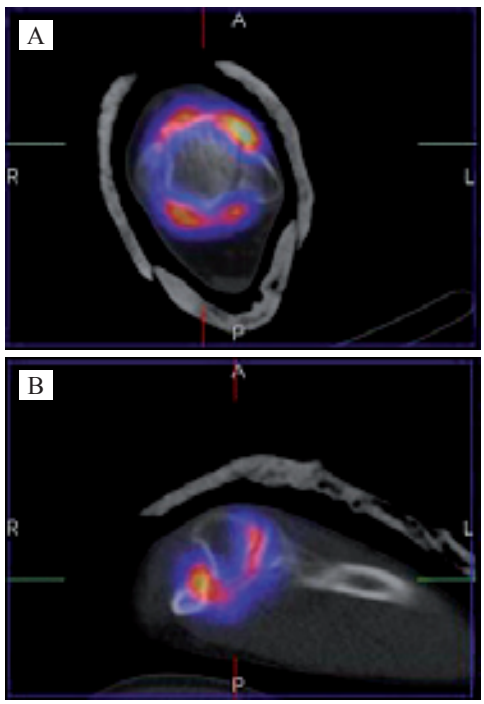

Figure 1. Fusion images (SPET/low dose CT), transversal view of left ankle (A) and right elbow (B). Homogenous distribution of ^{186} Re-S is seen intra-articularly.

Table 4. *Objective results of treatment in both Groups*

Result	Findings	No. (joints ^{90}Y-C) Σ 5 Group I	No. (joints ^{186}Re-S) Σ 17 Group II
Excellent	No joint bleeding, recuperation of function, no synovitis	0	2 elbows + 1 ankle
Good	Clinical improvement, synovitis, diminution of hemarthrosis, recovery of function	3	8 elbows + 3 ankles
Fair	Synovitis, diminution of hemarthrosis, no recovery of function	2 (after second application improved to good)	1 elbow (after second application improved to good)
Poor	Synovitis, recurrence of hemarthrosis	0	2 ankles

Table 5. *Doses of the radiocolloids, distribution and leakage*

Administration	Joint	Radiocolloid	MBq	Distribution
Group I				
1	knee	^{90}Y	180	focal
2	»	»	200	diffuse
3	knee	»	180	»
4	»	»	180	»
5	»	»	185	focal
6	»	»	220	diffuse
7	»	»	220	»
Group II				
1	elbow	^{186}Re	70	diffuse
2	»	»	70	»
3	»	»	70	»
4	»	»	70	»
5	»	»	70	»
6	»	»	74	focal
7	»	»	74	»
8	»	»	74	diffuse
9	»	»	74	focal
10	»	»	74	diffuse
11	»	»	70	»
12	»	»	74	»
13	ankle	»	74	»
14	»	»	74	»
15	»	»	74	»
16	»	»	70	»
17	»	»	74	»
18	»	»	40	»

Leakage of the radiopharmaceutical a) through the injection point was noticed only in patient No. 5 from Group I and b) through the lymph vessels also in patient No. 5 from Group I and in patients No. 2, 7 and 9 from Group II.

kles (Group II). Yttrium-90 is a pure β-emitted with a penetration range of 3-5mm in soft tissues, 2.8mm in cartilage with a half life of 2.7 days. Yttrium-90-C has a mean particle size of 10nm and ^{186}Re-S has a mean particle size of 5-10nm and is a combined β- and γ-emitter with a penetration range of 1.2mm in soft tissues, 0.9mm in cartilage and a half life of 3.7 days [5].

The radiocolloid was administered into the joint cavity under asceptic conditions adding dexamethasone natrium phosphate 8.75mg. Joint effusion liquid was aspirated when necessary.

To confirm the proper deposition of the radiopharmaceutical in the intra-articular cavity and to detect any possible outflow of fluid, post-treatment imaging was carried out 1-4h after radiocolloid injection (Fig. 1). Imaging was performed with static scintigrams of the joints in the anterior position (matrix 128x128, for 5min) using a single-head gamma camera Sopha, France or a dual-head gamma camera Symbia T, Germany, both equipped with low-energy high resolution collimators registering bremsstrahlung in energy window 70keV±15% for ^{90}Y, and γ-rays in energy window 137keV±15% for ^{186}Re.

For precise delineation of the activity of ^{186}Re-S in the joints single photon emission tomography (SPET)/low dose computed tomography (CT) acquisition was performed (matrix 128x128, 32 projections at 180° and 10s/frame) in all Group II patients. Data from SPET were reconstructed with iterative methods (ordered subset expectation maximization, 12 iterations, and 8 subsets).

According to the intra-articular distribution of the radiopharmaceutical we evaluated its distribution as focal or diffuse (Fig. 2, Table 5)

Results

In Table 1 we present patients' HJHS and MRI findings. In Table 2 we describe patients of both Groups classified according to the kind of their arthropathies. All PWH had synovitis, with persistent thickening of the synovial membrane and diminution of the range of motion, so RSO was mandatory. Treatment subjective and objective results in both Groups are shown in Tables 3 and 4.

The 2 older patients, from Group II had chronic arthropathy, stage III and "unsuccessful" or "poor" treatment. One of them, 44 years old man had an unchanged frequency of bleeding in his elbow and another, a 53 years old man had undergone total ankle replacement 11 months after treatment, because of recurrent bleeding. However, both described the procedure as acceptable and were willing, if necessary, to undergo this kind of treatment

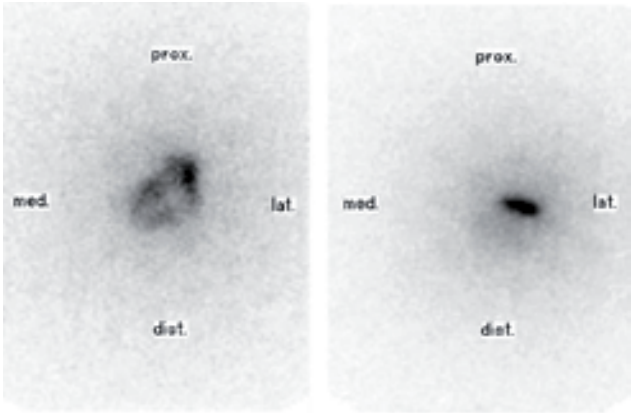

Figure 2. Planar images of left knee. Examples of diffuse intra-articular distribution of ^{90}Y-C (left) and focal retention in the lateral part of knee (right).

again. All patients considered this method of treatment as safe and effective, except one who wasn't satisfied having poor results (Table 3).

One year after treatment, 13/14 joints of patients, aged 6-23 years showed better HJHS score, while 9/11 joints of patients aged 26-51 years, showed better HJHS. Thickening of the synovial membrane, as shown by MRI, at the beginning of our study in 8 patients was the same as in the post-treatment images. These results agree with previous results of other researchers (Table 1) [6].

The distribution of radiocolloid in the joints was classified as diffuse in 20 cases and as focal in 5 cases. The final outcome was not affected by extravasation, which was seen in 1 case or by leakage into the lymph nodes, which was seen in 4 cases.

Discussion

As seen in Table 1 most of the PWH joints treated from both Groups had permanent synovitis, which did not seem to alter our overall conclusive remarks. Furthermore, Table 2 showed that HJHS was evenly distributed among the two Groups. MRI findings in 8 cases in Table 2 indicated that synovial membrane thickness did not relate to treatment prognosis.

Recent experiments in PWH with the application of ^{90}Y-C in 66 joints (knees, ankles and elbows) in 44 patients, aged 9-39 years gave good or excellent results in about half of the joints. The authors recommended to perform RSO at the early stages of synovitis [7]. Other researchers described a 80% good result of 115 PWH in the age between 11-15 years treated with ^{90}Y-C, that is a decreased number of bleeding episodes and in 15% of the cases bleeding stopped altogether in the treated joints [8]. Others, in young PWH patients, aged 3-25 years, also found favourable results [9, 10]. Because of the small number of our patients, we were unable to notice better results in younger patients, 6-23 years of age. Other researchers reported that using ^{90}Y-C was a very promising agent for the treatment of chronic PWH knee synovitis [11]. Others reported that for ^{90}Y-C, ^{90}Y-silicate and ^{186}Re-S radiocolloids median leakage values were 1.9%, 2.4% and 2.7%, respectively with differences being not statistically significant [12]. We observed the leakage through the injection point, in one PWH and through lymph vessels in 4 PWH.

For medium sized joints, while the EANM recommends using ^{186}Re-S for treatment, Chinese researchers compared the effect of using 3 different doses of ^{186}Re-S correlated to the thickness of synovial layer measured by MRI for the treatment of PWH in the knees and found that 22 out of the 29 patients had a significant reduction in synovial thickness. Frequency of bleeding episodes was diminished in 71% of these patients over a 18 months period, while no significant differences were found between the radioactivity dose-groups [13]. Other researchers found that in 49 PWH arthritis treated with ^{186}Re, no bleeding occured after 6 months in about 84% of PWH with grade II synovitis and in about 48% with grade III synovitis [14, 15].

In another study independent of the severity of synovial hyperplasia most joints bled less and showed improvement, while there was no change in the severity of synovial hyperplasia after treatment, as were our findings [6].

Other researchers, similarly to our results found no association between intra-articular distribution of ^{90}Y-C and the clinical effect of the RSO in 80 knees [16].

We did not notice a relation between the Ht of the patients and the treatment success (unpublished data).

In conclusion, in a small group of hemophilic patients with hemorrhagic arthropathy treated with ^{90}Y-C and with ^{186}Re-S, our study showed good results irrespective of age in 22/25 treatments after 3 months or 1 year. The thickness of synovial membrane in the 8 joints studied was not related to prognosis.

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The authors declare that they have no conflicts of interest.

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