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Comparison of extraarticular leakage values of radiopharmaceuticals used for radionuclide synovectomy

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Objectives: Radionuclide synovectomy is a reliable therapy in patients with chronic synovitis. However, radiation doses delivered to non-target organ systems due to leakage of radioactive material from the articular cavity are an important disadvantage of this procedure. In this study we compared extraarticular leakage values of the 3 commonly used radiopharmaceuticals; ^{90}Y-citrate, ^{90}Y-silicate and ^{186}Re-sulfide colloid. ***Materials and Methods:*** Thirty-five patients with persistent synovitis were enrolled in the study. Twenty-two hemophilic, 8 rheumatoid arthritis and 5 patients with pigmented villonodular synovitis were studied. ^{90}Y labeled silicate and citrate were used for knee joints and ^{186}Re-sulfide for intermediate sized joints. Radiocolloid leakage values were evaluated using a gamma camera with 20% window centered over the bremsstrahlung photopeak of ^{90}Y and a respective window over the 137 keV photopeak of ^{186}Re. Regions of interest were drawn over the injection site, the regional lymph nodes and the background areas. Leakage of radiocolloid was calculated by dividing the counts/pixel in the regional lymph node area to the counts/pixel in the injection site. ***Results:*** No visible leakage was observed. The median leakage values calculated for ^{90}Y-citrate, ^{90}Y-silicate and ^{186}Re-sulfide were found as 1.9%, 2.4% and 2.7%, respectively. The difference between the variability of leakage values was not statistically significant ($p > 0.05$). ***Conclusion:*** There was no significant difference in terms of extraarticular leakage between ^{90}Y-citrate, ^{90}Y-silicate and ^{186}Re-sulfide radiocolloids.

Key words: ^{90}Y-citrate, ^{90}Y-silicate, ^{186}Re-sulfide, chronic synovitis, radionuclide synovectomy

INTRODUCTION

RADIOSYNOVIORTHESIS, has been used successfully in the treatment of inflammatory joint diseases for years to alleviate the symptoms of pain and swelling.[1–6] However, in spite of these encouraging results with radiosynovectomy, whole body and lymph node irradiation due to extraarticular leakage of radioactive material arises as a disadvantage of this procedure. In cases of radioactive gold (^{186}Au), values up to 48% were reported to be leaked from the cavity through the draining lymph nodes.[7] Subsequently, new radiopharmaceuticals were created which were estimated to exhibit minimal leakage from the treated joint and attempts to quantify the amount of leakage have given values of 5–10% at 24 hours and 15–25% at 5 days[6] with reported radiation doses to lymph nodes in excess of 50 to 100 Gy.[8–10] Three ways have been recommended to overcome the leakage problem and to diminish organ absorbed doses: particle size, immobilization of the treated joint and choosing a radioisotope with a short half life.[6]

In this article, our aim was to compare the leakage values of three commonly used radiopharmaceuticals for radiosynoviorthesis: ^{90}Y-citrate, ^{90}Y-silicate and ^{186}Re-sulfide in patients with chronic synovitis.

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MATERIALS AND METHODS

Patients: From April 2002 to April 2005, 35 patients were enrolled in the study. Patient age ranged from 10 to 62 years (mean: 30.7). Twenty-two of the patients had hemophilic synovitis, 8 of them had rheumatoid arthritis and 5 were treated for pigmented villonodular synovitis. Hemophilic patients in the study group had a bleeding frequency of at least one episode per month in a target joint and had failed clotting factor replacement therapy. In patients with rheumatoid arthritis the indication of radiosynoviorthesis was planned according to the resistance to systemically used drugs such as non-steroidal antiinflammatory agents and glucocorticosteroids that were used for at least 6 months. Twenty-three knee, 9 elbow, 2 ankle and 1 shoulder chronic synovitis were treated with intraarticular radiocolloid injection among the patients with hemophilia. All of the patients with rheumatoid arthritis had been suffering from knee synovitis. In patients with pigmented villonodular synovitis 4 had persistent knee synovitis and 1 had hip synovitis.

Procedure: ^{90}Y-citrate and ^{90}Y-silicate were used for knee joints and ^{186}Re-sulfide was used for elbow, shoulder, ankle and hip joints. On the day of the procedure hemophilic patients received a dose of clotting factor 60 minutes before the therapy and continued this therapy twice a day for a week after the procedure. Using aseptic technique radionuclide therapies were performed under local anesthesia. In the knee treatments the aspiration of synovial fluid was regarded as evidence of the correct placement of the needle. In radiosynoviorthesis of elbow, ankle, shoulder and hip, fluoroscopic guidance was provided to ensure correct placement of the needle inside the joint cavity. 185 MBq of ^{90}Y-citrate (CIS Biointernational,

Table 1 Patient characteristics and individual leakage values

Patient No.	Age/Sex	Disease	Treated joint	Leakage %
1*	18, M	Hemophilia A	left knee, left knee	2.5–1.16
2*	19, M	Hemophilia A	left knee, left knee	13–4
3	35, M	Von Willebrand disease	right knee	0.7
4	18, M	Hemophilia B	left knee	0.75
5	18, M	Hemophilia A	right knee	0.5
6*	22, M	Hemophilia A	right knee, left shoulder	1.9–4
7*	20, M	Hemophilia A	left knee, left knee, left elbow	0.9–4–3
8	21, M	Hemophilia A	right ankle	2.7
9	12, M	Hemophilia A	right knee	5
10*	10, M	Hemophilia A	right knee, right knee, left elbow	0–6–2
11*	17, M	Hemophilia A	right knee, right knee, right elbow	3.5–2.5–2.4
12*	12, M	Hemophilia A	right knee, right knee	0–3.5
13*	20, M	Hemophilia A	right knee, right elbow	1.1–1.5
14	23, M	Hemophilia A	left elbow	6
15*	29, M	Hemophilia A	right knee, right knee	0.8–0
16	27, M	Hemophilia A	right elbow	1.1
17	30, M	Hemophilia A	left knee	0.7
18*	10, M	Hemophilia A	right elbow	2.9
19	10, M	Hemophilia A	left ankle	0.6
20*	20, M	Hemophilia B	right knee, left elbow	7–1.3
21	14, M	Hemophilia B	right knee	10
22	23, M	Hemophilia A	right elbow	2.9
23	35, F	RA	right knee	2.1
24*	53, M	RA	left knee, right knee	2.4–2.3
25	55, M	PVS	left knee	2.4
26	49, F	RA	right knee	3.2
27*	56, F	RA	left knee, right knee	3–1.7
28	45, F	PVS	right knee	2
29*	62, M	RA	left knee, right knee	3.1–2.4
30*	57, M	RA	left knee, right knee	2.6–2.8
31*	52, F	RA	left knee, right knee	1.7–1.9
32	46, F	PVS	right knee	2.8
33	55, F	RA	right knee	2.4
34	43, F	PVS	left knee	0.8
35	40, F	PVS	left hip	2.7

*: Indicates the patients who were treated more than once.

RA: Rheumatoid Arthritis, PVS: Pigmented Villonodular Synovitis

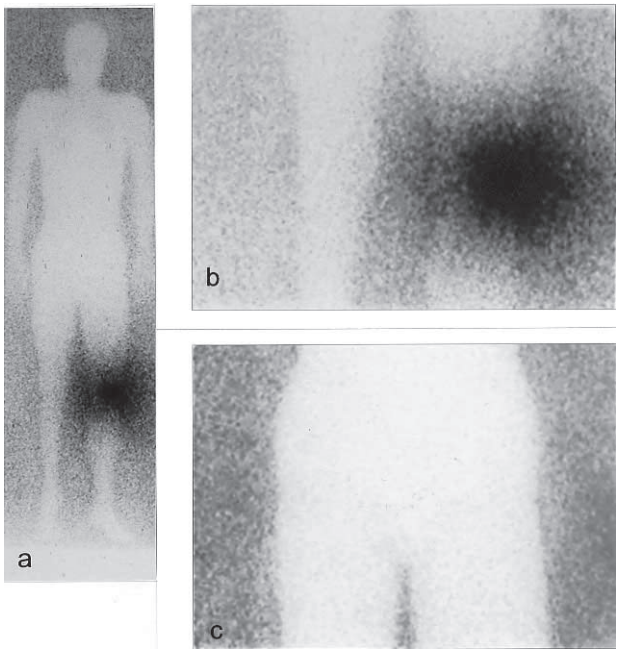

Fig. 1 ^{90}Y-silicate injection was performed to the left knee of an 18-year-old male patient with hemophilia B. Whole body (a), knee (b) and pelvis spot images (c) revealed no visible leakage. The calculated leakage value was 0.75% (patient no. 4).

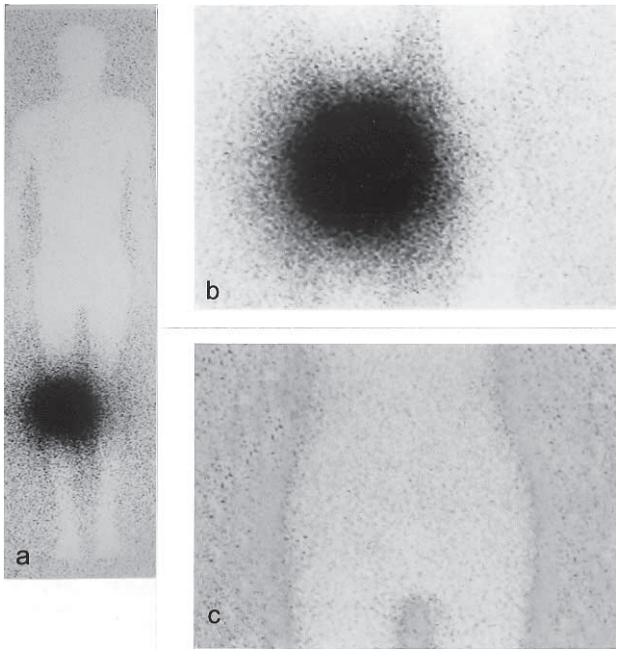

Fig. 2 ^{90}Y-citrate injection was performed to the right knee of a hemophilia A patient. Whole body (a) and spot views obtained from knee (b) and pelvis (c) showed a calculated leakage value of 1.1% in the inguinal region. There was no visible leakage (patient no. 13).

France) and ^{90}Y-silicate (Amersham, UK) and 74–111 MBq of ^{186}Re-sulfide (CIS Biointernational, France) were injected intraarticularly into the joints. The particle diameters of ^{90}Y-citrate, silicate and ^{186}Re-sulfide were 1000–2500 nm, 1000–2500 nm and 50–500 nm, respectively. After the injection the needle was flushed by additional lidocaine injection and the joint was extended full arc of motion to facilitate to distribution of the radioactive particles homogeneously in the intraarticlar space. After that, the joint was immobilized for 48 hours.

Scintigraphy: After the immobilization period planar whole body and spot scanning of the patients were performed, and radiocolloid leakage was evaluated using a gamma camera with dual head low energy high resolution collimator (Siemens, E-cam, Erlangen, Germany). Twenty percent window centered over the maximum bremsstrahlung photopeak of ^{90}Y and a respective window over the 137 keV photopeak of ^{186}Re was used. Region of interests were drawn to the injection site, the regional lymph nodes and background areas. For the knee, ankle and hip joints groin area and for elbow and shoulder, axilla was chosen as the regional lymph node area. For background areas, contralateral thigh was used in knee, hip and ankle treatments and contralateral lower trunk was used in elbow and shoulder radiosynoviorthesis. Leakage of radiocolloid was calculated by dividing the background substracted counts/pixel in the regional lymph node area to the background substracted counts/pixel in the injection site. ^{57}Co flood source transmission imaging was also used to delineate body contours.

RESULTS

Patients characteristics and individual leakage values are tabulated in Table 1. Total of 53 joints in 35 patients were treated. In 16 patients the procedure was performed more than once, with 7 hemophilic patients treated for the same knee joint at 6 month intervals because of recurrent bleeding (patient Nos. 1, 2, 7, 10, 11, 12 and 15; Table 1).

We did not observe any visible leakage in our study group (Figs. 1, 2, 3, 4 and 5). The mean calculated leakage values for ^{90}Y-citrate, ^{90}Y-silicate and ^{186}Re-sulfide were 3.15%, 2.3% and 2.5%, whereas the median leakage values were 1.9%, 2.4% and 2.7%, respectively (Table 2). The difference between the variability of the leakage values was not statistically significant ($p = 0.868$, Kruskal Wallis Test). The range of leakage values for ^{90}Y-citrate was 0–13%, for ^{90}Y-silicate 0.5–5% and for ^{186}Re-sulfide 1.1–6% (Table 2).

DISCUSSION

Since first described by Fellinger et al. in 1952, radionuclide synovectomy has been applied for more than 50 years for the treatment of synovitis.[2,11,12] It relieves pain and inflammation and is accepted as an alternative to

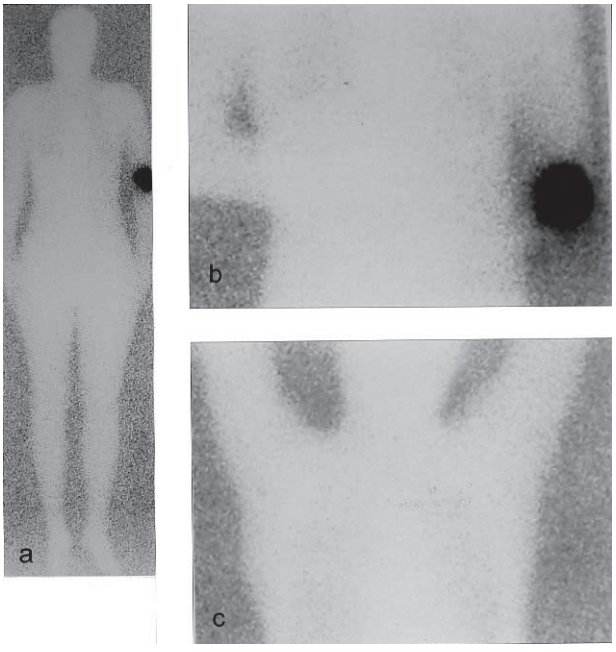

Fig. 3 ^{186}Re-sulfide injection was performed to the left elbow of a 20-year-old male patient with hemophilia B. Whole body (a) and spot images obtained from elbow (b) and axilla (c) revealed no visible leakage. The calculated leakage value was 1.3% (patient no. 20).

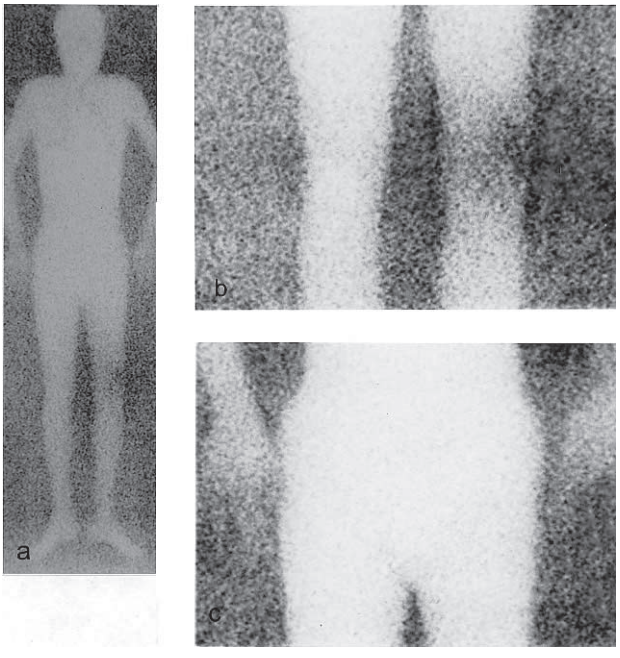

Fig. 4 ^{90}Y-citrate radiocolloid was used in the treatment of a 19-year-old male patient with hemophilia A. Whole body (a), and spot images of knee (b) and pelvis (c) showed no visible leakage (patient no. 2).

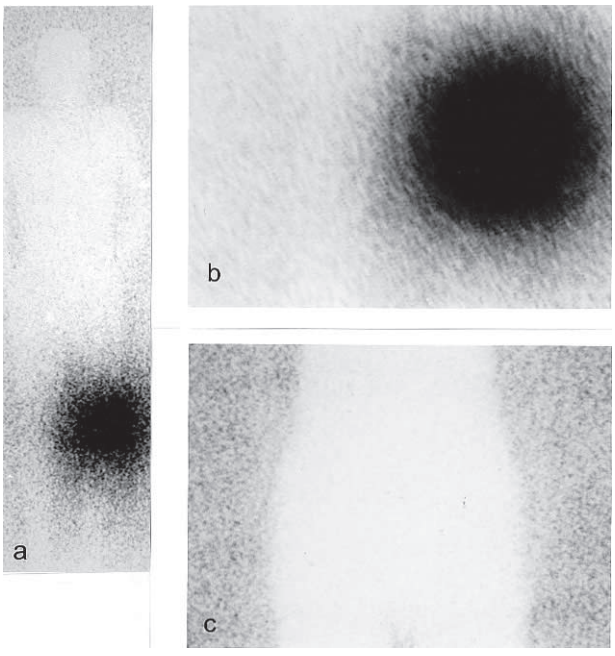

Fig. 5 ^{90}Y-citrate administration to the left knee of patient number 2 was repeated 2 years later. Whole body (a), knee spot (b) and pelvis spot views (c) were again free of visible leakage.

surgical synovectomy in cases of rheumatoid arthritis and other inflammatory arthropathies like hemophilic arthropathy and pigmented villonodular synovitis.

The first agents developed for use in radionuclide synovectomy were radiocolloids preparedwith ^{198}Au for treatment of rheumatoid arthritis.[2] ^{198}Au however could not gain popularity because of two drawbacks; an unnecessary high rate of gamma emission and the leakage of the small particle sized colloids from the joint cavity, which still threatens the widespread usage of this procedure. With efforts to find ideal radiopharmaceuticals for radiation synovectomy ^{188}Rh microspheres and ^{153}Sm particulate hydroxyapatite appeared to be promising radionuclides which are still being evaluated.[9]

A major concern regarding intra-articular therapy is the leakage of radionuclides to non-target organs outside the injected joint.[13] The causes an unacceptable radiation dose to be delivered to non-target organ systems such as draining lymph nodes, liver and spleen. Although the significance of this radiation hazard is unknown, the problem of extraarticular leakage has been an area of investigation. Gratz et al., reported the importance of joint immobilization and in cases with insufficient immobilization, a dose of 189 Gy was reported to be received by regional lymph nodes.[1] As well as joint immobilization, the choice of radionuclide with a short half life also an attractive approach to minimize the leakage and this leads to production of dysprosium-165-ferric hydroxide macroaggregates (^{165}Dy-FHMA) with a reproted leakage value of 0.3% of applied activity.[14] Many authors also recom-

Table 2 Leakage values for different radiocolloids

Radiocolloid	Treated joints	Range of leakage values	Mean of leakage values	Median of leakage values
^{90}Y-citrate	19	0–13%	3.15%	1.9%
^{90}Y-silicate	21	0.5–5%	2.3%	2.4%
^{186}Re-sulfide	13	1.1–6%	2.5%	2.7%
Total	53	0–13%	2.6%	2.4%

mended combined corticosteroid and radionuclide administration to reduce local inflammation and lymphatic clearance.[15] However, inference from the results of our preliminary study consisting of 12 patients is that steroid coinjection is not necessary in order to avoid extraarticular activity leakage.[16]

Using a radioactive particle of a proper size is another way to achieve an ideal radiopharmaceutical for radiosynoviorthesis. The radionuclide should be attached to a particle with a size range from 2 to 10 μm.[9] For years, ^{90}Y has been used in the silicate, citrate, ferric hydroxide and resin forms. ^{90}Y silicate with particle size of 10 to 100 nm was reported to leak 5% to 10% at 24 hours after administration and between 15% to 25% at 5 days.[6] In contrast to this study, Spooren et al. studied ^{90}Y-silicate in 33 patients and looked for radioactivity in regional lymph nodes in 10 patients. There was not any radioactivity observed in regional lymph nodes and ^{90}Y-silicate was reported as an efficient treatment for patients with chronic arthritis due to rheumatoid arthritis.[17] Davis et al. tested the two radioactive particles; ^{90}Y-Ca-oxalate and ^{90}Y-FHMA in animals. Using bremsstrahlung settings they found that for ^{90}Y-Ca-oxalate, average leakage was <5% of the injected dose at 3 days post injection and for ^{90}Y-FHMA the leakage value was 3.3% of the injected dose.[9] Song et al. evaluated the biodistribution of ^{166}Ho-chitosan complex for the treatment of knee synovitis in rheumatoid arthritis. Negligible amounts of extra-articular leakage values were reported such as 0.8% in pelvis and 0.7% in abdomen.[18] For mid sized joints, ^{186}Re-sulfide was also investigated in clinical trials and reaching a 6% leakage value of the injected activity was reported by Manil et al.[19] Although the attempts for minimizing leakage values are still continuing, the completely safe permissible leakage value to perform radiosynoviorthesis has not been determined; however it is always mentioned that it should be as low as possible.[10] Because of these discordant results in the literature and recent trends that lessens the enthusiasm to do radiosynovectomy due to this leakage problem, we designed the current study to compare the extraarticular leakage values of three commercially available radiocolloids: ^{90}Y-citrate, ^{90}Y-silicate and ^{186}Re-sulfide and searched for visible leakage. The immobilization period of 48 hours was also applied to the patients in order to inhibit leakage of colloid from the joint. Radioactive leakage was assessed using a gamma camera. No visible leakage was detected in regional lymph nodes, and variability of calculated leakage values was not statistically different between the three radiocolloids. Although ^{186}Re-sulfide had smaller a particle size compared to ^{90}Y-citrate and ^{90}Y-silicate (50–500 nm vs. 1000–2500 nm) we did not observe any visible leakage in this group. When we looked at the % leakage values, a large variation was observed especially in the ^{90}Y-citrate group (range: 0–13%; Table 2). The patients who had 13% leakage, was a 19-year-old male with Hemophilia A (Table 1). The bremsstrahlung images after his first treatment showed no visible leakage in his groin area (Fig. 4). However, the calculated value was high. The possible reason for this high value may be due to the low knee counts/pixel ratio compared to his second therapy (16.5 vs. 40.2). When background correction was performed, 13% leakage was calculated by dividing 1.4 (numerator) to 10.6 (denominator). If denominator decreases, the ratio increases. Since bremsstrahlung images are subject to attenuation because of the low energy of these photons, and the energy of bremsstrahlung photons can range from zero to full energy of incident beta particle, the interaction medium of particle becomes important.[20] The synovium thickness and synovial fluid components may change. The patient's second scans in March 2004 again revealed no visible leakage (Fig. 5). Although the same amount of activity was applied in each study, the counts/pixel ratio of knee joint was 40.2 in his second therapy. With a higher denominator value, a lesser ratio and so a lesser calculated leakage value was obtained (4%).

Since mean values may be affected by the extreme values in the group, we also calculated the median of the leakage values and used Kruskal Wallis test, as a non parametric test to investigate the statistical significance of the variations of the leakage values of the three radiocolloids.

One of the limitation of our study is measuring leakage using a gamma camera which lacks the sensitivity to measure values less than 1.85 MBq.[6] Davis et al. reported the challenge remains to prepare a particular agent that leaks <5% of the administered dose, with 5–10% leakage being an acceptable and optimistic assumption.[6] We thought that ^{90}Y-citrate, ^{90}Y-silicate and ^{186}Re-sulfide radiocolloids are all acceptable radiopharmaceuticals in terms of extraarticular leakage which had 3.15%, 2.3% and 2.5% mean calculated leakage values respectively (Table 2).

As the effects of radioactivity leakage on regional

lymph nodes and other non-target organs is not well known, the efforts to design new agents which will exhibit the least leakage will continue. The results of our study revealed that ^{90}Y-citrate, ^{90}Y-silicate and ^{186}Re-sulfide radiocolloids are all safe radiopharmaceuticals when appropriate particle size and joint immobilization are provided.

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