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ORIGINAL ARTICLE

Initial experience with intra-articular ^{188}Re-tin colloid as a "radiation synovectomy" agent in various joints

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ABSTRACT

Radiation synovectomy has been proposed as a promising palliative therapy for recurrent joint effusions for the last two or three decades. Ionizing radiations emitted by intrarticularly administered radiolabelled colloids. The aim of this study was to assess the effectiveness of radiation synovectomy (RSV) using ^{188}Re-tin colloid in the treatment of recurrent joint effusions and chronic synovitis of knee joints. Three phase bone scan was acquired for the concerned joint prior to radiosynovectomy. ^{188}Re-tin colloid was prepared as per the reported protocol. 9 patients, diagnosed with rheumatoid arthritis and suffering from chronic resistant synovitis of the knee, ankle or elbow joints were administered the radiopharmaceuticals, checked for radiochemical purity >95% by intraarticular route. A whole body scan was acquired 2 h post-radiosynovectomy. In all the 9 treatments, no leakage to non-target organs was visible in the whole body scan. Static scans of the joint revealed complete retention of ^{188}Re-tin colloid in the joints post administration of the agent. Clinically all patients exhibited a complete or partial response. RSV with ^{188}Re-tin colloid was safe and effective in patients with chronic synovitis of rheumatoid origin. ***J Radiopharm Mol Probes 1(2):109-117, 2015***

Key Words: Synovitis, Radiation synovectomy, ^{188}Re-tin colloid, chronic synovitis, rheumatoid arthritis

Introduction

Radiation synovectomy (RSV) or radiosynoviorthesis has been proposed as a promising palliative therapy for recurrent joint effusions for the last two to three decades (1,2). Ionizing radiation emitted by intra-articularly administered radiolabeled colloids or particles results in an inflammatory reaction that leads to necrosis of the superficial synovial layer and in this way reduces joint effusions. An ideal agent for RSV would be one which the radionuclide is irreversibly attached to pre-formed particles of appropriate size. The ideal size of such particles is reported to be 1-10 μm, so that they are small enough to be phagocytosed, but not so small that they may leak out of the cavity before phagocytizing resulting in high dose delivered to non-target organs (3). In addition, the particles should be bio-degradable, and the biological half-life of such particles should be longer than the physical half-life of the radio nuclide tagged with them (3).

The choice of the radionuclide in RSV is determined by the penetration range of beta radiation and synovial thickness in a treated joint. Radioactive particles should penetrate the synovia without reaching the articular cartilage.

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^{188}Re is a therapeutic isotope with favourable nuclear characteristics and is easily available on a need to use basis from a ^{188}W/^{188}Re generator. The radionuclide, ^{188}Re has a beta emission of maximum energy 2.11 MeV which is sufficient to penetrate tissue (e.g. synovial membrane) 5-10 mm of thick and its gamma emission of energy 155 KeV (abundance 15%) permits scintigraphic monitoring after injection without much radiation burden to the patients or practitioners. Its 16.9 h half-life is adequate for radiopharmaceutical preparation and to deliver sufficient therapeutic dose to the target site in a relatively short time.

There are several reports in the literature on the preparation of ^{188}Re-tin colloid. It can be prepared easily with bare minimum facilities with radiochemical purity (RCP) more than 95% (4,5). The colloid is stable for 24 h at room temperature and showed minimum leakage from the joint after intra articular injection into the rabbit's knee. The colloid offered greatest surface area in the 2-10 μm range in comparison to ^{188}Re-HA and Sn-Fe hydroxide MAA (4,5). The in-house cold kit preparation was simple to perform and no extensive post preparation processing requirement. The aim of this study was to assess the effectiveness of RSV using ^{188}Re-tin colloid in the treatment of recurrent joint (knee, wrist, ankle and elbow) effusions and chronic synovitis.

Materials and Methods

1. Materials

Stannous chloride dihydrate was purchased from Fluka, Germany. ^{188}Re in the form of $Na^{188}ReO_4$ was eluted from ^{188}W/^{188}Re generator purchased from (Polatom RadioIsotope Centre). A 20 mg/mL solution of stannous chloride dihydrate was prepared by dissolving 30 mg of stannous chloride dihydrate in 1.5 mL of nitrogen purged water for injection. Silica gel-based instant thin layer chromatography (ITLC-SG) paper was purchased from Merck, Germany.

2. Preparation of ^{188}Re-tin colloid

The ^{188}Re-tin colloid was prepared following a reported protocol (6) about 0.5 mL of freshly prepared stannous chloride solution (20 mg/mL concentration) was transferred into a sterile 10 mL vial through a 0.22 μm Millipore filter. To this vial, 0.5 mL of freshly eluted ^{188}Re activity (185-1110 MBq) was added, again, through a 0.22 μm Millipore filter (7). The solution in the vial was thoroughly mixed, the vial was sealed and incubated at 100°C for 2 h. After cooling, the pH of the preparation was adjusted to physiological range by adding required volume of 0.2 M phosphate buffer through 0.22 μm filter.

3. Determination of radiochemical purity

After the radioactive preparation was cooled to room temperature, about 2 μL of the preparation was spotted about 1.5 cm from the bottom of a 11.5-cm ITLC-SG strip. The strip was developed in normal saline till the solvent front reaches 1 cm from the top of the strip. The strip was cut into two equal segments and activity associated with each segment is determined. RCP of the preparation is determined from the following equation.

$$\%RCP = 100 - [A_{top}/A_{total}] \times 100$$

Where A_{top} is the activity associated with the top segment and A_{total} is the activity associated with the bottom segment.

4. Patient selection

The treated group consisted of 9 patients with rheumatoid arthritis (RA) or chronic painful synovitis involving the knee (5 patients), ankle (2 patients), wrist (1 patient) and elbow (1 patient) joints. The patients were included in this study only if the synovial thickening of the involved joints were above 5 mm. There were 6 women and 3 men; between 16 and 48 years of age (the mean age was 39 years ± 7 months).

Indication for RSV was persistent knee, ankle, wrist, or elbow joint effusion and painful synovitis that was recurrent in spite of local corticosteroid injections and optimal systemic treatment of disease with modifying drugs in a stable dose for a period not shorter than 8 weeks before RSV. Intraarticular injections with corticosteroid was prohibited within 4 weeks before RSV. The mean duration of the disease was 22.7 ± 14 months (range: 8-49 months). All the joints studied, had a history of pain at exercise, severe enough to limit their normal physical activity over the preceding 3 months, while 3 out of the 9 joints had also night pain. The flexibility was normal in 2

out of 9 joints and reduced < 20° in 4 , between 20° and 40° in 2 and > 40° in 1 joint. Changes in the joints caused by RA were consistent with radiological Steinbrocker's classification.

5. Pre-requisite to RSV

A Three-phase bone scan, X-ray and USG doppler study was performed prior to RSV therapy to confirm and document active synovitis. MRI was also done for all joints other than knee joint.

6. Bone scintigraphy before therapy

A Third-phase bone scintigraphy (BS3) was performed by intravenous injection of methylene diphosphonate ^{99m}Tc-MDP (740 MBq) with detectors positioned over the knee, ankle, wrists or elbow joints in anterior and posterior projections in all phases of the examination. They used dual head gamma-camera (Siemens Symbia True Point) equipped with a low-energy high-resolution collimator. The first phase (blood flow phase) was obtained immediately after radio-tracer administration. Dynamic acquisition was performed over a period of 2 min with a time resolution of 2 seconds. The second phase (blood pool phase) was carried out 5 min post injection with a 10 min static acquisition. Delayed static images (the third phase or metabolic phase) were obtained 2.5–4 h after radiotracer administration.

Bone scans were done both before the treatment to confirm synovitis and after treatment for response evaluation assessment of the second phase additionally included the four-degree scale of blood pool changes: (1) Normal blood pool (2) slightly increased blood pool (3) markedly increased blood pool and (4) severely increased blood pool. Semi quantitative evaluation of the third phase was performed by employing the region of interest method (ROI). The joint to blood ratio (J/B ratio) was calculated dividing the average number of counts per pixel in the region of the treated joint by the average number of counts per pixel in the distal part of the shaft on the side of the affected joint (2).

7. RadioSynovectomy injection and technique

RSV treatment was performed in 9 joints (elbow/ankle/knee) with precise intra-articular single injection of a typical dose of 726 ± 58 MBq (for knee joints) or 333 ± 46 MBq (for wrists, elbows and ankle joints) of ^{188}Re-tin colloid under sterile conditions. Before joint puncture, local anesthesia was administered with 2% lidocaine hydrochloride. Aspiration of synovial fluid prior to the administration of the radiopharmaceutical was performed in order to avoid back flushing due to high hydrostatic pressure. Depo-Medrol (40 mg/1 mL) was injected into the joint immediately before the injection of ^{188}Re-tin colloid particles in order to reduce the risk of acute radiation induced synovitis and also to avoid skin radiation necrosis (8). Subsequently, ^{188}Re-tin colloid particles dispersed in 1 mL of sterile, apyrogenic normal saline was administered intra-articularly. The needle was flushed with 2–4 mL of normal saline. In case of any uncertainty about the exact location of the needle tip, arthrography was performed to check the correct location. Immediately after injection, the joint was flexed to augment intra articular distribution and the range of flexion was recorded.

An orthopedic bandage was applied as a semi rigid splint. Patient remained non-weight bearing for 4 h with support. The treated joints were immobilized for about 48 h in order to prevent migration of radiolabeled particles to local lymph nodes. Radionuclide leakage along the needle track or any local and general side-effects were not observed in examined group of patients.

Patients were allowed to go home 4 h post-injection and advised to take rest. Imaging of activity distribution within 2-3 h post-administration with a dual head gamma camera showed appropriate homogeneously intra-articular distribution of the radionuclide within the joint space. Additional 24 h images were acquired to document extra articular deposition.

8. Follow-up evaluation

The analysis of RSV treatment outcome after 6 months follow-up, in all joints was based on detailed information from the patient, clinical examination and three phase BS. Treatment outcome was examined in terms of joint pain during exercise, improvement measured with a 100-point visual analog scale (VAS), pain score before and at 6 months after treatment. Any improvement of the knee pain was measured and calculated as

Table 1. Percentage of VAS improvement before and after therapy

No of Joints	Excellent VAS≥75-100	Good VAS ≥50-75	Fair VAS >25-50	Poor VAS<25	Success	Failure
9	6	2	1	0	8	1

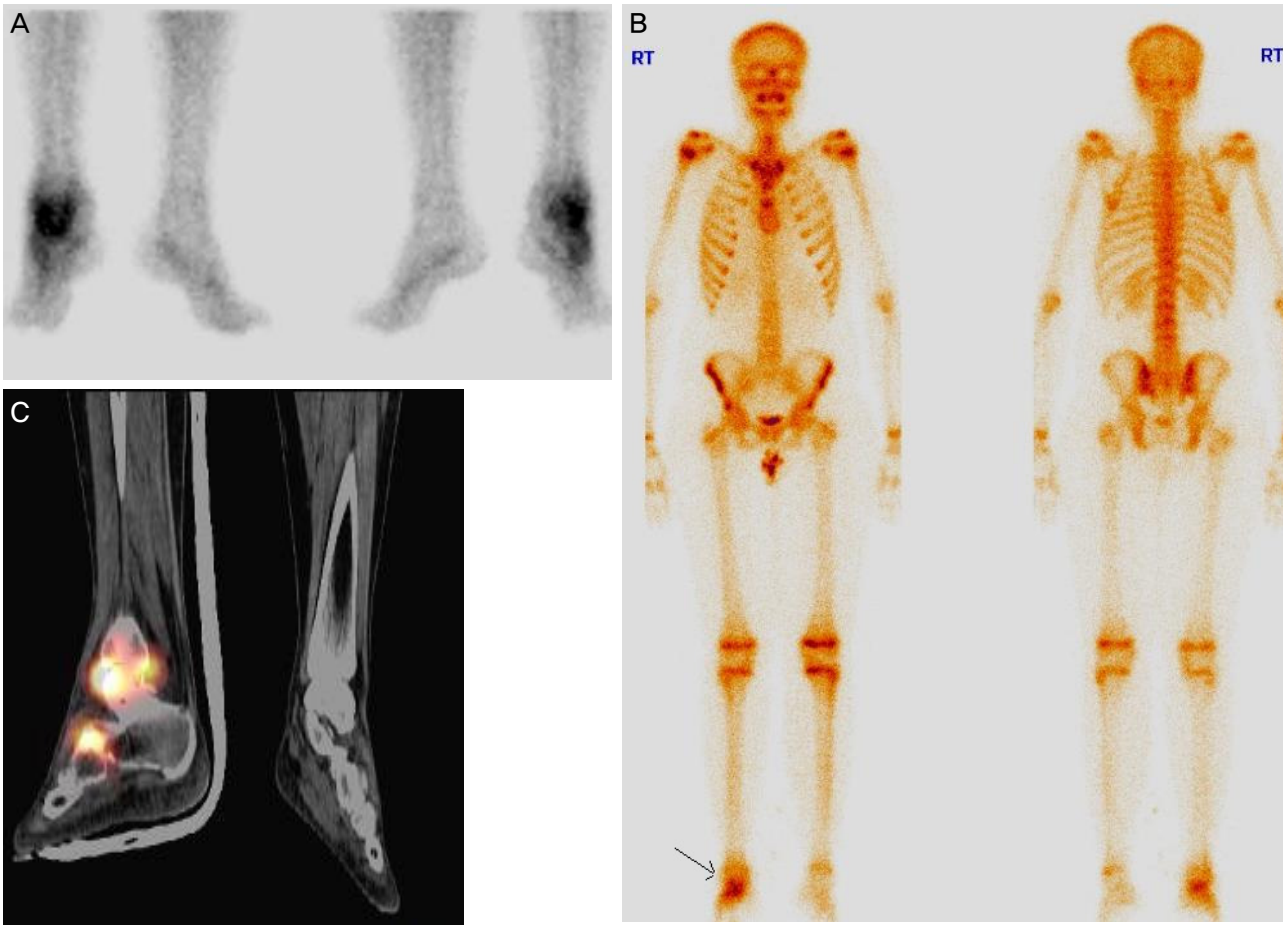

Figure 1. (A) Anterior and posterior blood pool images demonstrate increased blood pool concentration in the right ankle joint consistent with synovitis. (B) Whole-body images showing increased tracer uptake in the right ankle joint (indicating with arrow marks). (C) Coronal SPECT/CT of ankle joint showing good tracer distribution in the ankle, subtalar, and calcaneocuboid joint.

a mean (±standard deviation SD) percentage change from the baseline VAS score. The RSV treatment outcome was assessed as excellent, good, fair and poor (9,10). Excellent and good results were considered as treatment success, fair, and poor as treatment failure. Patients with excellent results had an improvement of VAS score equal or higher than 75%, patients with good response had VAS scores of 50–75%. Patients with a fair result had VAS scores 25–50%, while patients with a poor result had no benefit from treatment, their joint pain continued and VAS score was <25% (Table 1). The presence or absence of pain during the night before and after RSV treatment was recorded according to patient's judgment and was used as another treatment response variable. The improvement of patient's joint flexibility was considered as an objective treatment response, measured by the angle of joint flexion (<20°, between 20° and 40° or >40°). We also compared RSV influences with patient's age, the duration of symptoms and the X-ray grading. The joints were assigned in groups according to the radiographic RA findings using the Steinbrocker radiological grading system (Grades 0-IV) (11). Comparison of soft tissue hyperemia during the second phase of BS was also performed to see the decrease in inflammation. Results obtained were

subjected to statistical analysis, which included the calculation of mean values and standard deviations of all studied parameters. Correlations between parameters were analyzed and the significance of correlation coefficients was verified with the t-test. Differences in mean values of evaluated parameters were assessed by Student's paired t-test and the $P < 0.05$ was considered as significant.

Results

1. Preparation of ^{188}Re-tin colloid

Preparation of ^{188}Re-tin colloid was carried out following a reported procedure (6), briefly mentioned in the experimental section. Reported particle size distribution of ^{188}Re-tin colloid

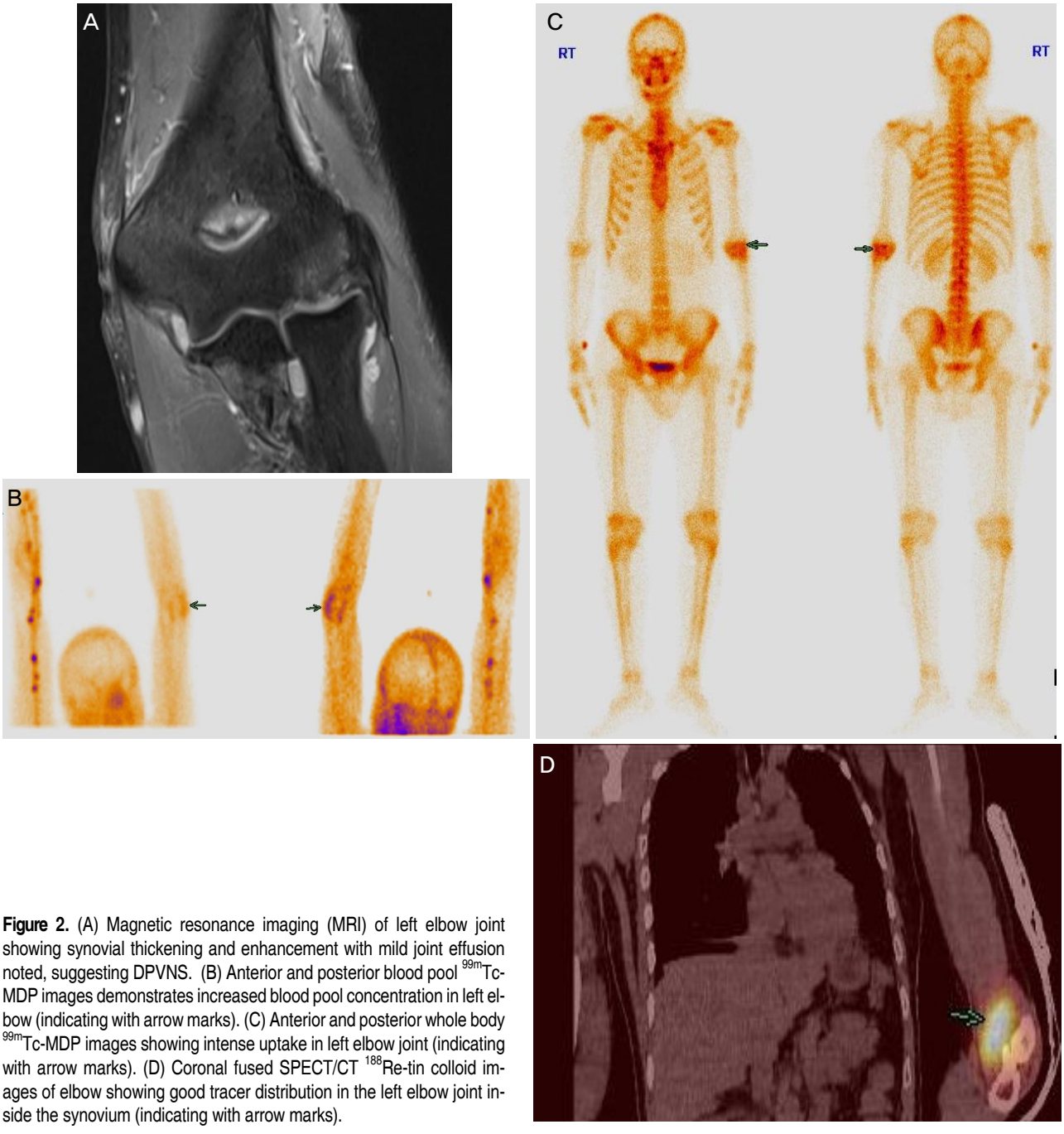

Figure 2. (A) Magnetic resonance imaging (MRI) of left elbow joint showing synovial thickening and enhancement with mild joint effusion noted, suggesting DPVNS. (B) Anterior and posterior blood pool ^{99m}Tc-MDP images demonstrates increased blood pool concentration in left elbow (indicating with arrow marks). (C) Anterior and posterior whole body ^{99m}Tc-MDP images showing intense uptake in left elbow joint (indicating with arrow marks). (D) Coronal fused SPECT/CT ^{188}Re-tin colloid images of elbow showing good tracer distribution in the left elbow joint inside the synovium (indicating with arrow marks).

prepared by this method had 25% particle size >10 μm size, more than 70% of particles between 1-10 μm and <3% particles below 1 μm size (7). Radiochemical purity of the preparation determined by ITLC-SG in normal saline was more than 95%.

2. Bone scintigraphy

All patients demonstrated that increased tracer activity in the afflicted joints and representative image of a patient. Anterior and posterior blood pool images demonstrate increased blood pool concentration in the right ankle joint consistent with synovitis (Figure 1A). Whole-body images showing increased tracer uptake in the right ankle joint (Figure 1B). Coronal SPECT/CT of ankle joint showing good tracer distribution in the ankle, subtalar, and calcaneocuboid joint (Figure 1C). Magnetic resonance imaging (MRI) of left elbow joint showing synovial thickening and enhancement with mild joint effusion noted, suggesting DPVNS (Figure 2A). Anterior and posterior blood pool ^{99m}Tc-MDP images demonstrates increased blood pool concentration in left elbow (indicating with arrow marks) (Figure 2B). Anterior and posterior whole body ^{99m}Tc-MDP images showing intense uptake in left elbow joint (indicating with arrow marks) (Figure 2C). Coronal fused SPECT/CT ^{188}Re-tin colloid images of elbow showing good tracer distribution in the left elbow joint inside the synovium (indicating with arrow marks) (Figure 2D).

3. Retention of ^{188}Re-tin colloid in the joints

In all patients treated with ^{188}Re-tin colloid, no detectable leakage of radioactivity from the joint cavity to any other non-target organs could be visible in the whole-body scans recorded using 155 keV gamma photon emission of ^{188}Re.

The representative static scan of the knee joints in the same patient recorded before and 6 h post-administration of ^{188}Re-tin colloid, indicating excellent localization of the radiopharmaceutical in the joint cavity with almost no detectable leakage (Figure 3).

Minimum or no leakage of activity to any other non-target organs is one of the important requirements of a successful RSV procedure. Routine whole-body sweep images were done

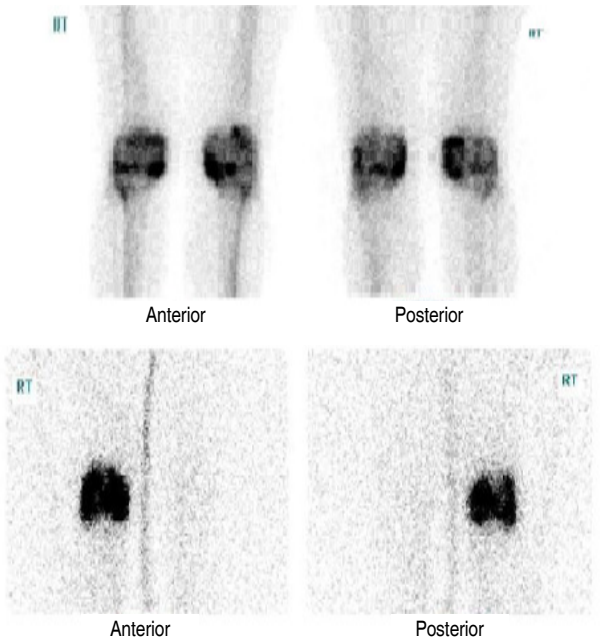

Figure 3. Anterior and posterior of the knee joints in the same patient recorded before and 6 hours post administration of ^{188}Re-tin colloid, indicating excellent localization of the radiopharmaceutical in the joint cavity with almost no detectable leakage.

on the next day of the RSV procedure.

In addition, the radiation dose to the gonads was negligible as all the injections were in the respective joints, which were far away from the gonads and no extra articular or inguinal node activity was present in any of the cases.

Efficacy of the treatment six months after RSV, the VAS improvement from baseline values of the joint pain for the whole group was 80.6±1.7%. For patients aged between 16-35 years and 35-50 years, the mean VAS improvement was 85.2±3.7% and 53.8±4.5%, respectively. There was significant difference (P=0.01) between these two groups. Patients with symptoms lasting <1 year, had a mean VAS improvement of 74.5±5.6%, which was significantly higher than the corresponding value of 60.2±4.9% of patients with the disease lasting for 1 or more years (P=0.01). Visual analog scale improvement for knees with Steinbrocker's Grades 0 and I, versus knees with more advanced (Steinbrocker's Grades III and IV) radiographic changes, was 78.1% versus 57.4% ($P < 0.001$), respectively. In a further analysis, concerning the radiographic changes, it seems that at 6 months after RSV treatment, the success rate was close to 100% for joints without or with mineral osteoarthritis (OA) radiographic changes (Steinbrocker's Grades 0 and I) and 77%

Table 2. Results of 3 phase bone scan before and after therapy : Blood pool images

	Pre therapy VAS score of 1/2	Pre therapy VAS score of 3/4
Percentage improvement at 6 months	68.00%	84.00%

for knees with moderate OA radiographic changes (Steinbrocker's Grade II). Advanced degenerative changes in knee joints (Steinbrocker's Grades III and IV), showed significantly lower RSV success rate (approximately 55% in 6 months), than the joints with no or minimal radiographic changes. The overall success rate of RSV is shown in Table 1.

None of the patients showed complete failure (VAS improvement score 0%), 1 patient showed VAS improvement of 25–50% termed as failure initially, but responded much better in the second sitting, 6 months later. Two patients showed VAS improvement between 50% -75% while 6 patients showed VAS improvement of 75–100%. Among all the joints that were treated complete response (VAS improvement score 100%) was seen in 1 joint. The outcome in terms of VAS for joint improvement related to the three phase BS changes are shown in Table 2. VAS improvement for knees with mild to moderately increased blood pooling (score 1 or 2) versus severely increased (score 3 or 4) scintigraphic changes was 68% and 84% ($P < 0.001$), respectively. In a further analysis concerning the scintigraphic changes, it was observed that 6 months post RSV treatment, the success rate was 77% for joints with mild to moderately increased blood pooling and 88% for knees with severe grade blood pooling. Thus, in knees with more increased blood pooling, the RSV success rate was significantly higher compared to the joints with mild or moderate scintigraphic changes. After 6 months, the improvement in knee pain correlated with the decrease in soft tissue pooling in the treated joints. More the improvement in VAS score, lesser is the blood pooling observed in the scintigraphic scan compared to the pre-therapy scintigraphic scan. In third-phase bone scintigraphy (BS3), joint to blood ratio (J/B ratio) were showing changes before therapy 2.8±0.3; after therapy 1.2±0.4 and p value ($P<0.05$) indicating statistically significant. Six months after RSV treatment, night pain was absent in all of the joints.

Flexibility was improved in 7/9 joints (77 %) at 6 months while no improvement was observed in 2 patients. The side-effects, including thromboses or skin radiation necrosis, during the follow-up period were minimal or absent.

Table 3. Results of 3 phase bone scan before and after therapy : 3rd phase delayed images

	No of patients	3-Phase Bone scan 3rd-Phase J/B ratio
Before therapy	9	2.8±0.3
6 months after Therapy		1.2±0.4
P-value		$P < 0.05$

Discussion

Present study demonstrated that ^{188}Re-tin colloid can be potentially used as a viable option for RSV of the wrist, elbow, ankle, and knee joints where in the syonvial thickening is grossly enhanced. The choice of this radiopharmaceutical was made based on the high penetration of beta radiation in the synovia.

Distribution of ^{188}Re-tin colloid in the joints can be easily monitored by scintigraphic imaging of the 155 Kev gamma photons emitted by ^{188}Re. Histopathological findings in the early phase, after intra-articular administration of ^{188}Re-tin colloid particles, revealed reduction in the quantity and size of the synovial villi, decreased hyperemia and the thickness of the synovia. In the late phase after RSV, synovial fibrosis was observed predominantly. The beta radiation from ^{188}Re, because of its adequate penetration distance, reached into the thickened synovium but not beyond the structures in the intermediate vicinity of the joint cavity. However, the gamma photons emitted by ^{188}Re can penetrate much further.

In this connection, the radiation dose to other organs, especially gonads, could be a cause of concern. The highest dose to gonads usually result from a RSV of the hip joint. For RSV of other joints, as in this study viz. knee, wrist, ankle and elbow, the dose to the gonads is clearly smaller because of the longer distance from the gonads and a relatively low injected dose.

Literature reports clearly indicate that ^{188}Re-tin colloid is highly stable in vivo and leakage from the synovial site is negligible (4,5). Based on the post-therapy whole-body imaging

studies conducted on human patients, we have observed that when the treated joint was immobilized, activity in the lymph nodes were not detectable and leakage was negligible even at 4 days post therapy. Significant intra-articular retention at 4 days also suggests excellent in vivo stability of the preparation. According to our prospective study, the overall success rate of RSV (VAS ≥ 50%) was greater than 80% at 6 months, indicating a high short-term beneficial effect in pain remission of knee joints. Similar beneficial effect was reported by Markou and Chatzopoulos (12) using Yttrium-90 silicate radiosynovectomy treatment of painful synovitis in knee. Overall success rate (VAS ≥ 50%) was 83.8% at 6 months, indicating a similarly short-term beneficial effect in pain remission at exercise of OA knee joints. An equally significant beneficial effect of RSV is complete remission of the joint pain during the night in all treated joints. Our results also correlated with that of Markou and Chatzopoulos (12), which showed night pain remission of 88.6%. Improvement of knee flexibility, as we have shown, has also been reported by others (8) and is probably associated with the ablation of the synovial membrane, reduction of knee effusion and pain remission. The mean VAS improvement observed at 6 months was inversely related to the duration of symptoms and the radiographic grading of OA. Similar to other studies, RSV seemed to be less beneficial in older patients, in cases of long duration of the disease and in advanced radiological stage (Steinbrocker's Grades III and IV) (12-14) . Considering indications for RSV, it should be kept in mind, that the response to the therapy is incomplete in patients with advanced articular changes (degree III and IV of Steinbrocker's classification), joint instability or synovial hypertrophy exceeding penetration rate of beta radiation. One of the conditions that qualify a patient for RSV is the presence of inflammatory changes in BS3 . In the present study, we have tried to assess the therapeutic effectiveness of RSV, by means of BS3. BS3 plays a crucial role in the diagnosis of early articular changes. In more advanced stages its role is complementary to radiographical investigations in the assessment of prognosis and therapy efficacy (15). Similar to other studies (15,16), we have observed a considerable normalization of the blood pool and to a lesser degree of metabolism after RSV. This observation proves BS3 to be a useful diagnostic tool that truly reflects joint changes. According to EANM guidelines, repeated RSV treatment procedures may be applied in the same joint after a minimum interval of 6 months (8). Onset of response after a single RSV treatment has a delay of 3–6 months but lasts up to 24 months. For this reason, we followed-up our patients for 6 months. The co-administration of glucocorticoids immediately after the ^{188}Re-tin colloid injection is considered to have a beneficial effect as early as the 1st week, and up to 4 months, and is used to reduce the risk of acute radiation induced synovitis due to ^{188}Re injection (17). The RSV side-effects and complications observed were minimal and not significant as is usually expected (18).

Conclusion

Preliminary clinical investigations were carried out on the efficacy of ^{188}Re-tin colloid particles in RSV after intra-articular administration of 726±58 MBq (for knee joints) or 333 ± 46 MBq (for wrists, elbows and ankle joints) in a small group of patients suffering from recurrent joint effusions and chronic synovitis of different joints. The study indicated the potentiality of the agent as a viable and cost-effective radiopharmaceutical for use for the treatment of chronic synovitis of different types of joints. The significant pain relief and improved mobility observed in all patients treated was encouraging. RSV efficacy can be confirmed by imaging and biochemical tests. Moreover, there is minimal radiation risk involved in the procedure and can be performed on outpatient basis.

Since, the number of centers performing radiation synovectomy is increasing all over the world, ^{188}Re-tin colloid particles shows the potential to emerge as a promising and cost-effective candidate, considering its generator based on site availablility, ease of preparation and hard beta emission for large joints as well as grossly thickened synovium.

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