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Review Article

Radiosynovectomy: Current Status and Clinical Utility

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ABSTRACT

Radiosynovectomy (RS), also known as radioisotopic synovectomy, radiation synovectomy or radiosynoviorthesis, is the application of radionuclide into the joint space. This is a non-surgical, minimally invasive and effective procedure, which can be undertaken in the outpatient department. Radiosynovectomy is indicated in the treatment of joint pain arising from rheumatoid arthritis, haemophilic arthritis, pigmented villonodular synovitis, spondyloarthropathies such as reactive or psoriatic arthritis, other inflammatory joint diseases such as Lyme and Behcet's disease, persistent synovial effusion, persistent effusion after joint prosthesis, calcium pyrophosphate dihydrate arthritis and undifferentiated arthritis which is characterized by synovitis, synovial thickening or effusion. ^{90}Y silicate/citrate, ^{186} Re sulphide and ^{169} Er citrate are the most commonly used radionuclides for RS. Radiation causes fibrosis of subsynovial connective tissue of the joint capsule and synovium. Side-effects are rare and self limiting. Pain reduction occurs in 1-3 weeks after RS. If there is no response after 6 weeks, treatment failure is likely and the cycle can be repeated up to three times. Most studies about RS have focussed on haemophilic synovitis, which has the highest response rate among the indications. Chronic inflammatory knee joints with a shorter duration of disease, normal or minor X-ray findings, little or no swelling, mild tenderness and better mobility are associated with a better response. In this review, the details are given of the indications, technique, side effects, and the therapeutic effect of RS with current status and clinical utility.

Key words: Radiosynovectomy; ^{90}Y; ^{186}Re; ^{169}Er.

INTRODUCTION

Radiosynovectomy (RS), which is the application of radioisotope into the joint, was first used by Fellinger et al in 1952. [1] Radiosynovectomy is a non-surgical and minimally invasive procedure, which can be undertaken in the outpatient department. [2] Radiosynovectomy is also known as radioisotopic synovectomy, radiation synovectomy or radiosynoviorthesis. Multidisciplinary team work is essential with the collaboration of the orthopedic surgeon, radiologist, nuclear medicine physician, clinical hematologist and physiotherapist for decisions about and application of RS. [3] Radiosynovectomy has been widely applied for the last two decades and new radionuclides have also been developed for RS such as ^{177}Lu macroaggregates, ^{177}Lu phytate complex and ^{166}Ho phytate complex. [4] The European Association of Nuclear Medicine advises the use of ^{90}Y silicate/citrate or ^{186}Re sulphide or ^{169}Er citrate for RS. [5]

^{90}Y silicate/citrate, ^{186}Re sulphide and ^{169}Er citrate include β particles which are essential for RS. Beta radiation produces highly reactive free radicals that cause coagulation necrosis thus attenuating the synovial folds. The occlusion of superficial capillaries induces fibrosis and a marked decrease in secretory activity and bleeding. [6] Radiation causes fibrosis of subsynovial connective tissue of the joint capsule and synovium. Radiation also causes obstructions in some vessels but the articular cartilage is not affected by radiation. [7] The selection of the radionuclide for the treatment of small (fingers), medium (wrist) and large (hip, knee) joints depends on the penetration range of the β particles of the radionuclide and the colloid particle size that should correspond to the thickness of the inflamed synovium. [8] ^{90}Y has a half-life of 2.7 days with a mean/maximum penetration depth of β-ray of 3.6/11mm, ^{186}Re has a half-life of 3.7 days with a mean/maximum penetration depth of 1.2/3.7 mm and ^{169}Er has a half-life of 9.4 days with a mean/maximum penetration depth of 0.3/1.0 mm. Therefore, ^{90}Y is used for the knee, ^{186}Re for medium sized joints and ^{169}Er for finger and toe joints. [9] In this paper, the current status and clinical utility of RS is described with indications and contraindications, techniques of application, side-effects and the therapeutic effect of RS.

Indications and Contraindications

Radiosynovectomy is indicated in the treatment of joint pain arising from rheumatoid arthritis, haemophilic arthritis, diffuse pigmented villonodular synovitis (DPVNS), spondyloarthropathies such as reactive or psoriatic arthritis, other inflammatory joint diseases such as Lyme and Behcet's disease, persistent synovial effusion, persistent effusion after joint prosthesis, calcium pyrophosphate dihydrate arthritis and undifferentiated arthritis which is characterized by synovitis, synovial thickening or effusion. [5]

Radiosynovectomy should be used in paediatric patients with haemophilia in cases of children with inhibitors or in children without inhibitors when bleeding is recurrent and persistent despite aggressive factor replacement. [10] There is ongoing controversy about the age of patients in haemophilic synovitis. Some authors perform RS on young children, whereas some authors recommend arthroscopic synovectomy as the first line therapy. If RS fails, arthroscopic synovectomy should be indicated ideally in patients older than 12 years of age. [11]

Contraindications for RS include pregnancy, breastfeeding, local infection, massive hemarthroses and ruptured baker cyst or semi-membranous bursa, a period of up to six weeks following joint surgery and a period of up to two weeks following the puncture of the joint. [12,13] Ruptured cyst and a short interval after joint surgery and puncture of the joint may cause extra-articular penetration of the radioisotope. [13] Age younger than 20 years, significant cartilage loss and joint instability with bone destruction are relative contraindications. The benefit of RS should be greater than the potential hazard of the radionuclide in patients younger than 20 years old. [14]

Side Effects

Side-effects are rare and self limiting. The main side-effects are tissue necrosis after extra-articular application of radionuclide or reflux from the joint, joint infection or side-effects induced due to immobilization. [15] An inflammatory reaction after injection may be seen, in which case, rest and nonsteroidal anti-inflammatory drugs will control these symptoms. [16] In the early period temporary increased synovitis may be seen and in the late period, radionecrosis. [5] Reversible erythema may be seen due to reflux from the joint, especially in joints with a low volume of joint space. [12] In a survey from Germany, a total of 53 severe complications were reported as 28 necroses, 13 joint infections and 12 thromboses. Tissue necroses from ^{90}Y were treated by surgical excision and closure of the defect, ulcers from ^{186}Re by hyperbaric oxygen therapy in 2 cases and lesions from ^{169}Er showed restoration with conservative treatment. [17]

Radiosynovectomy has not been found to be associated with growth retardation in skeletally immature patients. The bone surface/synovial dose is 25 % for

^{90}Y, 15 % for ^{32}P, 5 % for ^{198}Au and 4 % for ^{186}Re. In haemophilia, it is possible for the radiation dose to bone to be lower due to synovial membrane hypertrophy. [18] Radiosynovectomy with ^{166}Ho ferric hydroxide macroaggregate has been reported not to cause obvious chondrocyte damage or osteoarthritic changes in mature rabbits, whereas transient harmful effects have been seen on immature rabbit cartilage. Rapid cartilage matrix synthesis probably makes the chondrocytes susceptible to transient irradiation induced derangement of matrix production in immature rabbits. [19]

Particles of 5 and 20 μm diameter are believed to be ideal for RS. [20] Extra-articular leakage of radionuclide causes radiation of lymph nodes, liver, lung and spleen. Leakage of radioactivity causes an acceptable radiation dose to non-target organs. Very small sized particles or instability of the preparation leading to dissociation of the activity, results in leakage from the joint space.

In a previous study, the assumed estimated maximum whole body doses from a treated patient with ^{90}Y silicate colloid were reported to be 55 microSv for people living with the patient, 2.9-3.4 microSv for the nursing staff, 0.2-1.8 microSv for the therapist physician and 0.3-0.6 microSv for the technician. [21] ^{90}Y injection was shown to cause chromosome breakage, whereas there were fewer aberrations after immobilization for three days. ^{90}Y was seen to cause fewer chromosome aberrations when compared with ^{198}Au because far smaller doses are required with ^{90}Y. [22] Turkmen et al indicated that high doses are not obtained from peripheral blood lymphocytes in children with no extra-articular leakage after ^{90}Y and ^{186}Re RS, which contradicts a high cancer risk. [23,24] Sachinis et al reported chondrosarcoma in a patient who underwent three operations and three sessions of RS due to continuous recurrence of synovial chondromatosis on the elbow. It was stated that the role of RS in malignant changes should be examined, because there has only been one report of a case that progressed to chondrosarcoma from synovial chondromatosis. [25]

The radiation dose is minimal and neither articular nor systemic neoplastic changes have been reported, but patients should be warned about malignancy concerns. [11] Chromosomal abnormalities in peripheral lymphocytes have been shown in some studies. [22,26] Vuorela et al concluded that ^{90}Y RS does not increase the incidence of cancer in a period of over 30 years in patients with rheumatoid arthritis. [27] In a large study, 2412 adult patients were treated with at least one RS between 1976 and 2001 there was no increase in the risk of cancer. [28] Two haemophilia paediatric patients aged 9 and 14 years developed acute lymphocytic leukemia within one year of RS with ^{32}P. However, this situation was not thought to be associated with RS because the interval between the RS and the diagnosis of acute lymphocytic leukemia was short for the induction of cancer with radiation and acute myelogenous leukemia and chronic myelogenous leukemia are the usual types seen after radiation exposure. [29,30]

Technique of Radiosynovectomy

The dose selection of the radionuclide depends on the application area for the treatment of small (fingers), medium (wrist) and large (hip, knee) joints. ^{90}Y colloids are used only for the knee joint at a dose of 185-222 MBq (5-6 mCi); ^{186}Re sulphur colloid for hip at a dose of 74-185 MBq (2-5 mCi), shoulder 74-185 MBq (2-5 mCi), elbow 74-111 MBq (2-3 mCi), wrist 37-74 MBq (1-2 mCi), ankle 74 MBq (2 mCi), and subtalar joints 37-74 MBq (1-2 mCi); ^{169}Er citrate colloid for metacarpophalangeal joint at a dose of 20-40 MBq (0.5-1 mCi), metatarsophalangeal joint 30-40 MBq (0.8-1 mCi) and proximal interphalangeal joint 10-20 MBq (0.3-0.5 mCi). [5]

Informed consent should be obtained from the patients and/or their legal guardians. Factor prophylaxis was started 1-2 hours before the procedure and continued for 3 days after RS in patients with haemophilia. [31]

The intra-articular injection of radionuclide has to be applied as a sterile injection procedure. Local skin anesthesia is advisable before puncture (Figure 1a). Intra-articular positioning of the needle has to be verified by radiography under fluoroscopic guidance (Figure 1b). Intra-articular positioning for the knee is not difficult as aspirated fluid can verify the position and radiography is not mandatory. Intra-articular injection of the contrast media can indicate that the needle is in the joint space. USG can also verify the position of the needle, which is especially important in children due to the absence of radiation in USG. Before the injection of radionuclide, excess fluid in the joint should be drained. After the injection of radionuclide, the syringe is changed and prilocaine is injected into the joint space as anesthesia and to prevent extra-articular leakage. Glucocorticoids may also be injected to prevent synovitis. Manual pressure to the puncture site for 2 minutes is applied. Passive flexion of the extremity helps the dispersion of the radionuclide in the joint space. The joint is stabilized for 3 days with a splint to minimize extra-articular leakage and excessive physical activity is avoided for 2 weeks. Analgesia (paracetamol) can be used in case of pain. [14,32] Rigid splinting of the joint is necessary, but prolonged bed rest is not mandatory. These procedures prevent extravasation of the radionuclide from the joint space and reduce the lymphatic uptake. [33]

Draining of the synovial fluid before the radionuclide injection supports better contact of the radionuclide with the inflamed synovial membrane. [33] Excess fluid injection into the joint may increase intra-articular pressure which may lead to the leakage of radionuclide. Optimization and lessening the fluid volume may prevent leakage. [34] Injected corticosteroid with the radionuclide has some advantages. It may avoid radiation synovitis with effusion. It decreases the inflammatory component so that the therapeutic effect of RS is increased. It helps ^{186}Re to spread to the intercarpal component in the wrist joint and relieves the symptoms of patients before the onset of the effect of RS. [35]

Radiation exposure to hands and skin is mainly due to direct beta radiation from ^{90}Y containing syringes, but skin contamination increases this dose. Using a syringe shield with 5 mm perspex and forceps to hold the syringe during the fixation of the needle to the syringe effectively decreases the beta radiation exposure to the finger. Radiation resistant gloves protect the skin from beta radiation better than latex gloves, but only slightly reduce the beta radiation dose. [36] Using a manipulator for fixation of the needle has been reported to reduce the radiation dose to 0.6 microSv/MBq on the left forefinger and to 0.5 microSv/MBq on the left thumb. [37]

Leakage may be seen after RS. Leakage decreases the efficacy of treatment, because the dose of radionuclide decreases in the joint space. Leakage also increases the extra-articular radiation dose. The patients undergo whole body and static scintigraphic images to evaluate the distribution of the radionuclide in the joint space and the extra-articular leakage at 2 and 48-72 hours after the procedure (Figure 2).

The patients should be advised against getting pregnant for 4 months. Urinary excretion is of concern during the first 2 days after RS. Patients should avoid contaminating people who use the same toilet facility or the patient can be catheterised for 3-4 days with regular emptying of the bag. [5]

Mechanism and Effect of Radiosynovectomy

Radionuclides are labeled with colloid which keeps the active agents in the synovium and prevents lymphatic leakage. The radionuclides emit 70-100 Gy to destroy the proliferating synovium, stop mononuclear infiltration and cause fibrosis of the hypertrophied, hypervascular synovitis membrane. [38] Children receive approximately 0.74 mSv for knee RS and 0.32 mSv for elbow and ankle RS. [10] Radiation causes fibrosis of subsynovial connective tissue of the joint capsule and synovium. Radiation also obstructs some vessels, but the articular cartilage is not affected by radiation. [7] It may take up to 3 months for RS to take full effect. Symptoms may be apparent during this period and the effusion should be drained after 3 or 4 months. Injected corticosteroids during the procedure of RS may eliminate the complaints from the injection until RS becomes effective. [35]

Figure 1: Injection of Re-186 sulfide colloid to the right elbow (a) under the fluoroscopic guidance (b).

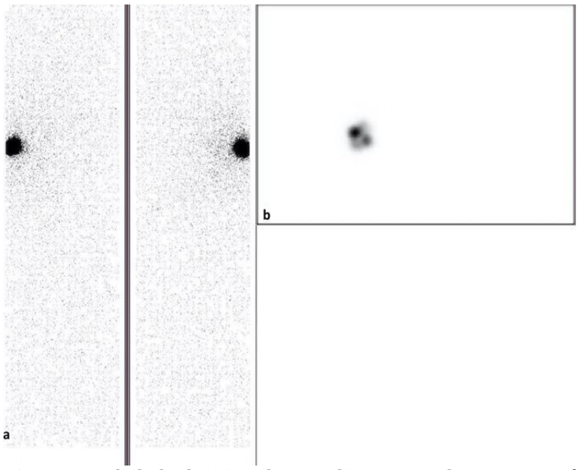

Figure 2: Whole body (a) and static (b) scintigraphic imaging of right elbow to evaluate the extra-articular leakage and the distribution of radionuclide in the joint two hours after radiosynovectom

Evaluation of Effectiveness of Radiosynovectomy

Pain reduction generally occurs in 1-3 weeks after RS. If no response is observed within 6 weeks, treatment failure is likely. [5] Patients should be evaluated at 6-8 weeks after RS for treatment response, synovial inflammation and possible radionecrosis. Tegner and Lysholm knee scores, the Marshall scoring system, musculoskeletal tumor society rating scale etc. can be used for the evaluation of the functional status of the patients. The number of bleeding episodes, pain relief, joint swelling and joint mobility are evaluated in the follow-up. The main predictor of outcome in haemophilia after RS is the number of bleeding episodes within 6 months after RS. [39] Synovial membrane thickness before and 3 months after treatment in Magnetic resonance imaging (MRI) has not been found to be related to prognosis. [40] In repeated RS in haemophilic synovitis, each consecutive RS behaves independently. [41] Chronic inflammatory knee joints with shorter duration of disease, normal or minor X-ray findings, little or no swelling, mild tenderness and better mobility are associated with a better response. Arthritis has the highest response rate in haemophilia and the response in osteoarthritis is lower depending on the stage of arthrosis. Patients with rheumatoid arthritis need 6 months of disease modifying therapy before RS. [12] Radiosynovectomy is indicated for rheumatoid arthritis patients with failure in at least one intra-articular injection with corticosteroids. [42]

Magnetic resonance imaging and Ultrasonography (USG) may be taken to document changes in synovial volume and vascularity, especially in patients where clinical evaluation cannot provide reliable indication of failure or response. [5] Ultrasonography can reveal a gradual reduction in the vascularity of the synovial membrane ultimately leading to fibrosis. [13] Ultrasonography and dynamic bone scintigraphy can be applied as part of the qualification process. Ultrasonography can determine the synovial membrane thickness and presence of effusions as well as examination of the ligament structures of the joint. Dynamic bone scintigraphy can determine physical functions of the joint synovial fluid. [43] Magnetic resonance imaging and plain radiography do not show a correlation with the therapeutic response, whereas MRI is more sensitive than plain radiography in the evaluation and follow-up of joints in patients with haemophilia. [44] Blood pool imaging with bone scintigraphy can be used to monitor objective therapy response. The elevated blood pool activity is expected to decrease after RS. [31]

Current Status and Clinical Utility

Radiosynovectomy is mainly used in recurrent joint bleedings in haemophilia. The recurrent joint bleedings suffered in haemophilia cause clinical symptoms of chronic synovitis. A vicious circle of haemarthrosis-synovitis-haemarthrosis causes hypervascularisation of the hypertrophic synovial membrane which causes more bleeds and joint degeneration within a few years. [45] Recurrent bleeding leads to iron deficiency and free radical induced damage, inflammatory cell infiltration, induction of angiogenic mediators and osteoclast activation, and impair chondrocyte proteoglycan synthesis, resulting in apoptosis and cartilage degeneration. [46] Bleeding in the joint affects the metabolism and repair of cartilage. Blood damages the cartilage function under weight-bearing conditions. [47] Postoperative mismanagement, the irresponsibility of patients and parents in managing self-care, lack of access, affordability of treatment and unavailability of proper treatment are the main reasons for recurrence in addition to the difficult nature of a patient with inhibitor. [48]

Arthropathy secondary to recurrent haemarthrosis and chronic synovitis is the most common clinical problem in haemophilia, but many countries lack this medication because of various economic and logistic barriers. [49] A significant number of patients around the world cannot access the optimal treatment and are at risk of the development of chronic synovitis after recurrent haemarthrosis. [39] The prevention of articular hemorrhages with prophylactic treatment is the main factor in avoiding hemophilic arthropathy. Prophylactic treatment of regular infusions of antihemophilic concentrate at an early age may still cause recurrent hemarthrosis and hemophilic arthropathy. [50] Persistent chronic synovitis should be considered for chemical and RS refractory to physiotherapy or anti-inflammatory drugs. [2] The synovium can reabsorb a small amount of blood in the joint. When the blood exceeds the capacity of reabsorption, the synovium will hypertrophy as a compensatory mechanism. The affected joint will show an increase in the size of the synovium known as hypertrophic chronic haemophilic synovitis. [7] Villous formation, markedly increased vascularity and the chronic presence of inflammatory cells are present in the hypertrophic synovium. Synovitis also causes hypertrophy of the epiphyseal growth plates. [16] Joint surface erosions often occur in early childhood and progress to advanced arthropathy by late adolescence in haemophilia. [51] Radiosynovectomy is effective in all patient groups in haemophilia, independent of the type of the joint, the degree of synovial membrane hypertrophy, the presence of arthropathy and the presence of circulating inhibitor antibody. Improvement of pain is more significant in elbows and ankles than in knees. Improvement of joint balance has been reported to be less significant in severe haemophilia and the ankle. [52]

Radiosynovectomy has many advantages when compared with open and arthroscopic synovectomy. Radiosynovectomy is a minimally invasive outpatient procedure that has a modest clotting factor requirement and can be performed successfully in patients with inhibitors. The cost of radiosynovectomy is ≤5 % that of surgical synovectomy and success rates is similar. Radiosynovectomy preserves the range of motion better than open and arthroscopic synovectomy. [18] Arthroscopic synovectomy has similar results to RS but it is a surgical procedure under general anesthesia with a certain number of complications common to surgical procedures. Radiosynovectomy usually has minimal pain and requires minimum replacement therapy. [16] Intramuscular injections should be avoided due to the risk of hematomas at the injection site, and aspirin and NSAIDs add to the risk of gastrointestinal bleeding in haemophilic patients. COX-2 agents are very effective in the management of articular pain and swelling in the affected joints. [50] Prophylactic replacement therapy and physiotherapy are the main approaches to slow the development of elbow synovitis and arthropathy in haemophilia. The immature skeleton is very sensitive to complications, so early treatment is very important. When synovitis develops, RS should not be delayed. [53] Arthroscopic synovectomy is indicated if synovitis persists after 3 applications of RS. The RS procedure is best performed before articular cartilage and bone damage develops. [46] When articular degeneration occurs, alignment osteotomy, arthroscopic joint debridement, arthrodesis and joint arthroplasty are the treatment options. [16]

Rodriguez-Merchan et al evaluated the results of 500 radiosynovectomies in 443 joints of 345 patients with haemophilia with a mean follow-up of 18.5 years. The bleeding episodes decreased by 64.1 %, joint pain by 69.4 %, the degree of clinical synovitis by 31.3 % and the World Federation of Haemophilia score was improved by 19 %, but there was no success in improving the World Federation of Haemophilia radiological score. [54] In another study by Rodriguez-Merchan et al, RS with ^{90}Y and ^{186}Re reduced the number of haemarthrosis, joint pain and synovial size, and improved muscle strength and range of motion. [45] In a study by De la Corte-Rodriguez et al, RS improved the number of episodes of hemarthrosis, articular pain, range of motion in flexion and extension, muscle strength in flexion and extension, the degree of synovitis detected on clinical examination, the size of the synovium, the clinical scale and the radiological scale developed by the World Federation of Haemophilia, but the World Federation of Haemophilia radiological score showed no improvement. [55] More severe synovitis requires a higher number of RS applications and the knee requires more injections than the elbow and the ankle. Second and third injections were required by 55.4 % of knees, whereas this rate was 24.25 % for elbows and 8.3% for ankles. [56] Turkmen et al stated that ^{90}Y RS markedly reduced joint bleeding and long term durability irrespective of the radiographic stage and inhibitor status. [49] Mortazavi et al applied ^{32}P chromic phosphate in haemophilia with a result of at least 50 % decrease in bleeding frequency in 77% of patients. The antihemophilic factor consumption dropped by 74 % and the range of motion remained stable or improved in most of the patients. [57] Rodriguez-Merchan et al compared the effectiveness of ^{90}Y and ^{186}Re in haemophilic synovitis of elbows and ankles. ^{90}Y and ^{186}Re were found to be equally effective in the reduction of the number of haemarthrosis and the size of the synovium in 6 months. [58]

Poly villonodular synovitis has the appearance of a soft tissue swelling or mass around the joint with joint space preservation. Effusion and the hemosiderin-laden soft tissue masses will be seen as areas of low signal intensity on T1 and T2 sequences in MRI. A common result of pigmented villonodular synovitis (PVNS) of the knee is the destruction of the joint and joint replacement. [59] The pigmented villonodular synovitis relapse rate is high and RS improves local control. The most comprehensive study of the treatment of DPVNS with RS belongs to our study team. Progression was not determined in any patient although DPVNS has high recurrence rates. The patients remained stable, 9 regressed and 4 were seen to be totally cured on MRI follow-up. Improvements in Lysholl m and Tegner scores were significant. [32] Nassar et al applied debulking surgery with RS in the treatment of extensive PVNS of the knee and obtained no recurrences and acceptable functional outcomes. [59] In multiple joint involvements, RS can be applied to multiple joints in same session. Koca et al applied RS to elbow and knee joints with DPVNS in the same session. [60] Kamaleshwaran et al used ^{90}Y hydroxyapatite as a primary treatment in DPVNS of the knee joint and reported pain relief, decrease in joint swelling and increase in joint mobility in a 3-month follow-up period. [61]

In a literature review of RS in rheumatological disease, Wong et al observed that in 167 treated joints with RS, rheumatoid arthropathy accounted for 28 %, psoriatic arthropathy 22 %, haemophilic arthropathy 23 %, large joint monoarthropathy 13 % and miscellaneous arthropathy 15 %. Clinical response was highest for large joint monoarthropathy at 85 %. [62] In Behcet's disease, arthritis is usually self-limiting, non-deforming mono or symmetrical oligoarthritic and occasionally can be erosive. Koca et al applied RS to the knee of a Behcet's disease patient with progressive symptoms refractory to the combination of sulfasalazine, methotrexate and colchicine treatment. The effusion decreased and ROM was improved. [63] Liepe evaluated the efficacy of RS in rheumatoid arthritis. An excellent or good response was obtained in 63 % of shoulders, 60 % of wrists, 54 % of thumb bases, 55 % of metacarpophalangeal joints, 54 % of proximal interphalangeal joints, 53 % of distal interphalangeal joints, 57 % of treated knees, 64 % of ankles, and 54 % of metatarsophalangeal joints. [15] Liepe compared RS and corticoid instillation for rheumatoid arthritis of the knee. The response rate between RS and corticoid groups was similar at 1 month and at 3, 6 and 12 months, the response rate was 86 %, 72 % and 46 % in the RS group, and 67 %, 46 % and 21 % in the corticoid group, respectively. [64] Glucocorticoids can be used with radionuclides. Glucocorticoids are generally indicated in RA with persistent monoarthritis or oligoarthritis. The effectiveness and tolerance of intra-articular glucocorticoids are superior to the systemic usage. [42] Markou et al used ^{90}Y silicate RS for the treatment of painful knee osteoarthritis. The overall success rate was 83.8 %, remission of nocturnal pain was achieved in 88.6% and knee flexibility was improved in 65.1 % with no significant side-effects. [65] Troise Rioda et al applied ^{90}Y RS to knee joints with rheumatoid arthritis and approximately 75 % of patients showed a significant reduction in presenting numbers of knee swelling events. [66] Kahan et al applied ^{169}Er citrate to treat rheumatoid arthritis affected finger joints after failure of local corticosteroids and compared these with a placebo injected group. A significant therapeutic effect of ^{169}Er citrate was as decreased pain or swelling (95 % vs 79 %), decreased pain and swelling (79 % vs 47 %) and increased mobility (64 % vs 42 %). [67]

Radiosynovectomy has also been used in different indications. Tan et al applied ^{90}Y citrate colloid to the knee of a patient with haemarthrosis secondary to warfarin usage that could not be stopped due to medical problems such as ischaemic heart disease, atrial fibrillation, or previous embolic stroke. The patient had a cessation of haemarthrosis for 8 months. [68] Kapetanos et al successfully treated recurrent spontaneous hemarthrosis after total knee arthroplasty with RS. [69] Luka et al applied RS for the treatment of chronic exudative arthritis of the knees. Symptomatic relief and functional improvements were achieved in 83% of the patients. [70] Miszczyk et al also used ^{90}Y RS for chronic exudative knee synovitis. The percentage of pain free patients increased from 12% to 50% in one year, the percentage of increased knee temperature fell from 42% to 31% and patients with exudates decreased from 76% to 27%, but no improvement was found in knee circumference. [71] Erselcan et al applied ^{90}Y to a case of lipoma arborescence which is a rare intra-articular lesion characterized by villous proliferation of the synovial membrane and hyperplasia of subsynovial fat. The patient benefited from the treatment which may also be applicable in suitable cases with lipoma arborescens. [72]

New radionuclides have been studied for RS. Yousefnia et al developed ^{177}Lu phytate complex with high radiochemical yield (>99 %) and can be used even 7 days after preparation. At 7 days after the injection, approximately the whole injected dose remained in the injection site. [4] Polyak et al described the preparation of ^{177}Lu labeled zirconia colloid. Preliminary physicochemical and biological suitability for RS was evaluated and it was reported that RS with ^{177}Lu labelled zirconia colloid provided a significant and long term improvement in clinical signs without any remarkable side-effects. [73] Abbasi et al studied the suitability of ^{177}Lu labelled hydroxyapatite on rabbits for RS and indicated its potential for application in RS of small joints. [74] Shinto et al investigated the efficacy of ^{177}Lu labelled hydroxyapatite particles in RS in patients suffering from recurrent joint effusions and chronic synovitis of knee joints. The agent was viable and cost-effective for the treatment of chronic RA of knee joints with significant pain relief and improved mobility in all patients. [75] Kamaleshwaran et al reported the first case of RS to the elbow joint synovitis in RA treated with ^{177}Lu labeled hydroxyapatite particles. [76] Kamaleshwaran et al have also recently used ^{188}Re labeled tin-colloid in small joints (proximal interphalangeal joint) in rheumatoid arthritis for the first time with a good response to RS. [77] Jankovic et al evaluated the physicochemical properties and biological behavior of ^{90}Y tin fluoride colloid (SnF-c) in a rat model. ^{90}Y SnF-c was well retained in the joint for 96 hours and leakage was 1.96 % over this period. It was stated that ^{90}Y SnF-c might be a promising agent for RS. [8] Chattopadhyay et al evaluated ^{111}Ag hydroxyapatite on rabbits for RS. The high labeling yield, radiochemical purity and excellent in vitro and in vivo stability could make ^{111}Ag hydroxyapatite useful as a therapeutic agent in arthritis. [20]

CONCLUSION

Radiosynovectomy is a reliable and efficient treatment method with successful clinical results, especially in haemophilic arthropathy, PVNS and rheumatoid arthritis with few, predictable, and generally avoidable side-effects. Researchers have used RS for other new indications such as chronic exudative arthritis with good results. However, RS still needs further research of some indications which have not been fully studied such as spondyloarthropathies, persistent effusion after joint prosthesis and some inflammatory joint diseases such as Lyme and Behcet's disease. In the future, new radionuclides will be added for intra-articular application and new indications may be added to the guidelines.

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