

## Radionuclide Synovectomy in Inflammatory Arthritis –Prospect in Bangladesh, Scientific Review

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### Abstract

### Review Article

Radionuclide synovectomy is an attractive alternative to surgical synovectomy for the management of the various joint diseases. Recently, the development of new radiopharmaceuticals labeled with  $^{90}\text{Y}$ ,  $^{32}\text{P}$ ,  $^{186}\text{Re}$ ,  $^{188}\text{Re}$ ,  $^{153}\text{Sm}$ ,  $^{165}\text{Dy}$  and  $^{166}\text{Ho}$ , for the effective management of synovial inflammation and related arthritic pain is gaining attention. The background and mechanism, radiopharmaceuticals and injection methods, clinical applications and results, patient's selection, assessment of efficacy, and complications and contraindications of radionuclide synovectomy are reviewed.

**Keywords:** Radionuclide synovectomy, diseases, surgical synovectomy.

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## BACKGROUND AND MECHANISM

Radionuclide synovectomy with various radiopharmaceuticals has been used to alleviate the pain and swelling of rheumatoid arthritis and related joint diseases for more than 40 years since Fellingner and Schmid reported using  $^{198}\text{Au}$ -colloid in 1952 [1]. Although the results achieved by Fellingner and Schmid [1] in the knee were not encouraging probably due to insufficient dosage with 1 mCi, a decade later, Ansell [2] reported more favorable results using high doses of  $^{198}\text{Au}$ -colloid. Subsequently the value of radionuclide synovectomy was confirmed by many studies.  $^{198}\text{Au}$ -colloid had two drawbacks: the 411 keV gamma emission creates an unnecessary radiation hazard, and the small particle size results in leakage from the joint cavity by lymphatic drainage causing high radiation absorbed doses to proximal lymph nodes and liver. Since 1971 radiocolloids labeled with  $^{90}\text{Y}$ ,  $^{32}\text{P}$ ,  $^{186}\text{Re}$ ,  $^{165}\text{Dy}$  and  $^{166}\text{Ho}$  have been used. Clinical improvement has been reported in up to 78% of treated joints. There is extensive literature covering radionuclide synovectomy, also known as radiation synovectomy (radiosynovectomy) or synoviorthesis (synoviolysis). Most of these studies have been generated in Europe and Australia. However, many studies from North America (Canada) indicate an expanding interest on radionuclide synovectomy. Presumably any condition that causes chronic synovial inflammation can lead to pannus formation and eventual destruction of the articular cartilage. Inflammatory arthritis is usually controlled with oral anti-

inflammatory drugs when symptoms are mild. However, in chronic, persistent inflammation, other measures must be used. Synovectomy is indicated in patients with progressive inflammatory signs and symptoms intractable to medical therapy including local intra-articular steroid injection. Chemical synovectomy using osmic acid or alkylating agents have achieved only limited acceptance. Surgical synovectomy has usually been the treatment of choice and expected to give 2 to 3 years of relief. However, the long recovery period, expense, technical difficulty and postsurgical complications, especially infection, provide clear incentives to explore alternative forms of treatment such as radionuclide synovectomy.

The object of radionuclide synovectomy is to destroy the diseased pannus and inflamed synovium by direct and highly selective irradiation, with the expectation that the regenerating synovium, after destruction, will be free of disease. The histological changes include:

1. Regression of hyperemia in the synovial villi,
2. Reduction of cellular infiltrations and
3. Eventual sclerosis of the synovium.

## Radiopharmaceuticals and Methods

The characteristics important in determining suitability of a radionuclide for synovectomy relate both to its physical characteristics and to knowledge of the nature and distribution of the biological target. The choice of radionuclide cannot be considered

independently from the radionuclide vehicle, as the chemical form of the final radiopharmaceutical is likely to play a vital part in the distribution and fate of the radionuclide within the joint and synovial tissue.

### Particle Characteristics

The most important physical quality of an intra-articular radiopharmaceutical is that it must have a large enough particle size and be sufficiently stable to remain within the joint cavity over the physical half life of the radionuclide. Ingrand [3] suggested that the ideal particle size should be about 100 nm to assure uniform distribution and minimal lymphatic clearance. However, the greater retention of  $^{32}\text{P}$ -colloid (0.6 to 4.0) and  $^{165}\text{Dy}$ -macroaggregates (3 to 10) suggests that the optimum particle size is larger. Animal leakage studies done by Noble [4] suggests that the ideal particle size to limit leakage and ensure uniform distribution is 2 to 5. Use of ferric hydroxide macroaggregates (FHMA) to hold the radionuclide might be a step in the right direction, but better carriers are required. We need either a larger-sized particle or one carrying adjuvant that prevent leakage from the joint space. Binding radionuclides to macro agents, such as hydroxyapatite particles or chitosan, may offer promising results.

### Radiation Dosimetry

Calculating radiation dosimetry in radionuclide synovectomy is difficult. The synovial membrane can range from 1 to 7 mm in thickness. This variation can drastically affect the distribution of radioactive particles and the absorbed radiation dose. The activities are estimated to deliver 6,000 to 8,000 rads to the synovium. However, Karesh<sup>5</sup> has calculated that these activities of  $^{166}\text{Ho}$  and  $^{165}\text{Dy}$  actually deliver radiation doses of about 10,000 rads to the synovium (with a whole-body exposure of 0.4 rads). The beta-particle energies emitted by these radionuclides may reach beyond the target tissue, since the maximum thickness of the synovial membrane is 7 mm, beta particles with a longer range (for example,  $^{90}\text{Y}$  and  $^{166}\text{Ho}$ ) may damage healthy cartilage and bone. This effect is somewhat minimized, though, since the average tissue penetration is only about one-third of the maximum range.

### Factors Affecting Outcome of Radionuclide Synovectomy

Rosenthal [6] has summarized much of the older literature on use of radiocolloids for radionuclide synovectomy. Patients with stage 1 disease (with no radiographic evidence of destructive changes) do best; >50% show an excellent result, with remission of pain and effusion. The greater the joint damage, as shown by radiography, the less satisfactory is the result of radionuclide synovectomy. Although maximal results appear in 4 to 6 months, the therapeutic effect often dissipates within 1 year. (This type of regression, however, does occur with other types of therapy for chronic synovitis.) Results of radionuclide synovectomy

appear related in part, to the synovial thickness at the time of treatment: the thicker the synovium, the less satisfactory the result.

### Injection Techniques

Strict asepsis is essential. The injection site is selected by radiographs in two planes with the joint positioned at the injection angle. Major nerves, vessels, and tendons should be avoided. The area of the joint to be injected is then marked with firm pressure using a ballpoint that has the writing tip retracted; this will leave an impression for 10-30 minutes. After careful cleansing and anesthesia with 1% lidocaine, the needle is then inserted through the ballpoint impression, using care to avoid hitting the cartilage. Following insertion, the needle position is checked fluoroscopically with a few ml of contrast media or 1 mCi of  $^{99\text{m}}\text{Tc}$ -sulfur colloid on the gamma camera table. Ensuring that the needle is positioned within the joint cavity is an important precaution, because loculated distribution is probably a common cause of treatment failure. After injecting the radiopharmaceuticals, the needle is flushed with 10 to 20 mg triamcinolone, or with 1% lidocaine during the withdrawal of the needle. The joint is then manipulated through a full arc of extension and flexion to distribute the radioactive particles throughout the joint space. The joint is splinted for two days to minimize leakage from the joint space (in the case of  $^{165}\text{Dy}$ -macroaggregates= 7-8 hrs bed rest is sufficient). The knee is the easiest and most popular joint to perform this procedure. The patient should be in a supine position with the knee fully extended. The puncture is made 1 to 2 cm medial to the medial margin of the patella using an 18 gauge by 4 cm needle directed slightly inferiorly toward the joint cavity. If osteophytes make this supine approach difficult, the knee can be injected with the knee flexed at sitting position. In this case, the needle is placed beneath the lower border of the patella and directed straight posteriorly or slightly superiorly to the joint cavity.

### Applications and Results

From the point of view of radionuclide synovectomy, the most common causes of synovial proliferation and chronic arthritis are rheumatoid arthritis (RA), psoriatic arthritis, calcium pyrophosphate deposition disease, and hemophilic arthropathy. Various authors have reported by far the largest experience with RA. We observed using  $^{90}\text{Y}$ -silicate in patients with RA. The lesions in RA joints are classified by anatomic stages according to the American Rheumatism Association classification (essentially same as Steinbroker's classification) as follows:

- Stage 1: No destructive changes on radiograph
- Stage 2: Osteoporosis with or without slight bone destruction and joint space narrowing
- Stage 3: Definite bone and cartilage destruction with joint space narrowing; joint deformity associated
- Stage 4: Fibrous or bony ankylosis

Patients with stage 1 or 2 RA, rather than stage 3 and 4 disease, are candidates for radionuclide synovectomy if they are failed the medical regimen and have not had knee surgery. Zukerman [7] uses dysporium-165 (<sup>165</sup>Dy) FHMA (T<sub>1/2</sub>= 2.3 Hr). The shortened half-life limits the leakage and allows the patients to be discharged in 8 hours. Leakage to the liver was measured at 0.64% of the injected dosage. In stage 1 knees 94% of patients showed good or fair results and in stage 2, 78% had similar results. Davis and Chinol [8] used yttrium-90 (<sup>90</sup>Y) colloid for the 2.3 MeV maximum energy of this pure beta emitter. It deposits 80% of its energy in the first 4 to 5 mm of tissue and has a 2.7 days' half-life. Both calcium oxalate and FHMA are acceptable particulate agents. Using proper-sized aggregates, by immobilizing the joint, and by using the short half-life radionuclide, reduces unwanted leakage. Chronic synovitis is a serious complication of recurrent bleeding in patients with hemophilia. At least 5 studies have reported radionuclide synovectomy in hemophilic arthropathy. The results have been generally satisfactory without clinical evidence of inflammatory reactions or postinjection hemarthrosis. Most patients experience objective and subjective improvement, as well as decreased incidence of hemorrhage.

#### Patient Selection and Assessment of Efficacy

Clearly, careful patient selection would be needed to exclude those with symptoms predominantly arising from a non-synovial origin.

## PATIENT SELECTION

#### Inclusion Criteria

- Those who remain persistently resistant to conventional forms of treatment.
- Over the age of 50 years and not planning to reproduce
- With a stable degree of pain and disability over the previous 3 months
- All patients will be required to read and sign an informed patient consent form

#### Exclusion Criteria

- Patient with abnormal liver function test
- Women who are pregnant or lactating
- Patients who will probably undergo knee surgery in the next 12 months
- Patients with significant skin infection that might preclude arthrocentesis
- A large synovial fluid residue
- Assessment of Efficacy
- Visual analogue scale of pain in the knee in walking
- Visual analogue scale of pain in the knee on resting
- Visual analogue scale of stiffness in the knee after rest
- The circumference of the knee through the midpoint of patella

- Complications and Contraindications

#### Early Side Effects

Radiodermatitis at the injection site is an occasional complication that is best prevented by flushing the needle with a small volume of triamcinolone. Aspirating the joint and limiting the volume injected also reduces back-flow along the needle tract. Ingrand [3] reported only 2 cases of skin necrosis in 11,000 treated joints. Septic arthritis is a rare complication of any synovial injection. Acute crystal synovitis had been reported in rare instances. Transient lymphedema occurs rarely following radionuclide synovectomy of the wrist.

#### Long-Term Effects

- Chromosomal alterations
- Postradiation malignancy
- Practical Means of Limiting Radiation Hazard

The chief mechanisms whereby radiocolloid may escape the joint space are leakage through the needle tract and by lymphatic clearance. The following precautions serve to limit such loss:

The needle should be flushed with a small volume of steroid or lidocaine following injection of the radiocolloid to prevent back flow along the needle tract, and thus limit the leakage of the injected particles along the needle tract. Van Soesbergen<sup>9</sup> showed that flushing the needle with saline decreased <sup>198</sup>Au-colloid leakage to the regional lymph nodes and liver by 3 times, and 4 times, respectively. Prior injection of radiocontrast material or <sup>99m</sup>Tc-sulfur colloid to confirm correct needle placement. Immobilization of the joint for 48 to 72 hours is essential to retard lymphatic clearance. In the case of large joints this is best accomplished by bed rest without splinting. If immobilization is not practical, splinting or a hard cast should be used to restrict joint motion. In an ambulatory patient, splinting is not likely to cause pulmonary embolism. In the case of smaller joints, splinting or casting, with ambulation is recommended. The use of such short-lived radionuclides as <sup>165</sup>Dy decreases the radiation burden to extrasynovial tissues. However, the therapeutic benefit from high-dose versus low-dose rates has not been established.

#### Contraindications to Intra-Articular Radionuclide Therapy

There are relatively few contraindications to the use of intra-articular radionuclide therapy. They include:

- Periarticular sepsis;
- Overlying cellulitis;
- Bacteremia;
- Unstable joint (including collapse of the tibial plateau);
- Intra-articular fracture;
- Septic joint.

Most of these represent contraindications to arthroscopy. A special case exists when there is a high synovial fluid fibrin content. This suggests active inflammation that should be controlled by steroids before radionuclide therapy.

## SUMMARY

An overview of the results from various literatures shows that although a radiopharmaceutical may be efficacious compared to placebo in the treatment of autoimmune synovitis such as RA, it may compare poorly to some therapeutic alternatives. This is especially relevant with respect to the long-acting injectable glucocorticoids such as triamcinolone. To determine fully the clinical utility of any radiopharmaceutical, its effect on clinical outcome should ideally be compared with the effect achieved with triamcinolone or other long-acting intraarticular glucocorticoid in large randomized studies. Awareness of radiopharmaceutical characteristics and injection techniques may reduce the hazard of radionuclide synovectomy. Careful patient selection would be needed to exclude those with symptoms predominantly arising from a non-synovial origin before performing radionuclide synovectomy.

## CONCLUSION

Rheumatoid disorders are one of the largest health problems in the world both develop and developing countries. In Bangladesh, a study on prevalence of rheumatic disease in adult population shows that the point prevalence of musculoskeletal complaints were 26.1% and life time prevalence was 32.2%. Although presently there is no cure for Inflammatory Arthritis, doctors and other healthcare providers can make lifestyle recommendations and prescribe medication that aim to control the inflammatory process and hence reduce its symptoms and signs. In patients in whom the process is well controlled, the progress - and potential damage resulting from the disease - can be slowed and often halted. Despite technical and methodological inconsistencies reported in the literature, there is considerable scope of radionuclide synovectomy for expanding the use of this in Bangladesh.

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