Review Article **Bhardwaj *et al.*, 9(5&6): May-June, 2018:5805-5809]**
CODEN (USA): IJPLCP ISSN: 0976-7126

INTERNATIONAL JOURNAL OF PHARMACY & LIFE SCIENCES
(Int. J. of Pharm. Life Sci.)

Radiosynovectomy in the treatment of arthritis by Erbium isotopes

Rita Bhardwaj*, Girvar Kelkar, Ragini Bundela, Paras Bodana and Revathi A Gupta
Institute of Pharmacy (SSS IOP), Dr. A.P.J. Abdul Kalam University Indore Bypass Road, Arandia Village, Post Jhalaria, Indore, (M.P.) - India

Abstract

Arthritis, especially rheumatoid arthritis is a common, chronic disease and systemic and local drug treatments are used. Radiosynovectomy is the best therapeutic option for the local treatment of arthritis. Rheumatic conditions tend to involve pain, aching, stiffness, and swelling in and around one or more joints .In radiosynovectomy radioactive labeled particles with a size of 0.05–2 µm are applied directly in the articular cavity. The radioactive particles are transported in the depth of synovia and phagocytized from macrophages and other inflammatory cells. The first treatment of arthritis using radioactive gold (^{198}AU) .The problem of ^{198}AU in radiosynovectomy is the high leakage rate after treatment caused by the small sizes of particles.In the last 20 years the radiosynovectomy showed a renaissance using erbium-169 citrate (^{169}Er) in small joints. Several constant synovitis of interdigital joints opposed to to suitable conventional anti-inflammatory treatment could benefit from radio-synoviorthesis through erbium-169. Erbium-169 synoviorthesis be technically simple to perform and free of side effects.

Keywords: Arthritis, Radiosynovectomy, AU(Gold) Er (Erbium), Free Side effects

Introduction

Joint disorders are relatively common in any society. Among the an assortment of forms of arthritis such because rheumatoid arthritis, osteoarthritis, villonodular synovitis, hemophilic arthropathies, psoriatic arthritis, ankylosing spondylitis and gout, acute and chronic rheumatoid arthritis and hemophilic arthropathies are most common, causing long suffering from pain, deformities and disability. It has been estimated that nearly 30 million people in the South East Asian region suffer from rheumatoid arthritis alone. Conventional long-term treatment with various combinations of drugs can bring relief in many cases. However, some joints need additional local therapy. Mostly corticosteroids are injected into the joints to suppress the inflammatory process localised in the synovium.

*** Corresponding Author**
E.mail: rita.bhardwaj06@gmail.com

Definition

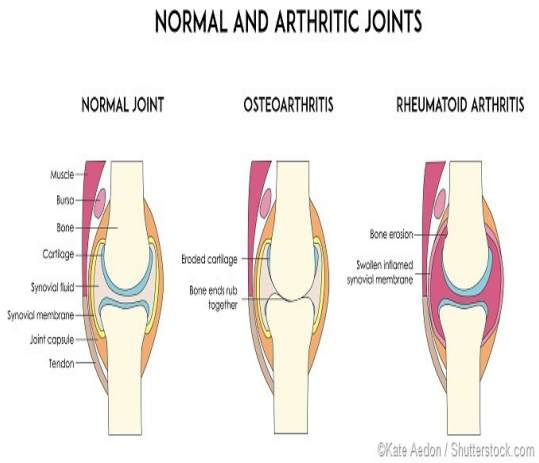
Radiation synovectomy/radiosynoviorthesis [RS] in this situation resources radionuclide therapy of cooperative synovitis or synovial processes by intra-articular injection of 90Y silicate/citrate OR 186Re sulphide OR 169Er citrate. Synovitis resources inflammation of the specialised connective tissue lining of a joint cavity (synovium)

1) 90Y emits a beta particle with maximum energy 2.27 MeV, mean energy 0.935 MeV and average soft tissue range 3.6 mm. The physical half life is 2.7 days.
2) 86Re emits a beta particle with maximum energy 1.07 MeV, mean energy 0.349 MeV, average soft-tissue range 1.1 mm and a 9% abundant gamma emission with a photopeak of 0.137 MeV. The physical half life is 3.7 days.
3) 169Er emits a beta particle with maximum energy 0.34 MeV, mean energy 0.099 MeV and average soft tissue range 0.3 mm. The physical half life is 9.4 days

Arthritis:

In some cases, surgery is also performed. Radiosynovectomy (also known as radiosynoviorthesis) is a novel method of treatment for such joints. The concept of radiosynovectomy was reported earlier, but Delbarre *et al*. in the year

1968. Introduced the term 'radio-synoviorthesis' for the first time and also reported their clinical experience. Radisynovectomy or radiosynoviorthesis is defined as the restoration of inflamed and damaged synovial membrane of the joints after application of radionuclides (radioisotopes). The beta rays emitted by the radionuclides are used to effectively control the inflammatory process of the synovial membrane and the technique is indicated as an alternative therapy to early surgical synovectom. Arthritis possessions joint inflammation, except the term is used to describe approximately 200 conditions to affect joints, the tissues that surround the joint, and further connective tissue is a rheumatic condition.



The most universal form of arthritis is osteoarthritis.Further frequent rheumatic conditions related headed for arthritis include gout, fibromyalgia, and rheumatoid arthritis (RA).Rheumatic conditions tend to involve pain, aching, stiffness, and swelling in and around one or more joints. The symptoms can develop gradually or unexpectedly. Definite rheumatic conditions can also involve the immune system and various internal organs of the body. Some forms of arthritis, such as rheumatoid arthritis and lupus (SLE), can involve multiple organs and cause widespread symptoms. According to the Centers for Disease Control and Prevention (CDC), 54.4 million adults in the United States surround received a diagnosis of a number of forms arthritis. Of these, 23.7 million people have their activity curtailed in some way by their condition.Arthritis is more common among adults aged 65 years or older, but it can affect people of all ages, including children.

Erbium isotopes in biology:-

Radiolabeled 171Er tablets have been used to study bowel movements of individuals using external **scintigraphy**. These tablets are made using enteric coated (coating that delays the release of medication until after it has passed through the stomach) tablets that contain small amounts of stable erbium oxide (170Er) and irradiating them in a small **neutron** flux to produce radioactive labeled 171Er tablets, via the 170Er (n, γ) 171Er reaction. This method is a noninvasive approach for determining gastric emptying rates and visualizing segments of the digestive system in an individual.

Erbium isotopes in medicine:-

169Er is used in **radiosynovectomy**, which is a regularly practiced **radiotherapy**, on rheumatoid arthritis patients whose condition is resistant to standard methods of treatment (Figure 1). Rheumatoid arthritis is a chronic, inflammatory, autoimmune disease of the joint capsule (synovial sac), which is lined with a thin membrane called the synovium, of an individual's moveable joints (synovial joints). In radiosynovectomy, the **radiopharmaceutical** called 169Er- citrate colloid, which contains colloidal particles that are labeled with β-emitting 169Er, is directly injected into the synovial cavity of the affected joint. These radioactive-colloid particles are then phagocytized (engulfed) by macrophage-like synoviocytes as well as other phagocytizing inflammatory cells in the patient's synovium. Necrosis (tissue death) and the inhabitation of cell proliferation (increase in number of cells) result from the radiation of the synovium and therefore, temporarily halts synovitis (which is the condition of when the synovium thickens with inflammation) and improves synovial joint function

Principles:-

Radioactive isotopes which emit beta rays be use for Radiosynovectomy. The radionuclides in the contour of colloids, taking place reaching the joint cavity be recognised as foreign bodies through the outermost cellular layer of the synovial membrane and are phagocytosed by these cells. Autoradiographic investigations show that Yttrium-colloids quickly enter the superficial layers and also to some extent the deeper layers of the synovial membrane but very little reaches the bones. Due to the selective radiation of the synovial membrane, there is necrosis of the cells and reduction in the inflammatory cellular proliferation. Arthroscopic examination shows a reduction in the number and size of the synovial villi and reduction in the hyperemic reaction. Later there is progressive fibrosis of the synovial stroma, the

vessels and rarely, mild diffuse damage to the bones of the joint. There is also prevention of the filtration and reabsorption of the synovial fluid.

There is complete disappearance of the mononuclear infiltration in the synovial membrane after a few months and the synovial membrane is fibrosed. Further destruction of the joint cavity otherwise caused by continuous immunological reactions is prevented. Since the fibrotic tissue replacing the synovial membrane cannot react to the immunological stimulation, there is no recurrence of the inflammatory process and a long term remission is achieved.

Magnitude of Problem:-

Rheumatoid arthritis (RA) is the most common chronic inflammatory disease of joints. It affects more than 1% of the population. This disease is more prevalent in women with a preponderance of 3:1 over men. It has been estimated that in Malaysia 0.22 million patients are suffering from this disease. It usually starts in fourth and fifth decade of life. However no age group in spared from this crippling disease. 80% of patients developing the disease are found to be between 35 to 50 years of age.

The causes of RA are not known, but there is strong evidence of involvement of cellular and humoral immune systems. This may be genetically predetermined as the incidence of sero-positive RA is more common in the population with HLA-DR4 (60%) than in normal controls (15%). It has also been suggested that RA manifests in response to certain environmental factors, and hormonal disturbances may play a role but the actual mechanism is not known. In many cases RA shows a “tumour like proliferation” with rapidly growing synovial membrane and pannus formation which behaves similar to a locally invasive tumour.

Clinically rheumatoid arthritis presents like a chronic multi-system disease with a variety of systemic manifestations but a characteristic feature is the persistent inflammatory synovitis. Most commonly involved joints are proximal inter-phalangeal joints, metacarpophalangeal joints, wrist and knee joints. In the long run synovial inflammation causes cartilage destruction, bone erosion and joint deformity with marked functional impairment.

Hemophilia is a common bleeding disorder in South East Asian countries. The incidence is more than 0.01%. More than half of the patients with this disorder suffer from arthropathy which cripples life at an early age.

The cause of hemophilia is a deficiency of clotting factors VIII (Hemophilia A) and IX (Hemophilia B). Inadequate replacement of factor VIII and IX, lack of patient education, lack of physician education regarding simple techniques (application of ice or ice packs, immobilisation of affected joints, use of slings), be deficient in physiotherapy and need of new therapy methods like radiation synovectomy contain contributed to the fact that more than 50% of these patients suffer from physical disability and crippling arthropathy.

Procedure:-

Facility

The facilities requisite determination depends on National legislation intended for the administration of pure beta emitting therapy agents. If inpatient treatment be compulsory by National legislation, this is supposed to take place in an approved facility by revenue of appropriately shielded rooms and en-suite bathroom facilities. The administration of 90Y silicate/citrate, 186Re sulphide and 169Er citrate is supposed to be undertaken surrounded by a dedicated room, equipped intended for sterile injection procedures, by appropriately experienced medical staff through supporting scientific and nursing staff.

Patient preparation:-

1. Patients considered for intra articular 90Y silicate/citrate, 186Re sulphide or 169Er citrate therapy will have failed at negligible amount one intra-articular injection of long-acting glucocorticoid (e.g. methylprednisolone acetate or triamcinolone).Pain will usually be severe enough to limit standard activities and/or require regular analgesics.

2. Radiographs of the joints to be treated should be obtained and reviewed proceeding to undertaking RS. Weight-bearing views of lower limb joints are supposed to be requested specifically. Symptoms attributable mainly or exclusively to cartilage damage are improbable to assistance from RS.

3. Additional imaging events possibly will be useful but are not essential in planning RS:

1) Scintigraphic assessment of soft tissues and severity of active inflammation (e.g. by 3-(2-) phase 99mTc MDP/HDP/HEDP bone scintigraphy and/or 99mTc-HIG scintigraphy) of the affected joints.

2) Ultrasound - to evaluate synovial structure and Thickness and eliminate ruptured Baker´s cyst. 3) Magnetic resonance imaging of the affected joint.

4. Time interval between arthroscopy or joint surgery and radiosynovectomy should be (2-)6 weeks and between joint puncture and radiosynovectomy 2 weeks. The smallest amount interval between repeated treatments in the same joint is

Radionuclides used in Radiosynovectomy:-

In early studies radionuclide gold-198 in colloidal form was used. However, due to its gamma component leading to unwanted whole body radiation exposure combined with spread to lymph nodes and liver, it has been almost abandoned. Present are a variety of radionuclides available now which are suitable for radiosynovectomy. The type of radionuclide to be second-hand is determined by the dimension of the joint to be treated. The lesser range (weaker) beta rays are used in smaller joints like Erbium-169 for finger joints. Similarly the medium range beta rays of Rhenium-186, Phosphorus-32, etc. are used for larger joints (wrist, elbow, shoulder, ankle and hip joints) while the high energy beta rays of Yttrium-90 with tissue penetration of 3 to 11 mm are used for knee joints. In modern years abundant other radionuclides like Holmium-166, Rhenium-188, Samarium-153, etc. have successfully been introduced

Dose Injection:-

Since even a slight extra- articular extravasation of the radioactive material can lead to tissue necrosis, it is very important to be perfect in the injection technique. All joints with the exception of knee joints must be injected only under radiological guidance. A x-ray machine called C-arm which is otherwise used for various radiological procedures can be used for the purpose.

In all joints (specially the small finger joints) arthrographic orientation of the joint space and the ideal position for the needle placement should be done before starting the procedure.

Subsequent to the procedure a distribution scintigram of the joint everywhere probable may be performed to document the distribution of the radionuclide in the joint.

It is advisable to inject a corticosteroid preparation along with the radio nuclide for following benefits:

- Radiation synovitis with effusion (knee joint) can be avoided.
- The inflammatory component will subside effectively through the corticosteroid so that the radionuclide therapy can be more effective.
- In the wrist joint, it helps Rhenium (Rh-186) to spread well in the distally located inter carpal compartments.
- It helps to relieve the patients of the symptoms immediately and thereby bridge the time till effects of intense radiation from the radionuclide sets in.

After the radiosynovectomy, the joint should be immobilised for 48 hours with help of a splint. It will help to prevent the lymphatic spread and reduce leakage rate if the joint is given rest for about a week

It takes up to 3 months to attain the full effects of radiosynovectomy. Symptoms might persist during this period and sometimes there might also be an effusion which needs to be drained during the follow up after 3 or 4 months. Condition corticosteroid has been injected simultaneously; patient might remain free of complaints smooth during the initial period till the radiosynovectomy becomes effective.

Discussion

A large number of procedures using Yittrium-90 for knee joints have been performed worldwide. Improvement rates ranging from 40 to 100% have been reported. In two years follow up of patients, knee joint swellings were reduced almost completely in 38%, pain relief was achieved in 88% and stretching deficiency corrected in 71% of the cases. Some reports quote an improvement rate of 85% after 3-4 years. Rhenium (Re-186) is used for middle sized joints. Good to excellent results are seen in 60-80% of the cases in hand, elbow, shoulder, ankle and hip joints. Good to very good results have been reported in 83% of the elbow joints.

Erbium (Er-169) is used in small joints of the fingers. Good to very good results leading to restoration of normal function has been reported in 54.6% in a study consisting 1261 finger joints

Similar results were reported by Boussiana *et al*. in a double blind study conducted involving PIP joints in 35 patients suffering from chronic polyarthritis who did not respond to intra articular corticosteroid injections good to excellent results were seen in 71.5% of cases in relation to pain relief and joint mobility 6 months after radiosynovectomy. After one year good to excellent results were seen in 79.4%, with no improvement in 20.6% of cases. The X-ray findings of the joints treated by radiosynovectomy showed no changes after 1 year as against those in placebo group (physiological NaCl) which showed reduction in the joint space. In addition, there was fibrosis and absence of inflammatory changes in those joints treated with Er-169 whereas persistence of all histological changes of rheumatoid arthritis was seen in the placebo group .

Since the radionuclides are applied in form of colloids of appropriate size, they remain mostly within the joints. There is no significant radiation exposure to other organ or parts of the body. Being beta emitters, they also don't pose any radiation to

the environment, so the procedure can be performed on ambulatory patients.

If adequate response has not been achieved or recurrence of the disease occurs it may be advisable to repeat the procedure, preferably 6 months after the first treatment. Favourable results have been reported after re-radiosynovectomy of the knee joints in cases of rheumatoid arthritis.

Conclusion

Radiosynovectomy represented a safe, fast and patient-friendly therapeutic option in the management of different kinds of arthritis. Average response rates of 60-80% were report, and the highest response of 90% are observed in hemophilic patients with repeated joint bleeding. The therapy should be performing early, before the development of advance stage of arthrosis. The rate of side effects and the radiation exposure for the patient is low. The team works with other treated colleagues is essential for the therapy.

References

1. Documents of the Project Coordinator's Meeting, 24-28 March 2003. Penang, Malaysia: IAEA; RAS/6/039.
2. Delbarre F, Cayla J, Menkes C, et al. [Synoviorthesis with radioisotopes] Presse Med. 1968; 76(22):1045–50
3. Webb FW, Lowe J, Bluestone R. Uptake of colloidal radioactive yttrium by synovial membrane. Ann Rheum Dis. 1969; 28(3):300–2.
4. Isomaki AM, Inoue H, Oka M. Uptake of 90 Y resin colloid by synovial fluid cells and synovial membrane in rheumatoid arthritis. A radioautographic and electron microscopic study. Scand J Rheumatol. 1972; 1(2):53–60.
5. Yates DB. Arthroscopy of the knee after the injection of 90Y. Ann Rheum Dis. 1973;32(Suppl 6:Suppl):48–50.
6. Wang SJ, Lin WY, Chen MN, et al. Histologic study of effects of radiation synovectomy with Rhenium-188 microsphere. Nucl Med Biol. 2001; 28(6):727–32.
7. Mohr W, Mohing W, Hersener J. [Morphological changes in the articular capsule tissue after preliminary synoviorthesis] Z Rheumatol. 1977; 36(9-10):316–31.
8. Menkes CJ. Gelenkverodung mittels radioaktiver Isotpe bei rheumatoider Arthritis. Therapiewoche. 1979; 29:498–501.
9. Steinbrocker O, Traeger CH, Batterman RC. Therapeutic criteria in rheumatoid arthritis. J Am Med Assoc. 1949; 140:659–63.
10. Makela O, Penttila P, Kolehmainen E, et al. Experimental radiation synovectomy in rabbit knee with holmium-166 ferric hydroxide macroaggregate. Nucl Med Biol. 2002;29 (5):593–8.

How to cite this article

Bhardwaj R., Kelkar G., Bundela R., Bodana P. and Gupta R.A (2018). Radiosynovectomy in the treatment of arthritis by Erbium isotopes. *Int. J. Pharm. Life Sci.*, 9(5&6):5805-5809.

Source of Support: Nil; Conflict of Interest: None declared

Received: 20.04.18; Revised: 27.05.18; Accepted: 30.05.18