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Treatment Response Evaluation using ^{90}Y (Yttrium) in Patients with Rheumatoid Arthritis of Knee Joint

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Abstract For radiosynovectomy using ^{90}Y(Yttrium) produced in a research institute of our country, I have measured the retention time of ^{90}Y hydroxyapatite(particle size $1 \sim 20\mu$m) within the knee joint space and evaluated the treatement responses in knees with rheumatoid arthritis. Radioactive measurements in region of knee after injection of ^{90}Y hydroxyapatite into the joint space were made with a single prove system designed to monitor radioactivity and showed retention of ^{90}Y in the knee ranged 76.6±5.4% after 4 days of injection. The clinical improvements in rheumatoid arthritis of knee joint with Steinbroker stages Ⅰ and Ⅱ were increased as time goes by, the improvement ratio is 72% at 6th month and 76% at 12th month after injection of ^{90}Y 185MBq (5mCi) per joint.
Key words ^{90}Y hydroxyapatite, radiosynovectomy

Introduction

The great leader Comrade **Kim Jong Il** said as follows.

"Drawing on the successes already achieved, medical science must open the fields of genetic engineering, immunology and molecular biology and stimulate research to adopt widely in curative and preventive services the latest scientific and technological achievements, including electronics and laser engineering."("ON THE FURTHER IMPROVEMENT OF THE HEALTH SERVICE" P. 18)

In rheumatoid arthritis, pain, joint swelling and functional disorder are often satisfactorily treated by oral anti-inflammatory or immunosuppressive drugs. However in chronic, persistent inflammation, additional local treatment must be used. Well-established local treatment options are surgical resection, intraarticular steroid application, and radiosynovectomy. Surgical procedures, ranging from open-joint surgery to minimally invasive arthroscopic synovectomy, are associated with risks of surgery and anesthesia, need for hospitalization, and a prolonged period of rehabilitation. Intra-articular injection of corticosteroids is the most frequently applied and widespread therapeutic approach in the local treatment of synovitis. However, many studies have described negative effects on articular cartilage metabolism and vitality. Furthermore, repeated intra-articular steroid applications often result in increasingly shorter time periods of effective pain relief [3, 10]. Owing to the limitations of local treatment modalities, radiosynovectomy has become an alternative and supplementary therapeutic approach for the treatment of painful inflammatory joint diseases, or chronic recurrent joint effusion [2, 8].

For radiosynovectomy, β-emitting radiocolloids are used for intra-articular application. Immediately after administration, the colloids are taken up by phagocytosis by type-A synoviocytes which partly build the surface layer in the synovial membrance as well as by phagocytosing immunocompetent cells such as macrophages. Therefore radiosynovectomy using ^{90}Y with β-particle emission is based on the well-documented phenomenon that the internal radiation technique is to distroy the diseased pannus (hyperplasia of the villous synovium) and inflamed synovium by direct and highly selective irradiation and with the expection that following synovium destruction, the regenerated synovium will be free of disease [5－7, 9].

^{90}Y is presently being considered as a suitable radionuclide in the knee joint with rheumatoid arthritis because of its deep tissue penetration (mean=3.6mm; max=11mm) [4]. At least the particle sizes of ^{90}Y 5～10nm or 2～5μm are enough to be taken up by the synovial cells and to achieve a homogenous distribution within the whole joint. If a particle diameter is not large enough to avoid leakage out of the joint cavity by venous or lymphatic drainage, it will result in an increased irradiation of the whole body and particulary of the locoregional lymph nodes, the liver and the spleen. For radiosynovectomy of the knee joint, the recommented activity per joint is usually 185～222MBq (5～6mCi) [4, 5]. Meta-analyses reported an overall rate of 67% of good or very good improvement after radiosynovectomy in more than 5 000 treated joints in patient with rheumatoid arthritis. Rates of clinical improvement range from 35% to 100% in knee joints treated with ^{90}Y [7]. And in rheumatoid arthritis, radiosynovectomy was successful in (66.7±15.4)%. There was a difference according to the Steinbroker stages(Steinbroker Ⅰ: (72.8 ± 12.3)%; Steinbroker Ⅱ: (64 ± 17.3)%; Steinbroker Ⅲ and Ⅳ: (52.4±23.6%) [4].

We used ^{90}Y hydroxyapatite which was produced in our country for radiosynovectomy of knee and, for that had measured the retention time of ^{90}Y within the joint space and evaluating the treatment response with rheumatoid arthritis.

1. Materials and Methods

1.1. Materials

A total of 25 patients (13 males and 12 females) with 40 rheumatoid knees and stage Ⅰ and Ⅱ classified according to the American Rheumatoid Association classification [11] were selected for the study. The age range was 45 to 60 years with mean age of 49.9 years. These patients were mandatory adequate standard baseline pharmacotherapy with anti-inflammatory drug or intra-articular steroid application for at least six months prior to radiosynovectomy and failed in those.

1.2. Methods

Each patient was treated with ^{90}Y hydroxyapatite 185MBq (5mCi) per joint for intra-articular therapy of the knee of which a particle size was 1 to 20μm. The puncture was made 1 to 2cm medial to the margin of the patella using an 18-gauge by 1.5-in in a supine

position of patient with the knee fully extended. Radioactive measurements in region of knee were made with a single prove system designed to monitor radioactivity at 0, 24, 48, 72, 96h after injection of ^{90}Y hydroxyapatite into the joint space. Physical half life of ^{90}Y (2.7d) is considered in calulation of the regional radioactivity in percent.

Treatment responses were evaluated as improvement of clinical signs and symptoms (pain, swelling, effusion, knee motion) at 6 and 12 months after injection. We defined "very good" results as complete disappearance of clinical arthritis; "good" implies a striking improvement of all clinical signs and symptoms; "fair" implies improvement of some clinical abnormalities and "none" implies to be the same as before the treatment.

2. Results and Analysis

2.1. Estimation of retention of ^{90}Y hydroxyapatite within the knees

Changes of radioactivity of the injected ^{90}Y hydroxyapatite in the knee at each time are shown in table 1.

Table 1. Radioactivity change of the injected hydroxyapatite in the knee (%)

Num. knee	Time interval after injection/d			
	1	2	3	4
5	92.6±3.0	89.6±3.8	80.5±3.4	76.6±3.6

Radioactivity in the knee after injection was (76.6±3.6)% at 4days. Assuming a surface area of the synovium of the knee is 250cm^2 and effective half life is not equal to physical half life, a dose of ^{90}Y hydroxyapatite 185MBq (5mCi) injected in the joint space of the knee would thus be expected to deliver about 8 500cGy to the synovium using the model of Berger [1].

2.2. Clinical improvement in rheumatoid knees

2.2.1. Reduction of pain in the knee

As shown in table 2, reduction of pain is above 80% and 77% in the knees with rheumatoid arthritis of stage Ⅰ and Ⅱ, respectively, 12 months after injection. And some patient did not review the treatment response at 12 months, only 6 months.

2.2.2. Reduction of swelling and effusion in the knee

As shown in table 3, reduction of swelling and effusion is above 80% and 76% in the knees with rheumatoid arthritis of stage Ⅰ and Ⅱ, respectively, 12 months after injection.

Table 2. Reduction of pain in the knee

Stage	Num. knee	Months after inj.	Results			
			Very good	Good	Fair	None
Ⅰ	15	6	7(47%)	3(20%)	2(13%)	3(20%)
	10	12	5(50%)	1(10%)	2(20%)	2(20%)
Ⅱ	25	6	11(44%)	4(16%)	4(16%)	6(24%)
	21	12	10(48%)	2(10%)	4(19%)	5(23%)

Table 3. Reduction of swelling and effusion in the knee

Stage	Num. knee	Months after inj.	Results			
			Very good	Good	Fair	None
Ⅰ	15	6	8(54%)	2(13%)	2(13%)	3(20%)
	10	12	6(60%)	1(10%)	2(20%)	2(20%)
Ⅱ	25	6	12(48%)	4(16%)	4(16%)	6(20%)
	21	12	12(57%)	—	4(19%)	5(24%)

2.2.3. Improvement of the knee motion

As shown in table 4, improvement of the knee motion is above 80% and 76% in the knees with rheumatoid arthritis of stage Ⅰand Ⅱ, respectively, 12 months after injection.

Table 4. Improvement of the knee motion

Stage	Num. knee	Months after inj.	Results			
			Very good	Good	Fair	None
Ⅰ	15	6	7(47%)	2(13%)	2(13%)	3(27%)
	10	12	6(60%)	1(10%)	2(20%)	2(20%)
Ⅱ	25	66	11(44%)	3(12%)	4(16%)	7(28%)
	21	12	10(47%)	1(5%)	5(24%)	5(24%)

The biological effects within the irradiated tissue are caused by both direct damage and indirect interaction. Secondary oxygen radicals generated by tissue irradiation are known to destroy the cellular membranes by lipid peroxidation and result in DNA strand damage and breaks. All these interactions result in fibrinoid necrosis, sclerosis, and fibrosis of the synovial stroma, the inflammatory cells, and capillaries within the synovial membrane. A significant reduction of the inflammatory pannus tissue and the occlusion of capillaries of the synovial membrane deceasing the secretory activity markedly would be within a few weeks. Thus, the clinical effects of radiosynovectomy for the patient seem to be reduction of pain, swelling, and effusion.

Conclusion

The loss of ^{90}Y hydroxyapatite(particle size 1～20μm) in the joint space of the knee is not beyond to 20% after 4 days. The radiation absorbed dose delivered to the synovial membrane is about 8 500cGy using the model of Berger for calculation after injecting a dose of ^{90}Y hydroxyapatite 185MBq (5mCi) in the joint space of the knee.

Radiosynovectomy using ^{90}Y hydroxyapatite showed good clinical improvement in the treatment of rheumatoid knee in Steinbroker stages Ⅰ and Ⅱ.

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