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Original Article

Effect of Radiosynovectomy with Rhenium-188 in the Treatment of Knee Joint Inflammation in Patients with Hemophilia

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Abstract

Background: One of the effective methods to control chronic hemophilic synovitis is radiosynovectomy. Rhenium-188 is a new radionuclide, and its half-life is 0.7 day. This study aimed to investigate the effect of radiosynovectomy with Rhenium-188 on the knee joint of hemophilic patients.

Methods: Thirty patients with hemophilic synovitis of the knee visited in the orthopedic clinic in 2019 and 2020, entered the study. They all had at least two bleeding per month; in the supine position with slight knee flexion, after local sterilization, 550 to 750 *MBq* Rhenium-188 was injected into the knee. A splint was installed for five days. The demographic characteristics, radiography, articular line tenderness, joint line tenderness, flexion and extension restrictions, and joint volume characteristics were evaluated before and six months after injection.

Results: The amount of monthly injected factors (VIII and IX) 6 months after injection was decreased from 5260.2±1836 units to 3870.83±1106 units ($p<0.001$). The radiographic classification has not changed within six months. The average knee pain score decreased from 7.3±1.2 to 2.3±1.1, after six months ($p<0.001$), and knee flexion increased from 84.6±26.22 to 114±21.58 degrees ($p<0.001$). None of the patients have experienced complications such as skin necrosis or joint infection. All patients have reported that the pain increases 24 *hr* after the injection were manageable.

Conclusion: The use of Rhenium-188 radiopharmaceutical in radiosynovectomy of 30 hemophilic patients' knees is effective in reducing pain, tenderness of the joint line, and the number of bleeding episodes, and it improved knee range of motion in the short term (6 months).

Keywords: Hemarthrosis, Hemophilia, Rhenium-188, Synovectomy

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Introduction

Radiosynovectomy is an effective method for the local treatment of joint inflammatory diseases, such as acute rheumatoid arthritis, chronic polyarthritis, psoriatic arthritis, Behcet's disease with joint involvement, hemarthrosis, and active osteoarthritis. This method was introduced by Fellinger *et al* in 1952 for the first time (1). In 1971, Ahlberg suggested using radiosynovectomy in hemophilic patients (2). In patients with severe hemophilia, 85% of spontaneous hemorrhages occur in joints. Knee, wrist, elbow, and to a lesser extent, hip and shoulder are the joints that are usually involved. Repeated hemorrhages into joint space can cause hemarthrosis with chronic vascular synovitis and progressive cartilage damage (3). In repeated hemorrhages into joint space and following inflammatory synovitis, free oxygen metabolites affect the joint's cartilage and cause more joint damage; finally, resulting in fibrotic changes, which are not reversible; a complication that is known in hemophilic patients (4). An effective method to control chronic hemophilic synovitis is radiosynovectomy and its effects are known today. Radiosynovectomy is a kind of non-invasive synovectomy that can decrease the episodes of bleeding in joint space. Ionizing radiations, including beta, produce free radicals, which result in necrosis and coagulation of superficial veins and reducing secretory activities and bleeding but have no effect on joint cartilage (5-11).

The dose used for radiosynovectomy depends on the amount of absorption by synovium tissue; in turn, the absorption amount depends on some factors, including the type of radionuclide and its activity, joint size and thickness of the synovium, distribution of radionuclide in synovial fluid, and inflammatory activity in the joint. Approximately 100 *Gy*/100 *g* of tissue should be absorbed to be effective. Different radionuclides have been suggested for radiosynovectomy, which is used for different joints based on their penetrating power, and the half-life of the used isotope is also important in these cases. Common radionuclides consist of Phosphorus-32, Yttrium-90, Rhenium-186, and Erbium-169. In recent years, Ho-166, Rhenium-188, and Sm-155 were newly introduced (12-18). Rhenium-186 has a half-life of 3.7 days and minimum and maximum penetration depths of 1.2 and 3.7 *mm* for medium-size joints. Rhenium-188 is a new radionuclide with a maximum beta energy of 2.11 *meV* and is effective on large joints similar to Yttrium-90, and its half-life is 0.7 of a day.

Moreover, it has a gamma energy of 155 *keV*, which can be used for imaging and external dosimetry. The minimum and maximum penetration depths of Rhenium-188 are 2.1 and 10.1 *mm*, respectively. Its side effects are limited. The most important possible complication is tissue necrosis after extra-articular injection of radionuclide or radiopharmaceutical leakage from the joint. With good care and proper injection, these side effects will be minimized. Besides, due to the high dose of injected radionuclide and the resulting elimination of bacteria by radiation, the risk of infection is shallow (19-23). Since few studies have evaluated the effect of Rhenium-188 on joints, this study aims to investigate the therapeutic effect of rhenium 188 on knee joints in hemophilic patients.

Materials and Methods

Settings and population

In this retrospective study, patients with hemophilic synovitis of the knee, the ones visited in the orthopedic clinic of Imam Khomeini Hospital in Urmia in 2019 and 2020, and underwent Rhenium-188 treatment, have entered the study. The Research and Ethics Committee of the Urmia University of Medical Sciences approved this study (IR.UMSU.REC.1398.270).

This study was implemented after being approved by the ethics and research committee of Urmia University of Medical Sciences and after obtaining informed consent from the patients and their companions. The entry criteria included patients with repeated hemorrhages in the knee joint (at least two episodes per month), which happened despite adequate medical treatment with factor replacement; they did not have severe radiological symptoms of knee joint involvement in their radiography. Patients with Pettersson grade over four and knee ankyloses (due to joint stiffness, motionless and without motion range) were excluded. The severity of hemophilic arthropathy was classified using the Pettersson score, and patients with grades 1,2, and 3 were evaluated (24). Among 31 patients, 30 entered the study based

on the Pettersson score, and just one 61-year-old patient, despite radiopharmaceutical injection, was excluded due to a higher Pettersson grade of knee joint involvement. The average age of 30 patients who entered the study was 20.4±8.1, with minimum and maximum ages of 8 and 40, respectively.

Preparation of Rhenium-188

Rhenium was used for radiosynovectomy. First, Rhenium-188 was obtained from W188/Re188 generator. For each patient, the injection was done in the supine position with slight knee flexion and in completely aseptic and sterile conditions.

Injection procedure of radiosynovectomy

Rhenium-188 was injected into the knee in the superolateral area; before injection, local anesthesia with 2% lidocaine was induced by subcutaneous injection. In patients with high effusion, initially, the knee joint fluid was aspirated slightly. In patients with low effusion, 10 *ml* of normal saline were injected into the joint to have an equal distribution of Rhenium-188 colloid.

Before the Rhenium-188 injection, to gain a 100% level of factor 8 in 27 A-type hemophilic patients and factor 9 in 3 patients with hemophilia B-type, a bolus dose of these factors was injected. For five days, the factor level was maintained at 50%, followed by routine prophylaxis injections once or twice a week to maintain the factor at 30 to 40% as before.

A dose of 555 to 750 *MBq* of Rhenium-188 radionuclide was injected into the joint. After injection, the patient was transferred to a gamma scan room to assess colloid distribution in the joint. A splint was installed in the proper position to prevent radiopharmaceutical leakage and pain for five days. Radiosynovectomy was performed on an outpatient basis, and patients were discharged after the procedure.

Intervention evaluation

All patients have followed up for at least six months. The pain was measured based on the Visual Analog Scale (VAS) as an observation ruler from zero to 10, painless to the most severe experimented pain (30). Joint tenderness was evaluated by lack of pain on touch, and the knee's range of motion (flexion and extension) was measured using a special goniometer from the anterior surface of the knee and parallel to the patellar tendon. The frequency of bleeding in the joint was recorded based on periodic clinical examinations.

Statistical analysis

The SPSS 23 (IBM Corp., Armonk, New York, USA) was used to analyze the data statistically. Results were presented in the tables and charts. Data were reported using descriptive statistics (frequency and percentage) and mean±standard deviation (Mean±SD). T-test was used to analyze quantitative data, and the Chi-square test was used for qualitative variables. A significant level is considered to be less than 0.05.

Results

Sixty percent of the patients were female, and 40% were male. 90 % of the patients had hemophilia type A, and 10% had hemophilia type B. Demographic characteristics and clinical data of the patients are elaborated in table 1.

Patterson classification

Among the 30 examined patients, 3 cases had no radiological changes in the joint (3% grade 0). Seventeen cases (56.7%) showed no radiological changes, but inflammation of the soft tissue around the knee was evident (Grade 1). Eight cases (26.7%) had too much epiphyseal growth, and 2 cases, by maintaining the joint space, had mild subchondral cystic changes. In these six months, no noticeable

Table 1. Demographic characteristics and clinical data of the patients

Variables		Number
Gender	Female	18 (60%)
Male	12 (40%)	
Age (year)		20.4±8.1
Weight (*Kg*)		62.12±5.72
Hemophilia type	Hemophilia A	27 (90%)
	Hemophilia B	3 (10%)
	Hemophilia C	0
	Von willebrand disease	0

radiological changes have been observed.

Factor VIII and IX

The number of injected factors (VIII and IX) per month before radiopharmaceutical injection was 5260.2±1836 units, which after radiopharmaceutical injection was decreased to 3870.83±1106 units; which showed a significant statistical difference ($p<0.001$). The pain increased in 23% of patients in the 24 first hours after injection, which was controlled using acetaminophen (Table 2).

Pain score

Average knee pain before radiopharmaceutical injection was 7.3±1.2, and average knee pain in rest position after six months' post-injection was 2.3±1.1, which was significant with a p-value of $p<0.0001$ (Table 2, Figure 1).

Bleeding episode

The frequency of intra-articular bleeding had a significant decrease after six months of radiopharmaceutical injection (Table 2, Figure 2).

Flexion rate

The mean amount of flexion in patients' knees before injection was about 84.66 with a standard deviation of 26.22 degrees, and after six months of injection, the average amount of flexion increased to 114 degrees with a standard deviation of 21.58 degrees.

Table 2. Comparison of the clinical findings before and after Rhenium-188 radiosynovectomy

Variables	Before treatment	6 months after treatment	p-value
Pain (VAS score)	7.3±1.2	2.3±1.1	<0.001
Factor VIII and IX consumption (unit)	5260.2±1836	3870.83±1106	<0.001
Joint volume (*cm*) (swelling)	34.9±3.8	33.4±3.6	<0.001
Thickness (*mm*)	3.9±1.31	3.1±1.07	<0.001
Knee flexion (degree)	84.66±26.22	114±21.58	<0.001
Knee extension restriction (degree)	8.8±3.3	4.7±1.4	0.01
Tenderness	1.9±0.52	0.71±0.23	0.01
Bleeding episode	3.1±1.72	0.71±0.84	0.01

Visual Analogue Scale (VAS).

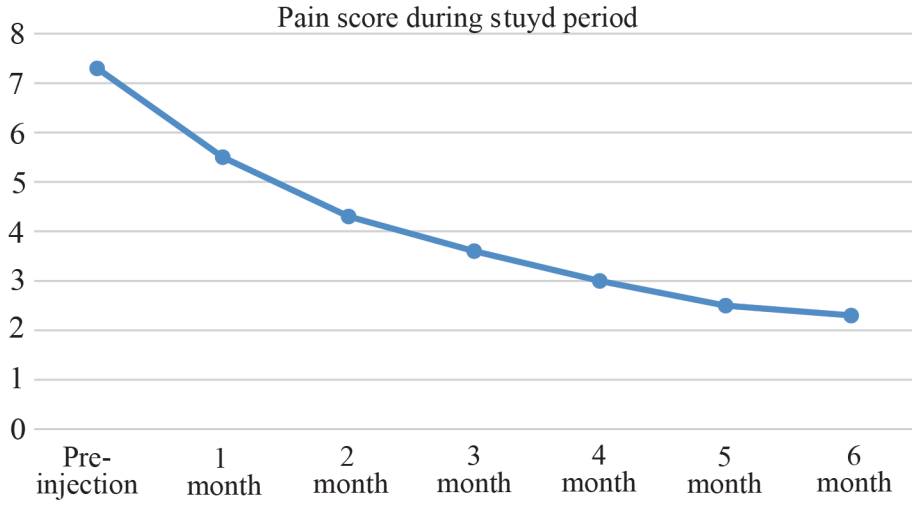

Figure 1. Comparison of Visual Analogue Scale (VAS) score in patients before and after Rhenium-188 radiosynovectomy.

This difference was significant in paired T-test with p<0.001 (Table 2, Figure 3).

Extension limitation

The average limitation of knee extension in patients before the injection was 8.8 with a standard deviation of 3.3 degrees, which was reduced to 4.7 degrees with a standard deviation of 1.4 after six months. This difference was statistically significant (p=0.01) (Table 2, Figure 4).

Knee joint size and thickness

Joint volume in the circumference of the joint just above the patella before injection averaged 34.9 *cm* with a standard deviation of 3.8. The amount of joint volume 6 months after radiopharmaceutical injection was 33.4 with a standard deviation of 3.6. The mean synovial thickness (measured by ultrasound probe) significantly decreased from 3.9±1.31 *mm* to 3.1± 1.07 *mm* six months after the Rhenium-188 injection (Table 2).

Joint line tenderness

The mean tenderness score of the joint line before radiosynovectomy was about 1.9 with a standard deviation of 0.52, and after radiosynovectomy, the mean tenderness score decreased to 0.71 with a standard deviation of 0.23 (Table 2, Figure 5).

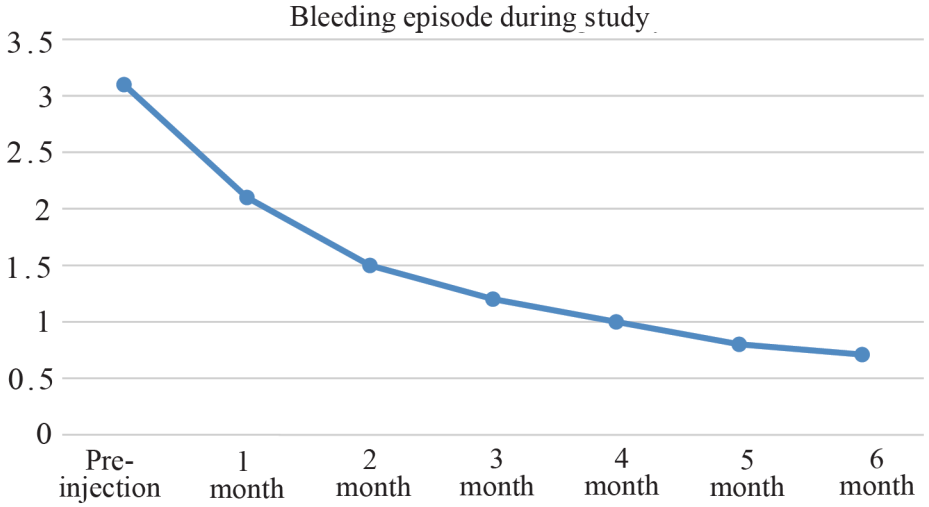

Figure 2. Comparison of bleeding episode in patients before and after Rhenium-188 radiosynovectomy.

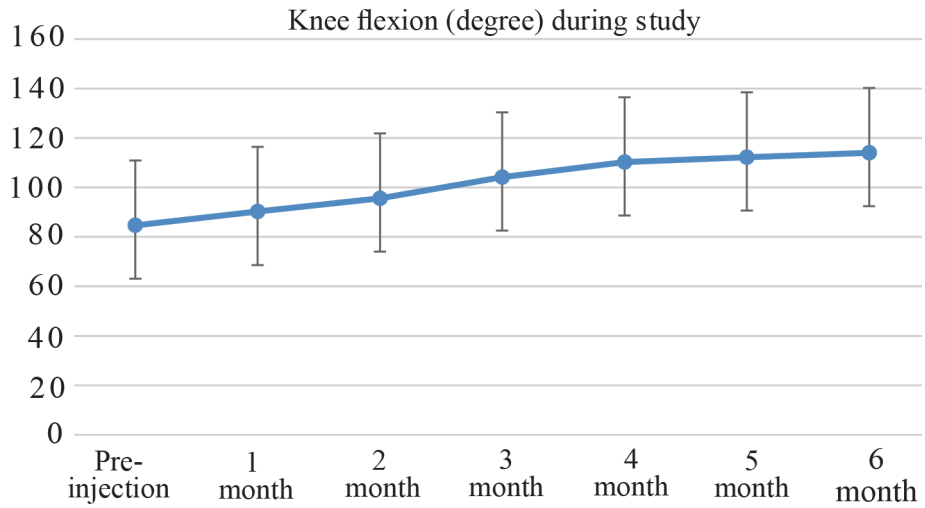

Figure 3. Comparison of knee flexion degree in patients before and after Rhenium-188 radiosynovectomy.

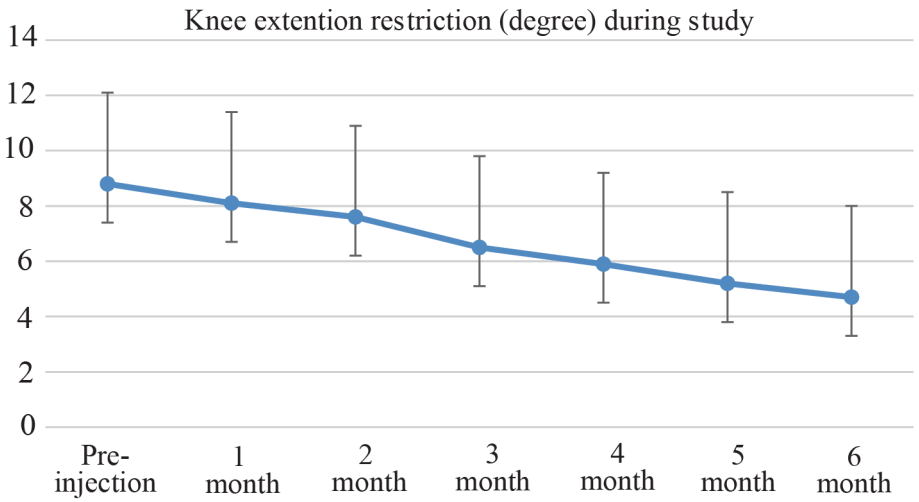

Figure 4. Comparison of knee extension restriction degree in patients before and after Rhenium-188 radiosynovectomy

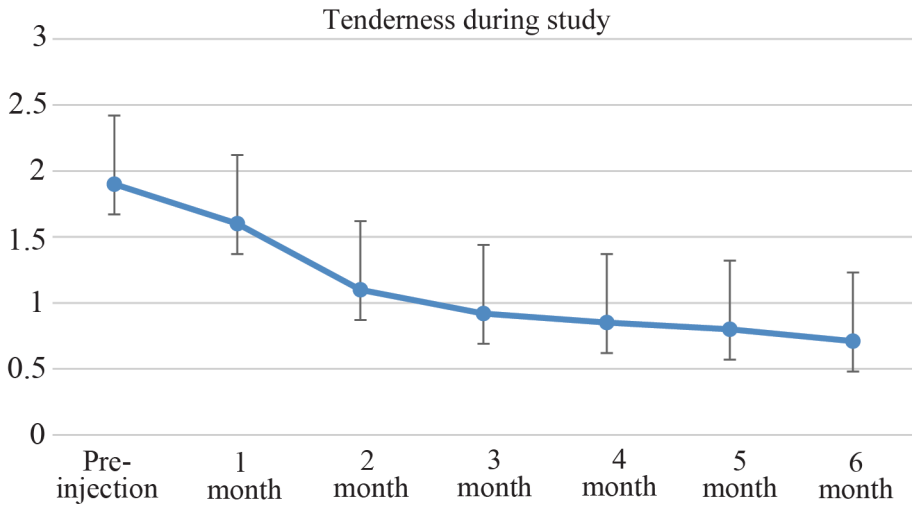

Figure 5. Comparison of knee tenderness in patients before and after Rhenium-188 radiosynovectomy.

Moreover, according to the comparison Table, there was a significant difference in knee joint function, joint volume, and joint line tenderness before and after the treatment.

Patients' satisfaction with radiosynovectomy

All patients had moderate-to-high satisfaction six months after the radiosynovectomy injection and demanded that the procedure be repeated if bleeding and pain recurred. 23.3% had moderate satisfaction, 56.7% had reasonable satisfaction, and 20% had perfect satisfaction.

Discussion

Radiosynovectomy is the local injection of radionuclide colloid into the joint, decreasing joint inflammation, joint pain, and knee range of motion. It can also decrease joint swelling by 60% to 80% approximately. This method was used by Fellinger *et al* for the first time (1,13). In 1952, this technique was approved for inflammatory joints, unresponsive to oral medications, and intra-articular corticosteroid injections. Three commonly used radionuclides are Yttrium-90 (half-life of 2.7 days and maximum beta energy of 2.2 *MeV*), Rhenium-186 (half-life of 3.7 days and maximum beta energy of 0.77 *MeV*), and Erbium-169 (half-life of about 9.6 days and maximum beta energy of 0.38 *MeV*), respectively, which in turn are used for large, medium-sized and small joints (14). Limited access to these

radiopharmaceuticals has made it difficult to use them. Rhenium-188 is an interesting radionuclide for radiosynovectomy, since it has a half-life of about 16.9 *hr*, beta energy of 2.1 *MeV*, and a penetration depth of 11 *mm*, which makes it a good candidate for knee and ankle radiosynovectomy (9). Rhenium-188 is transformed into stable Osmium-188 and releases a gamma energy of 155 *keV* for gamma imaging. Radiopharmaceutical leakage during Yttrium-90 and P-32 cannot be evaluated by dosimetry and gamma cameras because they do not have gamma radiation, and their emission is pure beta radiation. Considering this fact, evaluation of the radiopharmaceutical absorption and also its transmission in lymphatic tissue is possible. Besides, Rhenium-188 is produced in a Tungsten-188/Rhenium-188 generator which lasts for several months (15,16). In research on animal models with joint arthritis caused by ovalbumin, Rhenium-188 was reported to effectively improve the macroscopic score, histology, and joint diameter (18). In the first human trial of Rhenium-188, by Lee *et al*, on 21 patients with rheumatoid arthritis, improvement of the inflammatory status of the joints was described, and the radiopharmaceutical was well tolerated by patients (25).

In another human study, radiosynovectomy using Rhenium-188 in patients with treatment-resistant rheumatoid arthritis was described to be effective in terms of clinical and MRI results (26). Agnieszka Gazda *et al*, evaluated the use of radiosynovectomy in juvenile patients with idiopathic arthritis. The mean children age was 10.4. The study revealed the greatest clinical improvement in patients after RS (radiosynovectomy) was observed in the first 6 weeks after the procedure (23). In a study by Shamim *et al*, 61 knees in 48 patients with chronic inflammation, which was resistant to standard treatments, underwent radiosynovectomy using Rhenium-188, and the results were reported to be satisfactory (27). Kamaleshwaran *et al* have suggested that response to radiosynovectomy treatment using Rhenium-188 is more effective in patients with a shorter duration of illness, lower swelling, approximately normal radiography, more mobility, and less tenderness (28). In a study by Chew *et al* in Singapore on 12 hemophilia patients with 31 months of follow-up, they reported an 80% decrease in hemarthrosis and a reduction in the dose of factor 8 and the joint's pain (29).

In a study by Kachooei *et al* conducted on 20 joints (8 ankles, nine knees, two elbows, and one shoulder) of hemophilic patients, it was demonstrated that radiosynovectomy using Rhenium-188 is effective in the reduction of rest pain, frequency of bleedings, dose of factor, and synovium thickness. In this study, 20% of the patients had complications such as ecchymosis, swelling, warmth, and joint line tenderness, which were improved with rest and symptomatic treatment. One of these patients had skin reactions at the injection site, which was healed after six months (19). In a study by Liepe *et al*, 99 rheumatoid arthritis patients were treated using radiosynovectomy with Yttrium-90, P-32, and Rhenium-188, which 16% of the patients experienced swelling and an increase in pain after the injection (30).

In research by Tebib *et al*, side effects related to Rhenium-186, including pain, swelling, and skin rashes, was observed in 30% of the patients, which lasted more than 12 *hr* (31). In our study, a mild increase in pain was observed in 23% of the patients in the 24 first hours after injection, which was controlled using splint implantation and symptomatic treatment with NSAID. In other patients, radiopharmaceutical leakage was not observed using a gamma camera, and no infection and tenderness at the injection site were observed. A new clinical approach with the integration of clinical knowledge and experience to generalize the results of evidence-based clinical studies will have an essential role in the treatment and survival of patients (32-37). Also, increasing the level of patient's awareness of their disease and improving their level of self-care knowledge can reduce the complications and disabilities of this disease.

Conclusion

Our results suggest that the use of rhenium 188 has been effective in reducing the frequency of intra-articular bleedings, the amount of required factor, VAS for pain, swelling of the joint, and knee's range of motion in a small series of 30 patients in the short term (6 months follow-up).

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Conflict of Interest

There is no conflict of interest to be reported.

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