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ARAŞTIRMA YAZISI / RESEARCH ARTICLE

PEDİYATRİK HEMOFİLİKLERDE KRONİK SİNOVİT İÇİN YTTRIUM- 90 VE RHENIUM- 186 İLE RADYOİZOTOP SİNOVEKTOMİNİN UZUN SÜRELİ DEĞERLENDİRMESİ: AKDENİZ ÜNİVERSİTESİ DENEYİMİ

LONG-TERM EVALUATION OF RADIOISOTOPE SYNOVECTOMY WITH YTTRIUM-90 AND RHENIUM-186 FOR CHRONIC SYNOVITIS IN PEDIATRIC HEMOPHILIA: AKDENIZ UNIVERSITY EXPERIENCE

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ÖZET

AMAÇ: Bu çalışmanın amacı, kronik hemofilik sinoviti olan hastaların eklemlerinde Yttrium- 90 ve Rhenium- 186 ile radyoizotop sinovektominin etkisini değerlendirmektir.

GEREÇ VE YÖNTEM: Haziran 2005 - Eylül 2014 yılları arasında Akdeniz Üniversitesi Tıp Fakültesi`nde Yttrium- 90 ve Rhenium-186 ile radyoizotop sinovektomi yapılan pediyatrik hemofili hastalarımızın verileri geriye dönük olarak analiz edildi.

BULGULAR: Çalışmamızdaki 18 ağır hemofili hastasına (12,55 ± 4,93 yıl) uygulanan 32 radyoizotop sinovektomi işleminin; 13'ü (% 40,6) dirsek, 9'u (% 28,2) diz, 9'u (%28,1) tibiotalar ve biri (%3,1) de metatars eklemine yapıldı. Hastaların 10'unda (% 55,5) bir ekleme radyoizotop sinovektomi uygulandı. Aynı seansta birden çok ekleme uygulama yapılan beş (%27,8) hasta vardı ve eş zamanlı olarak en fazla iki ekleme uygulama yapıldı. İnhibitör pozitifliği olan üç hastaya toplam beş (% 15,6) işlem gerçekleştirildi. İşlem sonrası hastaların 15` inde (% 83,3) radyoizotop sinovektomi uygulanan eklemlerde kanamaların azaldığı ve izlemde tekrar bir cerrahi ya da radyoizotop sinovektomi uygulanması gerekmediği görüldü. Diğer üç hastanın dört eklemine ortalama 20,75 ±14,77 ay sonra ikinci kez uygulama yapıldı. Hastalarımızın ortalama izlem süresi 8,81 ± 4,87 yıldı [9,42 yıl (min-max; 1-22,58)]. Radyoizotop sinovektomi sırasında ve sonrasında kontrol altına alınamayan kanama, ek doz koagülasyon faktör tedavi ihtiyacı, radyoizotop sızıntısı, lokal enflamatuar reaksiyon gözlenmedi.

SONUÇ: Radyoizotop sinovektomi, hemartrozda kalıcı eklem hasarını önlemek, kanama sıklığını ve pıhtılaşma faktörü kullanımını azaltmak için kullanılabilecek etkin bir tedavi yöntemidir. Radyoizotop sinovektomi, ilerleyici eklem hasarı gelişmeden önce düşünülmelidir.

ANAHTAR KELİMELER: Hemofilik artropati, Radyoizotop sinovektomi, Kronik sinovit

ABSTRACT

OBJECTIVE: This study aimed to evaluate the effect of radioisotope synovectomy with Yttrium-90 and Rhenium-186 on the joints of patients with chronic hemophilic synovitis.

MATERIAL AND METHODS: Retrospective analysis of radioisotope synovectomy using Yttrium-90 and Rhenium-186 in pediatric hemophilia patients treated in the Akdeniz University School of Medicine between June 2005 and September 2014 was carried out.

RESULTS: Eighteen patients with severe hemophilia (mean age 12.55±4.93 years) underwent a total of 32 radioisotope synovectomy procedures: 13 elbow (40.6%), nine knee (28.2%), nine tibiotalar (28.2%), and 1 metatarsal (3.1%) joint. Ten patients (55.5%) had radioisotope synovectomy to a single joint; five patients (27.8%) had simultaneous radioisotope synovectomy to two joints. Three patients with inhibitors underwent a total of five radioisotope synovectomy procedures (15.6%). In 15 patients (83.3%), hemarthrosis was reduced after radioisotope synovectomy and no further treatment was required. The other three patients (four joints) underwent repeat radioisotope synovectomy after a mean of 20.75±14.77 months. The mean follow-up period of our patients was 8.81 ± 4.87 years [9.42 years (min-max; 1-22.58)]. Uncontrolled bleeding, need for additional dose factor treatment, radioisotope leakage, and local inflammatory reaction were not observed during and after radioisotope synovectomy.

CONCLUSIONS: Radioisotope synovectomy is an effective treatment method that can be used to prevent permanent joint damage in hemarthrosis and to reduce the frequency of bleeding and the use of coagulation factors. Treatment of radioisotope synovectomy should be considered before progressive joint damage has developed.

KEYWORDS: Hemophilic arthropathy, Radioisotope synovectomy, Chronic synovitis

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INTRODUCTION

Recurrent intra-articular bleeding is common in hemophilia and is regarded as the main cause of hemophilic arthropathy, which severely impairs patients' quality of life due to permanent joint damage (1). The articular cartilage has no blood supply; it is nourished via the synovial fluid produced by synovial tissue. Tissue factor has a key role in the extrinsic coagulation pathway, and its absence in the synovial tissue is a contributor to articular bleeding in hemophilia, in which the intrinsic system is impaired. In hemarthrosis, blood seeps into the joint and synovial cavity, triggering inflammation and causing synovitis. Repeated intra-articular hemorrhage induces an uncontrolled chronic inflammatory response and leads to chronic synovitis, which begins with synovial membrane proliferation and angiogenesis and leads to hemophilic arthropathy due to progressive cartilage and bone tissue damage (2).

The synovitis process is important in progressive arthropathy because various mediators released by the synovial tissue accelerate cartilage and joint damage. If synovitis is not treated at this stage, permanent joint damage is inevitable, even at a very young age. Medical treatment options for synovitis are very limited. Synovectomy is recommended in patients with chronic synovitis to prevent the development of major joint surface erosion that will lead to end-stage arthropathy (3 - 5).

In hemophilic arthropathy, synovectomy while still in the synovitis stage, before progression to end-stage hemophilic arthropathy, helps to reduce hemarthrosis frequency and bleeding severity. Synovectomy can be performed surgically or using nonsurgical methods involving arthroscopic injection of a radionuclide or chemical agent into the joint (1, 6). The radiopharmaceuticals used in radioisotope synovectomy (RS) aim to deliver a high dose of radiation to the thin layer of synovial cells lining the joint capsule to induce fibrosis of the subsynovial connective tissue and fragile and hypertrophic joint synovium, which cause frequent bleeding (3). The most affected joints are the knees, elbows, and ankles, which account for 80% of hemarthrosis episodes in patients with severe hemophilia (1). Yttrium-90 (Y-90) is used in large joints such as the knees, rhenium-186 (Re-186) colloid is used in joints such as wrists and elbows, and erbium-169 is used in smaller joints (5). RS is performed to reduce the frequency of bleeding in the target joint and to protect the cartilage and existing joint function before permanent damage occurs, and is an easy, inexpensive, minimally invasive procedure that can be performed in a short hospital stay and can be repeated when necessary (7 - 13). It is a valuable therapeutic option for preventing joint damage in countries with insufficient use of clotting factors for prophylaxis and treatment of bleeding. The aim of this study was to evaluate treatment responses and short- and long-term adverse effects in hemophilia patients who underwent RS in our center over a period of 14 years.

MATERIAL AND METHODS

Study Design and Patient Group

Of the 131 hemophilia patients who were followed up and treated in the pediatric hematology department of Akdeniz University between January 2005 and January 2021, those who underwent RS for hemophilic arthropathy were included in the study. When the data were evaluated, it was seen that RS was performed between June 2005 and September 2014. After this date, RS could not be performed because radionuclides could not be obtained in our country. Data pertaining to 32 RS procedures performed in 18 hemophilic patients were evaluated in this study.

If multiple RS procedures were performed in the same patient or the same joint, each procedure was recorded separately. Patient data were obtained from the hospital records system and department files.

Radioisotope synovectomy procedure

To analyze the effect of RS on hemarthrosis frequency, the number of bleeds in the target joint during the 12 months before and after each procedure was recorded.

Arthropathy was assessed according to the patient's age, based on the most recent X-ray (Pettersson score) and/or MRI (Denver MRI Scale) data together with clinical condition and exa-

mination findings by a committee comprising pediatric hematology, orthopedics, radiology, and nuclear medicine specialists in the hemophilia council. According to the council's decision, RS was performed in patients with joints that met the criteria for a target joint (≥ 3 bleeds in the last 6 months) and in whom RS was indicated for joints with hemophilic arthropathy. Informed consent was obtained before all RS procedures.

Patients with a score of 9 or 10 on the Denver MRI Scale were not considered suitable for RS due to the possibility of radionuclide leakage resulting from cartilage loss, and the decision was made to treat these patients surgically. The Denver MRI Scale is presented in **Table 1**(14).

Table 1: Denver MRI Scale

SCORE	FINDINGS
0=	Normal Joint
Effusion/Hemarthrosis	
1=	Mild
2=	Moderate
3=	Severe
Synovial hyperplasia/Hemosiderosis	
4=	Mild
5=	Moderate
6=	Severe
Cyst/Erosion	
7=	1 cyst or partial surface erosion
8=	1 cyst or full surface erosion
Cartilage loss	
9=	<50% cartilage loss
10=	>50% cartilage loss

Patient age, hemophilia type and severity, inhibitor presence, treated joint, number of bleeds in the treated joint within the 12 months before and after RS, need for repeated RS or surgical intervention in the treated joint, the radiopharmaceutical agent used, and side effects were recorded. Radionuclide dose was determined by the nuclear medicine specialist according to the patient's characteristics (age and weight) and the joint being treated. Y-90 (IBA, France) was used for knee joints and Re-186 colloid in ankle and elbow joints. The procedure was performed in sterile conditions by a nuclear medicine specialist and an orthopedist.

Ethical Committee

This retrospective observational study conducted in the hemophilic patient population was approved by the Akdeniz University Medical Faculty Clinical Research Ethics Committee (KAEK 117/10.02.2021).

Statistical Analysis

Statistical analyses were performed using IBM SPSS version 23.0 (IBM Corp, Armonk, NY). Numerical variables were expressed as mean ± standard deviation and categorical variables as number and percentage.

RESULTS

Patient Characteristics

A total of 32 RS procedures were performed on 18 patients in the pediatric hematology department of the Akdeniz University Faculty of Medicine during the 9-year period between June 2005 and September 2014. The last RS procedure was performed in 2014 because radionuclides could not be obtained.

The mean age of the patients in our cohort at the time of RS was 12.55 ± 4.93 years, and the median age was 11.5 years (range, 5.08 - 26.33 years). Of these 18 patients, 94.5% (n = 17) had severe hemophilia A, 5.5% (n = 1) had severe hemophilia B, and 16.7% (n = 3) had high inhibitor titers. Two of the patients with inhibitors had severe hemophilia A and 1 had severe hemophilia B.

RS was performed in a single joint in 10 patients (55.5%) and 2 joints in 5 patients (27.8%). The other 3 patients underwent 3, 4 and 5 RS procedures, respectively.

Five patients (28%) had multiple joints treated in the same session (maximum 2 joints treated simultaneously).

Characteristics of procedure and joints

The mean number of RS procedures per patient was 1.8 (range: 1-5). Of the 32 RS procedures, 13 (40.6%) were applied to the elbow, 9 (28.1%) to the knee, 9 (28.1%) to the tibiotalar, and 1 (3.1%) to the metatarsal joint.

Re-186 was used in 24 of the procedures (75%). Y-90 was preferred for the knee joint when available and was used in 8 procedures (25%). However, Re-186 was used in 2 procedures to the knee joint because Y-90 could not be obtained. Treatment response was achieved in 87.5% (n=28) of the treated joints and 83.3% (n=15) of the patients, and repeat surgery or RS

was not performed during the follow-up period. A second RS procedure was performed in 4 joints (14.3%) of 3 patients due to continued hemarthrosis episodes. The joints that underwent repeat RS were two ankles, one elbow, and one knee. The mean time to the second RS was 20.75 ± 14.77 months (median: 19 months, min-max: 6 - 39 months).

The 3 patients with inhibitors underwent RS in a total of 5 joints and none required retreatment during the follow-up period. The patients who underwent a second RS procedure did not have factor inhibitors.

No uncontrolled bleeding, need for additional doses of clotting factor, radionuclide leakage, or local inflammatory reaction were observed during or after RS. The patients' mean follow-up time was 8.81 ± 4.87 years (median: 9.42 years, min-max: 1 - 22.58). During the follow-up period, one patient was diagnosed with acute myelocytic leukemia 15 months after the RS procedure. Malignancy was not detected in any other patient during follow-up.

The characteristics of the patients are presented in **Table 2**.

Table 2: Characteristics of the patients and radiosynovectomy (RS) procedures

Patient	Diagnosis	Age at the time of RS (years)	Date of RS (DMY)	Joint	Radionuclide Used	
1	HA	12.9	01.06.2005	Left elbow	Re-186	
2	HA	7.66	10.03.2006	Right elbow	Re-186	
		8.75	13.04.2007	Left elbow	Re-186	
		10.91	19.06.2009	*Left elbow*¥	Re-186	*Concurrent administration*
		10.91	19.06.2009	*Right tibiotalar*	Re-186	
		11.91	25.06.2010	Right tibiotalar¥	Re-186	
3	HA	6.83	10.03.2006	Right tibiotalar	Re-186	
		7.91	13.04.2007	Left tibiotalar	Re-186	
		10.08	19.06.2009	Right tibiotalar¥	Re-186	
		10.58	11.12.2009	Right first metatarsal	Re-186	
4*	HA	26.3	20.04.2007	Left elbow	Re-186	
5	HA	9.08	02.11.2007	Right knee	Re-186	
6	HA	11.75	02.11.2007	*Right elbow*	Re-186	*Concurrent administration*
		11.75	02.11.2007	*Right tibiotalar*	Re-186	
7	HA	5.08	02.11.2007	Right elbow	Y-90	
8	HB*	12.33	31.10.2008	Left tibiotalar	Re-186	
		14.33	01.10.2010	Right knee	Y-90	
9	HA	19	11.12.2009	Left elbow	Re-186	
10	HA	16	11.12.2009	Right elbow	Re-186	
11	HA	16.41	11.12.2009	Right elbow	Re-186	
12	HA	10.91	11.12.2009	*Right elbow*	Re-186	*Concurrent administration*
		10.91	11.12.2009	*Right tibiotalar*	Re-186	
13	HA	26.33	24.09.2010	Left knee	Y-90	
14	HA	17.75	01.10.2010	*Right knee*	Y-90	*Concurrent administration*
		17.75	01.10.2010	*Left knee*	Y-90	
15	HA	11.5	16.12.2011	Left knee	Re-186	*Concurrent administration*
		11.5	16.12.2011	Right elbow	Re-186	
		12	29.06.2012	Left knee¥	Y-90	
16*	HA	8.08	29.02.2010	*Right knee*	Y-90	*Concurrent administration*
		8.08	29.02.2010	*Left knee*	Y-90	
17	HA	9.83	16.11.2012	Right tibiotalar	Re-186	
18	HA	16.75	19.09.2014	Right elbow	Re-186	

HA: Hemophilia A, **HB:** Hemophilia B, **DMY**: Day.Month.Year format, *: Inhibitor-positive, ¥: Joint undergoing repeat RS

DISCUSSION

Hemophilic arthropathy involves joint swelling, cartilage and bone damage, and the eventual development of osteoarthritis in the joint due to recurrent hemarthrosis (15). Early primary prophylaxis is the only approach that prevents arthropathy in hemophilia (16). Therefore, although early primary prophylaxis is the gold standard in hemophilia treatment to prevent joint damage caused by the effect of blood on the synovium and chondrocytes, it is not always an appropriate treatment or the most cost-effective treatment in the case of patients with inhibitors (3). Despite the fact that clotting factor products are covered by social insurance in Turkey, the development of hemarthrosis is common due to reasons such as treatment noncompliance, late initiation of treatment, or presence of inhibitors.

In synovitis, many mediators released by the synovial tissue trigger progressive arthropathy by accelerating cartilage and joint damage (6, 7). If synovitis cannot be treated in the early stage, permanent joint damage and disability at a young age is unavoidable in patients with hemophilia. A similar clinical presentation of chronic synovitis is seen in patients with rheumatoid arthritis. Five decades of experience using RS to treat this debilitating condition was transferred to the hemophilia population and due to the promising results, RS has been used as the current treatment method for chronic hemophilic synovitis since 2000 (8).

RS aims to reduce the chronic synovitis and recurrent hemarthrosis episodes that will eventually cause joint degeneration (hemophilic arthropathy) by injecting a radionuclide substance into the joint.

In patients who have two or more hemarthrosis episodes in the same joint within a period of six months, RS should be performed in experienced hemophilia centers as soon as possible after demonstrating chronic synovitis findings in the joint by synovitis MRI and/or ultrasound. RS can be repeated in patients who have two or more episodes of hemarthrosis within six months after the procedure. Treating recurrent articular bleeding early with clotting factor con-

centrates at an appropriate dose and frequency is of crucial importance. MRI is routinely used to detect joint damage and stage hemophilic arthropathy, to determine indication for RS, and to monitor treatment response (14, 17).

RS has several advantages compared to surgical synovectomy. It is an attractive treatment option for hemophilic patients with hemarthrosis because it is minimally invasive and easy to perform, does not require a long hospital stay, preserves joint range of motion, creates less need for additional doses of clotting factor concentrate, and offers a short rehabilitation period (9). In addition, as costs are highly dependent on length of hospital stay and need for clotting factor products, RS is less costly than surgical synovectomies (3). Considering the postoperative side effects, cost, and quality of life improvement, RS is regarded as an alternative to surgical synovectomy (1, 3). Erken et al. (18) published their results using Y-90 and reported no further bleeding episodes in 13 of 58 knee joints with hemophilic arthropathy at the end of the 7-year follow-up period. During the follow-up of these patients, the mean frequency of bleeding in the treated joints decreased from 4 per month to 2 per year. RS was reported to (12, 13) completely stop bleeding in 15% and reduce the number of bleeds in 80% of hemophilic patients over long-term follow-up.

Querol-Giner et al. (1) evaluated 174 RS procedures in 71 patients and showed that the number of bleeds before RS was 582 and decreased to 168 after the procedure ($P < 0.001$), whereas in patients who did not undergo RS, significant progression of arthropathy was observed in every joint ($P < 0.05$). Alioglu et al. (19) performed 37 RS procedures in the joints of 18 severe hemophilic patients with grade II or III synovitis and showed that the number of bleeds in ankle and elbow joints decreased significantly. None of the patients had major post-RS complications that required treatment.

Rodriguez-Merchan et al. (20) performed 500 RS procedures in 443 joints of 345 hemophilia patients diagnosed with chronic synovitis over a period of 38 years (1976 - 2013). They reported mean reductions of 64.1% in the number of hemarthrosis episodes, 69.4% in joint pain, and 31.3% in synovitis grade. Koç et al. (21) performed RS in 51 joints of 22 inhibitor-positive hemophilia patients diagnosed with chronic hemophilic synovitis and reported that the mean frequency of bleeds in the treated joints decreased from 11.2 ± 6.2 (median: 9) during the 6 months before RS to 1.2 ± 2.8 (median: 0) in the first 6 months after RS ($P < 0.0001$). Their study (21) demonstrated that RS is an effective and safe intervention in hemophilia patients with inhibitors. In addition, they observed that the success rate of RS was lower in patients with more than 12 bleeding episodes within the last 6 months before the RS procedure. In the present study, bleeding control was achieved safely and effectively using bypassing agents in 5 different joints of 3 patients with inhibitors. No complications were observed in any of the procedures and no additional doses of clotting factors were required to ensure bleeding control. Furthermore, these patients did not need surgery or repeated RS in the treated joints during follow-up.

Kavaklı et al. (4) performed 105 RS procedures (56 knees, 24 elbows, 23 ankles, and 2 shoulder joints) on 65 patients (53 with severe hemophilia A, 12 with severe hemophilia B) in 4 years and used Y-90 for all joints. The patients had a mean age of 15 years and were followed for 2 years (range, 6 months - 3.5 years) after RS. Ten of the patients who underwent RS had high-titer inhibitors and RS was performed in 17 different joints in these patients. After 2 years of post-RS follow-up, all patients were evaluated and it was found that all of the treated joints improved significantly, with an 83% reduction in bleeding frequency. Successful outcomes were also achieved in the patients with inhibitors. In another study by Kavaklı et al. (11) a total of 63 RS procedures using Re-186 were performed in 49 patients. While the team always preferred Y-90 for knee joints, with this study they demonstrated the efficacy and reliability of Re-186 for mid-sized joints (elbow, ankle, and shoulder).

RS was performed on 32 joints in our center and there were no complications during or after the procedures. The mean follow-up time for our patients was 8.81 ± 4.87 years (median: 9.42

years, range: 1 - 22.58 years). No complications were observed during follow-up. The number of bleeds in the target joint decreased by at least 50% in all patients.

While RS appears to be a safe and simple therapeutic option in hemophilic synovitis, exposure to ionizing radiation is known to potentially cause chromosomal abnormalities, especially in young children. Although there have been recent reports of patients developing acute lymphoblastic leukemia within 1 year after RS, a causal relationship could not be established in these cases due to the presence of autoimmunity, radiation exposure, and the short interval to malignancy. Regarding chromosomal changes after RS, several authors showed that the doses of genotoxic radiation to the peripheral lymphocytes were not statistically significant. The available literature on the long-term cancer risk is limited; however, a retrospective study (22) including 2412 adult patients treated with RS revealed no increase in cancer risk compared to the general population. One of our patients developed acute myelocytic leukemia, but it is very difficult to determine the causal relationship between radionuclide substance use and malignancy.

No acute complications were observed in our patients due to the RS procedure, and no additional doses of medication were required to control bleeding, which is consistent with the literature.

During the period in which we were not able to procure Y-90 for knee joints, we used Re-186 in two knee joints and had to repeat RS with Y-90 in one of these joints. However, the treatment response in the other patient was sufficient. While the use of Y-90 for large joints and Re-186 for medium to small joints is ideal in RS, due to problems obtaining the ideal radionuclide, the procedure can be performed using other available substances at suitable doses to reduce hemarthrosis frequency.

By decreasing the frequency of bleeding, RS not only lowers costs associated with clotting factor products but also benefits the patient by reducing hospital length of stay, chronic joint sequelae, and the need for orthopedic surgery later in life. Decreasing the frequency of bleeding episodes and preventing joint injuries will significantly increase the quality of life among hemophilic individuals and their social environment.

In conclusion, RS appears to be useful in reducing bleeding in hemophilic patients, including those with inhibitors, when administered before the appearance of signs of advanced hemophilic arthropathy.

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