ORIGINAL RESEARCH ORİJİNAL ARAŞTIRMA

DOI: 10.5336/medsci.2023-99918

Twenty Years of Experience; Hemophilic Arthropathy Rates and Correlation with Treatment Modalities: Ege Hemophilia Council Data. A Single-Center Experience Among 583 Turkish Patients: A Cohort Study

Yirmi Yıllık Tecrübe; Hemofilik Artropati Oranları ve Tedavi Yöntemleriyle İlişkisi: Ege Hemofili Konseyi Verileri. 583 Türk Hastada Tek Merkez Deneyimi: Kohort Çalışması

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ABSTRACT Objective: This study aims to investigate the evolving landscape of hemophilia care over two decades, focusing on patients with hemophilic arthropathy. We analyze demographic shifts, treatment patterns, and their impact on patient outcomes, providing insights into the challenges and progress in managing this rare but debilitating disorder. **Material and Methods:** Data from the Ege Hemophilia Joint Council spanning 20 years, covering 583 patients, were examined. Patient demographics, treatment patterns, and outcomes were comprehensively evaluated. The analysis involved descriptive statistics, comparative analyses, regression models, subgroup assessments, and temporal trend visualizations. **Results:** Demographically, the study revealed an increasing average age of patients, with a predominant male population. Hemophilia A and B patients, primarily those with severe cases, were the focus of the study, with 10% of patients having inhibitors. The Ege Hemophilia Joint Council's reach extended to patients from across Türkiye. Prophylactic treatment witnessed a rising trend, particularly in the last decade. Joint complications, especially knee issues, remained a primary concern, with emerging trends in ankle involvement and decreasing elbow complications. Use of orthopedic aids declined, indicating improved care. **Conclusion:** This research highlights the importance of tailored care, prophylaxis, and timely orthopedic interventions in managing hemophilic arthropathy. The Ege Hemophilia Joint Council serves as a national center for comprehensive care. While progress is evident, the study emphasizes the ongoing commitment needed to ensure accessible and effective treatment, reducing the impact of hemophilic arthropathy on patients' lives.

Keywords: Hemophilia A; hemophilia B; radioisotopes; joint diseases; arthritis

ÖZET Amaç: Bu çalışma, hemofilik artropatili hastalara odaklanarak, hemofili bakımının 20 yıl boyunca gelişen manzarasını araştırmayı amaçlamaktadır. Çalışma; demografik değişiklikleri, tedavi modellerini ve bunların hastalar üzerindeki etkilerini analiz ederek, bu nadir fakat yıpratıcı hastalığın yönetimindeki zorluklara ve ilerlemeye ilişkin içgörüler sağlamaktadır. **Gereç ve Yöntemler:** Ege Hemofili Ortak Konseyi'nin 20 yıllık 583 hastayı kapsayan verileri incelendi. Hasta demografik özellikleri, tedavi modelleri ve sonuçları kapsamlı bir şekilde değerlendirildi. Analiz, tanımlayıcı istatistikleri, karşılaştırmalı analizleri, regresyon modellerini, alt grup değerlendirmelerini ve zamansal eğilim görselleştirmelerini içeriyordu. **Bulgular:** Demografik olarak, çalışma, erkek nüfusun ağırlıklı olduğu, hastaların ortalama yaşının arttığını ortaya çıkardı. Hemofili A ve B hastaları, özellikle de ciddi vakaları olan hastalar, çalışmanın odak noktasıydı; hastaların %10'unda inhibitör vardı. Ege Hemofili Ortak Konseyi'nin erişimi Türkiye'nin her yerinden hastalara ulaştı. Profilaktik tedavi, özellikle son 10 yılda artış eğilimine girmiştir. Eklem komplikasyonları, özellikle de diz sorunları, ayak bileği tutulumunda ortaya çıkan eğilimler ve dirsek komplikasyonlarının azalmasıyla birlikte birincil endişe kaynağı olmaya devam etti. Ortopedik yardımların kullanımı azaldı, bu da bakımın iyileştiğine işaret etmektedir. **Sonuç:** Bu araştırma, hemofilik artropati tedavisinde kişiye özel bakım, profilaksi ve zamanında ortopedik müdahalelerin önemini vurgulamaktadır. Ege Hemofili Konseyi, kapsamlı bakım için ulusal bir merkez olarak hizmet vermektedir. Bu çalışma, hemofilik artropatinin, hastaların yaşamları üzerindeki etkisini azaltarak, erişilebilir ve etkili tedaviyi sağlamak için gereken kararlılığı vurgulamaktadır.

Anahtar Kelimeler: Hemofili A; hemofili B; radyoizotop; eklem hastalıkları; artrit

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Peer review under responsibility of Turkiye Klinikleri Journal of Medical Sciences.

Received: 17 Oct 2023 ***Accepted:*** 26 Nov 2023 ***Available online:*** 30 Nov 2023

Hemophilia is an inherited bleeding disorder that results from a complete or partial deficiency of blood coagulation factors, affecting approximately one in 10,000 individuals and estimated to impact 400,000 people worldwide.[1-5] It is classically characterized by a propensity for bleeding, with the specific bleeding sites varying with age, including intra-articular, intramuscular, central nervous system, oral mucosal, and intranasal bleeding, as well as hematuria. Patients often experience recurrent bleeding episodes, and the severity of these attacks, along with the effectiveness of treatment, determine the extent of complications and morbidities.[1-5]

The primary objective of hemophilia treatment is to restore the functionality of the secondary hemostasis process by replacing the missing Factor VIII (FVIII) in blood coagulation factors. This approach aims to reduce the duration and frequency of bleeding episodes, minimize complications resulting from recurrent bleeding, and enhance the overall quality of life for patients.[6] Joint bleeding (hemarthrosis) is the most prevalent clinical manifestation in children and adults with severe hemophilia (plasma FVIII or FIX levels <1 U/dL). Nevertheless, joint issues can also occur, albeit less frequently, in individuals with moderate (FVIII levels 1-5 IU/dL) or mild hemophilia (FVIII levels >5 IU/dL).[1-5] Intra-articular hemorrhages can manifest from infancy when a child starts to move independently, and as the child begins to walk, bleeding episodes frequently affect weight-bearing knee and hip joints, particularly in the ankles. Intra-articular bleeding represents one of the primary challenges that significantly impact the quality of life for individuals with hemophilia.[1-5]

Over the last 2 decades, therapeutic advancements have markedly enhanced the life expectancy and quality of life for hemophilia patients. The increased accessibility of factor concentrates has led to the widespread adoption of prophylaxis treatment. These developments have shifted the focus of treatment from merely extending life expectancy to primarily preventing joint damage and safeguarding against intra-articular bleeding and hemophilic arthropathy.

In light of these therapeutic advancements and the shift toward prophylaxis treatment, we hypothesize that the reduction in the frequency of bleeding episodes and the focus on preventing joint damage will lead to a substantial improvement in the overall quality of life for patients with hemophilia.

MATERIAL AND METHODS

DATA COLLECTION

This study was designed to comprehensively evaluate the official records of the Ege Hemophilia Joint Council spanning two decades, from December 2000 to January 2021. The dataset under examination comprised 583 patients, while the study encompassed a total of 1,580 patient records over this 20-year timeframe, taking into account the contributions of the Hemophilia Council.

To supplement the official council minutes, efforts were made to cross-reference this data with patient records from various clinical departments, including pediatric hematology, orthopedics, physical therapy, and nuclear medicine. Additionally, retrospective analysis of joint-related data from the Ege Hemophilia Center, established at our hospital with approval from the European Union, was carried out by scanning patient files.

The study was conducted in accordance with the principles of the Helsinki Declaration.

DATA PARAMETERS

The examination covered a wide array of patient characteristics and medical information, including but not limited to gender, age at the time of council application, date of birth, diagnosis, date of council registration, factor levels, disease severity, inhibitor status, the hospital followed, hematologist involvement, the city where patients sought council services, social security status, current treatment protocols, concurrent medical conditions, the number of existing arthropathies, problematic target joints, council decisions, implementation status of council decisions, and the utilization of assistive devices.

OUTCOME MEASURES

Evaluation of the council decisions, which encompassed medical treatment, intra-articular isotope applications, and orthopedic joint operations, was a key

focus. Realization rates for these interventions were considered as well.

DATA ANALYSIS

The data collected for this study underwent a rigorous analytical process to investigate trends, associations, and changes over the specified two 10-year periods.

DESCRIPTIVE STATISTICS

We employed descriptive statistics to provide a comprehensive overview of the patient population. This included summary statistics such as mean, median, standard deviation, and percentages for variables like age at council application, factor levels, disease severity, and more.

COMPARATIVE ANALYSES

To explore significant differences between the two 10-year periods, we utilized several statistical tests:

t-tests: We employed independent samples t-tests to compare continuous variables, such as age at council application, between the two time periods.

Chi-squared tests: We employed chi-squared tests for categorical variables, investigating differences in gender distribution, inhibitor status, and other categorical variables.

Outcome measures: We assessed the realization rates of actions taken by the council, including medical treatment, intra-articular isotope applications, and orthopedic joint operations. We calculated success rates for medical therapy and examined the impact of these decisions on patient outcomes.

Hypothesis testing: To test the hypothesis that recent years have seen improvements in patient outcomes due to increased prophylaxis usage, we used regression models to assess the relationships between various independent variables (e.g., prophylaxis usage, patient age, and surgical interventions) and dependent variables (e.g., joint injuries and the average age at council application).

Subgroup analyses: To gain insights into specific patient groups, we conducted subgroup analyses based on factors such as disease severity, inhibitor status, and the presence of existing arthropathies.

Temporal trends: We plotted temporal trends using graphical representations to visualize changes in patient demographics, treatment approaches, and clinical outcomes over the two decades.

The aim of our detailed data analysis was to explore how the evolution of hemophilia care and the adoption of prophylaxis have influenced patient outcomes, demographic changes, and the need for surgical interventions. We utilized a combination of descriptive statistics, comparative analyses, regression models, and subgroup analyses to provide a comprehensive understanding of the data. This allowed us to rigorously test our hypothesis and draw meaningful conclusions from the study.

HYPOTHESIS

Our hypothesis centers on the last decade of this study, positing that in recent years, all hemophilia patients in our country have achieved social security coverage. Furthermore, it suggests that the increased utilization of prophylaxis opportunities has resulted in a substantial reduction in joint injuries among patients, an appreciable increase in the average age of council applications, and variable shifts in the demand for orthopedic surgeries.

INCLUSION CRITERIA

Patients diagnosed with similar factor deficiencies such as hemophilia A, hemophilia B, or von Willebrand disease. Patients, regardless of age, who exhibit both inhibitor-positive and inhibitor-negative statuses. Patients seeking services at the Ege Hemophilia Joint Council due to joint-related complaints and similar conditions.

EXCLUSION CRITERIA

Patients with blood disorders other than hemophilia and related factor deficiencies. Patients who have not undergone evaluation at the Ege Hemophilia Council.

RESEARCH ETHICS STANDARDS COMPLIANCE

Our study was approved by Ege University Medical Research Ethics Committee at date October 7, 2021 and no. 21-10T/37. Informed consent was obtained from all subjects participating in our study.

RESULTS

Over the last two decades, a total of 1,580 patient records were reviewed at the Ege Hemophilia Council, with 583 unique patients accessing care during this period. The majority of patients were male (551 patients, 95%), while female patients represented a smaller proportion (32 patients, 5%). The mean age of the patients was 23.6±12.4 years, with a median age of 22 years and an age range spanning from 0.5 to 68 years. Notably, the mean age differed between the two 10-year periods, with the first decade exhibiting an average age of 19±9 years and the last decade showing an average age of 26±13 years.

Regarding patient diagnoses, the most prevalent conditions were hemophilia A (n=426, 73.1%) and hemophilia B (n=81, 13.9%). Subsequent diagnoses included von Willebrand disease (n=17, 2.9%) and rare factor deficiency (n=15, 2.6%). Additionally, 44 patients (7.5%) were assessed in the council but were not included in the study due to joint synovitis resulting from rheumatological reasons and subsequent intra-articular isotope administration (Table 1).

When evaluating factor levels in hemophilia patients, approximately 24.5% of the patients exhibited factor levels less than 1%, while 69.1% had factor levels at 1%. Altogether, 93.6% of the patient group had factor levels at or below 1%. Patients with mild hemophilia, characterized by factor levels exceeding 5%, comprised a mere 0.2%, while those with factor levels between 1% and 5% accounted for 6.2%.

The presence of inhibitors was noted in 10% of the entire patient group (60/583). However, when specifically considering hemophilia A patients, this rate was 13.4%.

The majority of patients (58%) were referred to the council from Ministry of Health Hospitals, while 42% came from University Hospitals. Notably, while 35% of patients accessed the child and adult departments at Ege University, the remaining 65% came from outside Ege University.

In terms of patients' geographical origins, 31.7% came from İzmir, and 56.5% were from the entire Ege Region. The remainder hailed from Anatolian cities.

The study observed that 72.6% of patients who sought council services due to joint complaints opted for an on-demand treatment approach, while 27.4% opted for prophylaxis. Comparing the two 10-year periods, the rate of patients choosing prophylaxis increased from 23.5% in the first decade to 31.6% in the last decade (Table 2).

Among non-hemophilic orthopedic problems in hemophilia patients, pes planus (n=12) and Perthes disease (n=6) were the most common. Besides hemophilic arthropathy, 94% of patients exhibited no signs of additional diseases.

Knee joints were the most commonly affected target joints in patients presenting with joint complaints, representing 58.3% in the first 10-year period and subsequently decreasing to 56.9%. Ankle joints (17.9% after 24.5%) and elbow joints (19.4% after 10.2%) followed (Table 3).

The presence of target joints in more than one joint was noted in 25.2% of patients, while 73.7% had a single target joint, and 1.1% had no target joint. In the inhibitor group, 69.8% had a single target joint, and 24.4% had two target joints.

The use of assistive orthopedic devices, such as crutches or wheelchairs, was observed in 2.9% of pa-

TABLE 1: Diagnosis distribution of the patients.

	n	f (%)
Hemophilia A	426	73.1
Hemophilia B	81	13.9
Non hemophilia isotope group	44	7.5
Von willebrand disease	17	2.9
Rare factor deficiencies	15	2.6
Total	583	100

TABLE 2: Treatment distribution of the patients.

		n	f (%)
2000-2010	Episodic (on-demand)	228	76.5
	Prophylaxis	70	23.5
2011-2021	Episodic (on-demand)	195	68.4
	Prophylaxis	90	31.6
Total	Episodic (on-demand)	423	72.6
	Prophylaxis	160	27.4

TABLE 3: Target joint distribution of the patients.

		n	f (%)			n	f (%)
Knee	2000-2010	334	51.1	Elbow	2000-2010	100	15.3
	2011-2021	471	50.9		2011-2021	81	8.7
	Total	805	50.9		Total	181	11.5
Ankle	2000-2010	95	14.5	Hip	2000-2010	6	0.9
	2011-2021	204	22		2011-2021	41	4.4
	Total	299	18.9		Total	47	3
Other	2000-2010	111	17	Shoulder	2000-2010	8	1.2
	2011-2021	121	13.1		2011-2021	8	0.9
	Total	232	14.7		Total	16	1

tients (n=19) during the first 10-year period, decreasing to 0.6% (n=6) in the subsequent decade.

Upon council evaluation, 402 patients were recommended for medical treatment. In cases where intra-articular isotope application was deemed suitable, it was successfully completed in 81.8% of patients. Notably, only 46.3% of patients receiving a major operation recommendation underwent the planned procedure (Table 4).

The success rate for medical treatment was 50.2%, with radioisotope synovectomy performed in 21.9% of patients who did not experience success, while major orthopedic operation was conducted in 27.9% of these cases (Table 5).

Of the 224 patients who underwent intra-articular radioisotope application, 222 were male (99.1%), while 2 were female (0.9%). Examination of the distribution of patient diagnoses revealed that 181 (80.8%) had hemophilia A, 35 (15.6%) had hemophilia B, 4 (1.8%) were diagnosed with von Willebrand disease, and 4 (1.8%) had rare factor deficiencies. Among these patients, 22 (9.8%) were inhibitor-positive, and 202 (90.2%) were inhibitor-negative (Table 6).

Between 2000 and 2018, a total of 581 intra-articular radioisotope applications were performed on 224 patients. The joints subjected to radioisotope application were predominantly knee joints (336 joints,

TABLE 4: Council decisions and the implementation rates.

	Implementation	n	f (%)	n	f (%)
Medical	Yes	402	100	402	25.44
Minor operation (radioisotope)	Yes	443	81.89	541	34.24
	No	68	12.57		
	No drugs	30	5.54		
Major operation (orthopedic operation)	Yes	295	46.31	637	40.32
	No	342	53.69		

TABLE 5: Success rates of the council decisions.

		n	f (%)	n	f (%)
Medical treatment only		202	50.2	202	50.2
Medical treatment & radioisotope/operation	Radioisotope	88	21.9	200	49.8
	Operation	112	27.9		
Total		402	100	402	100

TABLE 6: Rates of intraarticular radioisotope administration in the last twenty years.

		n	f (%)
Gender distribution	Male	222	99.1
	Female	2	0.9
Diagnosis distribution	Hemophilia A	181	80.8
	Hemophilia B	35	15.6
	Von Willebrand disease	4	1.8
	Rare factor deficiencies	4	1.8
Inhibitory status	Positive	22	9.8
	Negative	202	90.2
Total patient		224	100
Joint distribution	Knee	336	57.8
	Elbow	133	22.9
	Ankle	103	17.7
	Shoulder	8	1.4
	Wrist	1	0.2
Total joint		581	100

57.8%), followed by elbow joints (133 joints, 22.9%), ankle joints (103 joints, 17.7%), shoulder joints (8 joints, 1.4%), and wrist joints (1 joint, 0.2%) (Table 6).

The age distribution of patients receiving intra-articular radioisotope application ranged from 3 to 58 years, with an average age of 15. Notably, 32 patients aged below 10 years underwent the procedure.

DISCUSSION

Hemophilia is a rare condition, affecting 1 in 10,000 individuals, with approximately 2,500 severe hemophilia patients in our country. This study examined data from 583 hemophilia patients, representing nearly 20-25% of hemophilia cases in our country, based on a total of 1,580 council sessions. The data collected from patients attending the Ege University Hemophilia Council due to joint issues holds valuable insights in terms of "national representation".[1-5]

In the context of demographic data from council participants, it is noteworthy that 94.5% of these individuals are male. This predominance of male patients is consistent with the X-linked recessive inheritance pattern of hemophilia A and B, which are primarily associated with arthropathy and other joint issues.[1,2,6,7]

The increasing prevalence of prophylaxis in childhood is a notable trend in our country, reducing joint complications and delaying the onset of joint problems until later in life. Analysis of the age distribution among patients seeking council services reveals a shift, with the average age increasing from 19±9 in the first decade to 26±13 in the last decade. This observation supports our hypothesis that the age at which arthropathy develops is rising, resulting in fewer cases among children.[8-12]

The overwhelming majority (87%) of council patients present with hemophilia A and B, underscoring that arthropathy and other joint issues are predominantly a concern for this group, as opposed to patients with von Willebrand disease and rare factor deficiencies.[1,2,5,13] This finding is consistent with the results of Fisgin and colleagues.[14]

Patients with factor levels of 1% or lower in hemophilia A and hemophilia B make up 93% of council patients, aligning with the traditional understanding that severe arthropathy is expected in this group. However, it is noteworthy that arthropathy may also be anticipated in some moderate hemophilia patients with factor levels ranging from 1% to 5%, given that nearly all council patients are either moderate or severe hemophilia cases.[1,2,5,13]

When assessing all council patients, 10.3% are found to be inhibitor-positive. Previous studies indicate a 10% prevalence of inhibitors in our overall hemophilia population, which aligns with the prevalence observed in council patients and underscores the representativeness of our patient group for the national hemophilia population.[15-23] This concurs with the results obtained by Koc et al.[23]

Analysis of patient referrals to the Ege Hemophilia Council indicates that patients come from 48 different cities across Türkiye, with 31.7% of patients originating from İzmir and 56.5% from the Aegean region. These numbers demonstrate the extensive reach of the Ege Council, which accommodates patients from across the country.[15]

Regarding treatment concepts, it is observed that 72.6% of patients with arthropathy receive on-demand treatment, while 27.4% are on prophylactic treatment. Furthermore, the data shows a rise in the

proportion of patients receiving prophylaxis over the years, suggesting a positive trend in prophylaxis adoption. However, in the context of international data, it is apparent that many of our patients are not utilizing this opportunity, potentially due to the absence of joint complaints among those benefiting from prophylaxis.[9-12]

Prophylactic treatment, considered the "gold standard" in hemophilia care, remains underutilized, despite being fully reimbursed by the state. Consequently, many patients who do not employ prophylaxis continue to present at the joint council, underscoring the critical importance of prophylaxis in preventing joint complications.[6,23]

The distribution of patients referred to the Ege Hemophilia Council reveals a considerable proportion (58%) coming from state hospitals. Notably, around 42% of patients are referred from university hospitals across Anatolia. The diversity in the geographic origin of patients underlines the council's role as a national network, as it can provide intra-articular radioisotope synovectomy and perform all elective major orthopedic surgeries.[24]

Examining the distribution of patients attending the council over the last 20 years, it is evident that one-third of patients are referred from Ege University, while the remaining two-thirds come from external institutions. This information reaffirms our belief that the Ege Hemophilia Joint Council caters to the entire country.[3-5]

The concept of target joints holds significant importance in hemophilia management, signaling the early signs of permanent joint disability. In this study, the knee joint has consistently been the most affected target joint, a phenomenon attributed to its high synovial tissue content. Recent Western publications have highlighted an increasing prominence of ankle joint involvement, a trend reflected in our data, with ankle joint arthropathy rising from 17.9% to 24.5% in recent years.[25]

Moreover, our analysis reveals a decrease in elbow joint involvement from 19.4% to 10.2%. It is important to note that the presence of multiple target joints is not surprising in patients where appropriate treatment was unavailable.[26-32]

Looking at the application of orthopedic aids, we have witnessed a decline in their use among patients attending the council in recent years, reflecting the improving quality of treatment and care practices.[33-35]

Patients with hemophilia and joint issues from all corners of our country seek assistance from the Ege Hemophilia Council. In cases of mild arthropathy in children, medical treatment in the form of prophylaxis is often sufficient. As arthropathy advances, intra-articular radioisotope synovectomy is the preferred treatment. For advanced-stage arthropathies, joint prosthetic surgeries are performed as the final option.[21-23]

While radioisotope synovectomy was planned for approximately 50 joints in 30 arthropathy patients in the last 3 years, its implementation was hindered due to issues with isotope importation. As a result, many patients had to undergo more intensive medical treatment or major orthopedic procedures, such as arthroscopic or open synovectomy.[21-23]

In conclusion, the findings of this study reinforce the importance of tailored care, prophylaxis, and prompt orthopedic interventions in preventing and managing hemophilic arthropathy. By providing a comprehensive analysis of patient demographics and treatment patterns, this research contributes valuable insights that can inform future improvements in hemophilia care. The high representation of patients across the country highlights the pivotal role of the Ege Hemophilia Council as a national center for comprehensive hemophilia care.

LIMITATION OF THE STUDY

This research conducted a retrospective evaluation; nonetheless, the extensive twenty-year dataset, specifically focused on individuals with hemophilia and joint complications, effectively captured and represented the prevalence of joint issues among hemophilia patients in Türkiye.

CONCLUSION

This comprehensive analysis of 2 decades of data on hemophilia patients with joint complications underscores the critical importance of proactive and acces-

sible medical care in the management of this rare but debilitating disorder. The findings reveal an evolving landscape of hemophilia care, marked by shifting demographics, improved prophylaxis rates, and the ongoing challenges posed by inhibitor-positive patients. The data further highlight the fundamental role of early intervention, prophylactic treatment, and a multidisciplinary approach in mitigating hemophilic arthropathy and enhancing the quality of life for affected individuals.

Notably, this research reflects the significance of the Ege Hemophilia Joint Council as a nationwide beacon of hope for patients hailing from all regions of Türkiye. The center's holistic approach, offering both medical and orthopedic interventions, illustrates the impact of consistent access to a comprehensive range of treatment options in reducing joint complications. Furthermore, the study raises awareness of the ongoing challenges surrounding inhibitor management, stressing the need for accessible and affordable prophylactic regimens to ensure the longevity of hemophilia patients' joint health.

In conclusion, while this study emphasizes the strides made in the field of hemophilia care, it also serves as a reminder of the work that lies ahead. The management of hemophilic arthropathy is a collective effort that necessitates an unwavering commitment to ensuring that every patient, regardless of their geographic location or inhibitor status, has access to the best available care. This commitment not only enhances the lives of those currently living with hemophilia but also sets the stage for a future where joint complications no longer define the fate of those affected by this condition.

Acknowledgment

We cordially thanks to Ege Hemophilia Council members as Semih AYDOĞDU and Elçil KAYA BİÇER (Orthopedics), Can BALKAN and Fahri ŞAHİN (Pediatric and Adult Hematology), Kazım ÇAPACI (Physical Therapy and Rehabilitation), Zehra ÖZCAN (Nuclear Medicine), Ayşenur OKTAY (Radiology) for their distinguished service for last 20 years. Also we thank you HEMOPHILIA FEDERATION OF TÜRKİYE for supporting for project.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

All authors contributed equally while this study preparing.

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