Original Article

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Clinical Evaluation of the Joints of Patients with Hemophilia

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Abstract

Objective: Hemophilia is the most common and serious disease of congenital coagulation factor deficiency and causes arthropathy by hemarthrosis. A proper and timely treatment can decrease morbidity in patients. The objective of this study to evaluate the joints of patients with hemophilia in the Van region.

Method: 30 patients of hemophilia who applied to our clinic between March 2009 and October 2010 were included to study. The patients were between 18–60 years old (the mean age is 29,9) and, based on clinical and radiological criteria, were diagnosed with hemophilic arthropathy. The clinical examination of the patients' joints, frequency of intra-articular bleeding, age of diagnosis and factor levels were evaluated, and whether patients were given prophylaxis or not was taken in consideration.

Results: 25 of the patients (83,3%) had severe hemophilia and their factor level was below 1%. The mean diagnosis age of our patients was 11,1. 7 of the patients (23,3%) were not given prophylaxis treatment. Limited range of motion of the joints, except shoulders, was statistically meaningful when compared to the control group ($p<0.001$). Knee was the most commonly affected joint (48,2%). In order of decreasing frequency, the elbow, hip, ankle and shoulder were the other affected joints. Surgical procedures were applied on 9 patients (30%).

Conclusion: Treatment and monitoring of patients with hemophilia requires a multidisciplinary approach. Early diagnosis, treatment, rehabilitation and a constant monitoring will be effective in preventing arthropaty.

Key words: *Hemophilia, joint, treatment*

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Introduction

Hemophilia is the most common and serious disease of congenital coagulation factor deficiency [1]. This disease is observed at a frequency of 1 in 10000 male-born children [1]. There are nearly 4000 patients in Turkey. The disease is characterized by FVIII (Hemophilia A, 85% of all) or FIX (Hemophilia B, 12% of all) deficiency or this factor defective structure in the coagulation cascade [2,3]. It frequently causes hemarthrosis, i.e., bleeding into the joints. Hemophilia is divided into three groups according to the level of factors. Severe he-

mophilia (the level of factor is less than 1%), moderate hemophilia (the level of factor is between 1-5%), and mild hemophilia (the level of factor is between 5-40%) [4,5]. The disease goes with clinical pictures whose severity varies from mild bleeding and ecchymosed to spontaneous or posttraumatic systematic bleedings. Patients with severe hemophilia, though, may have severe bleedings from the beginning of the neonatal period. If these patients fail to get effective treatment, chronic hemophilic arthropathy may develop in the young adult [6]. The most common musculoskeletal disorders in patients with hemophilia are, in decreasing order of frequency, acute hemarthrosis, chronic hemophilic arthropathy, intramuscular bleeding, pseudo tumors and septic arthritis [7]. The frequency of hemarthrosis in patients with severe hemophilia is 75-90% [8]. Hemarthrosis mostly occur in the 12th-18th month period, when children start to walk. Hemophilia-driven changes coming to light in the still-developing skeleton systems of children may cause structural deformities like length difference between extremities, angulation in joints and posture disorders [9]. Hemarthorosis, associated with pain, panicula and a decrease in the joint range of motion, eventually leads to degenerative changes in joints. Although hemophilia, with the exception of some rare cases, does not threaten life, it may cause permanent disabilities. Therefore, preventing bleeding is extremely important. The goal of the treatment is to replace the deficient coagulation factors and to apply the appropriate rehabilitation [10]. The patients' life quality is also improved by providing muscle strength and articular stability [11].

The objective of this study is to evaluate patients with hemophilia in the province Van with respect to the range of motion in their involved joints, the age when diagnosed with haemophilia, the types of factor deficiencies and the frequency of hemarthrosis, taking into account whether they were given prophylaxis factors or not.

Materials and Methods

In this study, 85 joints with hemophilic arthropathy of 30 patients diagnosed with hemophilia were evaluated. The ages of the patients were between 18-60 years old and they started being followed at the orthopedic and traumatology, hematology, physical therapy and rehabilitation clinics of Van Yuzuncu Yil University Medical Faculty Hospital between March 2009–September 2010.

The frequency of intra articular bleedings, diagnosis age, occupation and factor level of the patients, along with whether they got factor prophylaxis or not were questioned. The examination of patients' joints was done by comparison to the normal joint range of motion (ROM) and the levels of movement inability limitation degrees were also evaluated. The classification of Arnold-Hilgartner (1977) and Petterson (1980) were used for evaluating the radiographies [12,13].

The patients having diabetes, hypertension, renal failure, rheumatic medical history and chronic diseases alike, along with patients with hemophilia having arthritic trauma, were excluded from the study.

The study was put into practice after the local ethics committee approved it. Informed consent of patients was taken verbally and orally.

Statistical Analysis

While continuous variables for descriptive statistics are shown as average, standard deviation, minimum and maximum values.; in order to observe whether they are different from standard values or not, a Student-t test was applied. Categorical variables are given in numbers and percentage. Student-t test was used in group average comparison with regard to descriptive variables. SPSS 16 was used and the statistical significance level was measured as 5%.

Results

The mean age of the patients was 29.97 (18-60) years old and the mean age of the first diagnosis of the disease was 11.13 years (1-52). 93.3% (28) of the patients had Hemophilia A (FVIII deficiency) and 2 patients had Hemophilia B (FIX deficiency). The number of patients with severe hemophilia was 22 (73.3%), 5 (17%) patients had moderate hemophilia and 3 (10%) were diagnosed with mild hemophilia. 77% (23 patients) of the patients received factor treatment but 23% (7 patients) of the patients did not.

9 patients (30%) had had surgical operation due to hemophilic arthropathy. Surgical treatment types were arthroplasty, arthroscopic debridement and arthrotomy. In Figure 1 the distribution of these surgical operations is displayed. 5 patients (16.6%) had expe-

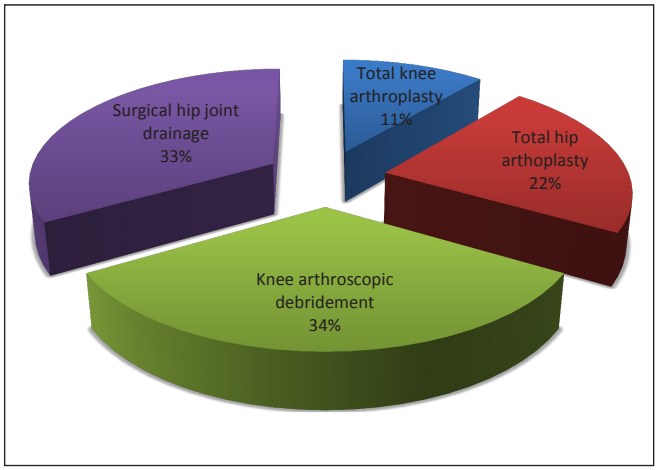

Figure 1. Previously undergone surgical procedures.

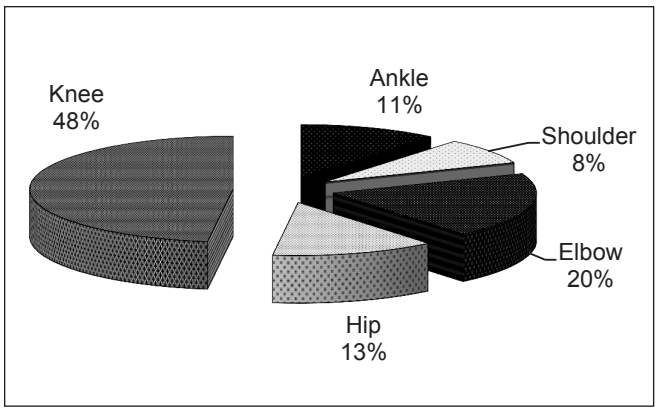

Figure 2. The frequency of different joints involved in hemophilic arthropathy.

rienced radioactive synovectomy; (3 on the knee, 1 in the shoulder 1 in the elbow). A progress was observed in the joint range of motion of the patients that received radioactive synovectomy. All patients who had surgery felt better after surgery, experiencing a decrease in the pain and a lower frequency of intra-articular bleeding, but their joints ROM had not increased.

The most commonly affected joint was the knee, with 41(48.2%) joints (Figure 2). Other effected joints were the elbow, with 7 (20%) joints, the hip, with 11 (12.9%) joints, the ankle, with 9 (10.6%) joints, and the shoulder, with 7 (8.2%) joints. For the joints with hemophilic arthropathy, ROM is displayed on Table 1. The most affected patient had problems in 7 joints scored 7, while the mean number was 2.8 joints per patient (Figure 3).

When considering the frequency of intra-articular bleeding, we observed that 63% (19 patients) of the patients were suffering from this in 1-3 months intervals. This was followed by the 30% (9 patients) who were suffering from intra-articular bleeding in 1-3 days intervals bleeding and by 7% (2 patients) that had bleedings of 4 days to 3 weeks intervals.

In the evaluation of the affected joints by ROM,

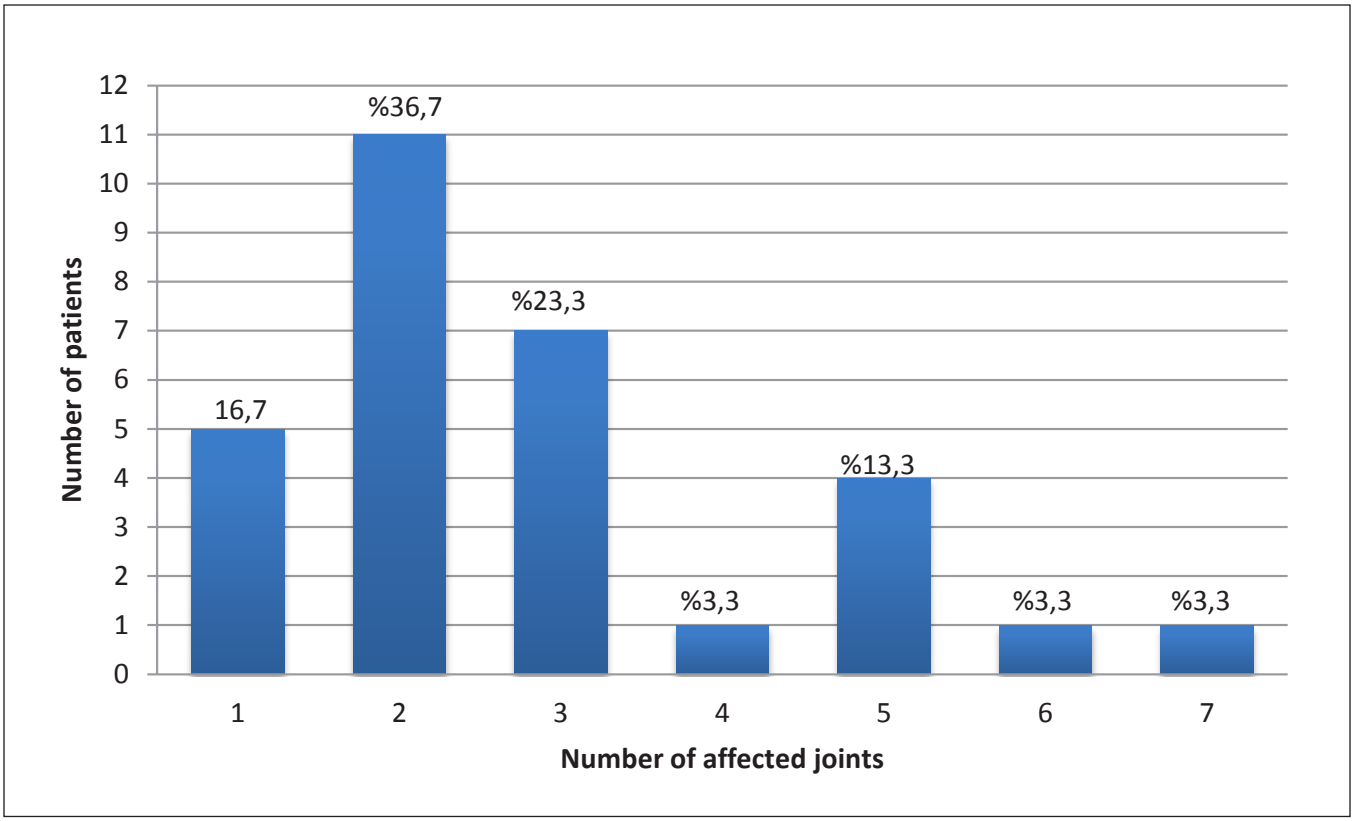

Figure 3. Number of affected joints per patient .

Table 1. Patients' involved joints' range of motion.

Joints	Articular Range of Motion	Number	Max. (degree)	Min. (degree)	Average	SD	p
Knee	Flexion	41	135	10	101,59	28,92	P< 0,001
	Extension limitation	41	45	5	17,07	17,13	P< 0,001
Elbow	Flexion	17	150	90	118,24	21,86	P< 0,001
	Extension limitation	17	45	10	17,94	10,31	P< 0,001
Ankle	Dorsiflexion	9	30	10	15,00	6,61	P< 0,001
	Plantarflexion	9	40	15	25,56	7,26	P< 0,001
Hip	Flexion	11	130	45	109,55	25,73	,008
	Extension	11	30	20	22,73	4,67	,000
	Abduction	11	90	30	60,91	22,89	,002
	Adduction	11	40	10	26,82	8,44	,000
	Internal Rotation	11	60	20	35,45	13,50	,000
	External Rotation	11	40	10	27,27	9,04	,001
Shoulder	Flexion	7	180	70	151,43	46,34	,154
	Extension	7	60	40	54,29	9,75	,172
	Abduction	7	170	40	138,57	52,41	,164
	Adduction	7	45	30	41,43	5,56	,140
	Internal Rotation	7	90	40	80,00	12,91	,086
	External Rotation	7	90	60	80,00	11,54	,062

Max: Maximum; Min: Minimum; SD: Standard Deviation

significant decreases were observed extensively in the knee, elbow, ankle and hip joints, whereas the decrease in the shoulder joints was not significant (Table 1). For the patients who had not received factor treatment, ROM values were significantly low.

Discussion

Hemophilia is a disease characterized by bleedings within or at the surface of the body [4]. Gastrointestinal, genitourinary, intracranial, muscle, soft tissue or intra-articular bleedings are observed at different rates within the hemophilia clinic picture [14].

80% of the patients, mostly from undeveloped and developing countries, are not able to benefit from treatment opportunities and as a result are exposed to various complications or pass away due to bleedings [15]. In our patients with hemophilia we observed severe joint involvement, which was particularly obvious in the lower extremities (Table 1).

Clinical findings in hemophilia are closely related to the factor level. In our study, when patients with hemophilia were categorized as severe, moderate and mild, according to coagulation activity, it was observed that the percentage of patients with severe hemophilia having 0-1% factor level was 73.3%. In the literature, the percentage of severe hemophilia is 65-70% and the slightly higher value we obtained in our study could be explained by the fact that patients with severe hemophilia necessarily seek hospitals more frequently than patients with mild and moderate hemophilia. This bias and the socioeconomic conditions of the region can be taken as two of the reasons for the disparity between the percentages [15,16].

The most frequently observed bleeding in hemophilia is hemarthrosis [16,17]. The repeating bleedings are generally observed in the form of monoarticular [18]. Joint involvement during hemophilia is much more frequent in the lower than the higher extremities [19], as shown by the following frequencies: 44-45% in the knee, 25-30% in the elbow, 15% in the ankle, 3-8 in the shoulder, 2-5% in the hips and 3% in the other joints. The first three positions in this list are occupied by the hinge type joints because these are richer in synovial tissues than the spheroid-joints, like the hips and shoulders [20]. Arnold WD et al. stated in their study

that the involvement frequency in the lower extremities, higher extremities and other joints is 64%, 33% and 3%, respectively [12]. Dalyan et al., in a study of 25 patients with hemophilia, reported in their study that the average joint involvement per patient is 3.3 [21]. Considering that in our study with 30 patients involvement was observed in 85 joints, the average joint involvement is 2.8, a value close to the one reported by Dalyan et al.

When examining the involved joints in our study, the lower extremities predominate (71.7%); however, the ankle joint involvement was low, particularly with respect to the study of M. J. Manco-Johnson et al. [22]. One of the reasons for this discrepancy is that the average age (12.6) in the study of these authors is lower than the average age (29.97) in our study. Another reason might be connected to the living conditions and cultural differences such as dining on the floor, sitting cross-legged, praying and using alla turca toilet, which are characteristic of the regions where the literature studies were carried out. It is observed that with regard to the joint involvement frequency, the 30 patients with hemophilia included in our study were close to the literature studies and that the most frequently involved joint was the knee joint (48.2), followed by the elbow joint (20%). However, it is observed in our study that the hip joint compared to the literature studies had a slightly higher rate involvement than the ankle joint (12.9% versus 10.6%, respectively). In turn, shoulder joint involvement (8.2%) was observed at a much higher frequency than in the literature studies.

Manco-Johnson et al., in the study they made on 49 children, adolescents and adults with hemophilia, found that 42 of the cases suffered from hemophilia A FVIII deficiency (97.6%) and 1 of the cases suffered from hemophilia B FIX deficiency (2.4%) [22]. However, in our study, 93.3% of the patients suffered from FVIII deficiency, 1 of the patient was suffering from FIX deficiency and another from FVII deficiency.

While the average diagnosis age of Hemophilia A is 9 months, for moderate hemophilia it is 22 months [23]. In our study, the average diagnosis age of the 30 patients with hemophilia was 11.13 years. We consider that the reason for the average age of diagnosis being so late may result from the socioeconomic conditions of the region, which probably delays the moment the patients' family first decide to seek help from health professionals.

Banta and et al., stated that the average bleeding frequency of 26 patients with hemophilia having acute medial knee bleeding is 2.2 days [3]. In our study, the average acute medial knee bleeding frequency of 9 of the 30 patients (%30) included in our study is 0-3 days. It was observed that 19 of the cases (63.3%) had a medial knee bleeding frequency varying between 1-3 months.

In our study, the loss of knee, elbow, ankle and hip joint range of motion is statistically significant (Table 1). Due to the frequently applied primer prophylactic programs in developed countries, recurrent intra-articular bleedings of patients are becoming less frequent. As a result, joints are less damaged [24]. However, in developing countries like ours, patients can use their factor concentrate only when they have bleedings. Our patients took factor concentrate for the first time approximately 13 years ago. A considerable number of the older patients with hemophilia have the disease for a longer time than that, and developed serious damages in their joints [25-28].

Certain surgical operations are undertaken in hemophilic arthropathy. The patients with hemophilia included in our study had surgical operations like synovectomy, arthroscopic debridement and total joint prosthesis (Figure 1). 9 patients (30%) of the 30 included in the study had surgical operations in their involved joints. 3 cases (33.3%) of those 9 had knee arthroplasty, 2 (22.2%) had total hip arthroplasty, 1 (11.1%) had total knee arthroplasty and 3 (33.3%) had surgical drainage due to hematomas in the hips. Patients having had total hip and knee arthroplasty mentioned that although their pain had lessened distinctively compared to the period before the surgery, no significant change improved their range of motion. It was observed that after the knee arthroscopy the bleeding intervals of 2 of the 3 patients with arthroscopic synovectomy decreased and that with the physiotherapy applied their range of motion partly increased. In the other patient, no particular change was observed in the range of motion.

The patients took part in the study in small numbers and some lacked the education for a proper com-

munication of their health condition, which did not allow the evaluation of a set of measures. These facts are considered as shortcomings of this study.

In conclusion, according to the results of the literature studies and the results here reported, patients with hemophilia, if not treated properly and in time, are at risk of disability. Therefore, the follow up of these patients must be carried out sensitively, taking in consideration the diagnosis of patients with hemophilia, factor treatments and necessary surgical operations through which the complications the patients encounter may be reduced to the minimum level. In addition, we must look for the potential hemophilic patients in low socioeconomic areas and we should begin the factor treatment of the detected patients.

Conflict of interest statement

The authors have no conflicts of interest to declare.

References

1. Montgomery RR, Scott P. Hemorrhagic and Thrombotic Diseases. In: Behrman RE, Kliegman RM (eds.) Nelson Textbook of Pediatrics. W.B Saunders, Philadelphia, 2003; 1657–1660.
2. Kruse-Jarres R. Current controversies in the formation and treatment of alloantibodies to factor VIII in congenital hemophilia A. Hematology Am Soc Hematol Educ Program 2011;2011:407-412.
3. Banta JV, Boone DC, Smith CF. Arthrocentesis of the knee in acute hemophilic arthropathy. West J Med 1975 ;122:285-288.
4. Tonbary YA, Elashry R, Zaki Mel S. Descriptive epidemiology of hemophilia and other coagulation disorders in mansoura, egypt: retrospective analysis. Mediterr J Hematol Infect Dis 2010;2:e2010025.
5. White GC 2nd, Rosendaal F, Aledort LM, Lusher JM, Rothschild C, Ingerslev J. Factor VIII and Factor IX Subcommittee. Definitions in hemophilia. Recommendation of the scientific subcommittee on factor VIII and factor IX of the scientific and standardization committee of the International Society on Thrombosis and Haemostasis. Thromb Haemost 2001;85:560.
6. Gilbert MS. Musculoskeletal manifestations of hemophilia. Mt Sinai J Med 1977;44:339-358.
7. Rickard KA. Guidelines for therapy and optimal dosages of coagulation factors for treatment of bleeding and surgery in haemophilia. Haemophilia 1995;1(S1):8–13.
8. Aronstam A, Rainsford SG, Painter MJ. Patterns of bleeding in adolescents with severe haemophilia A. Br Med J 1979;1:469-470.
9. Rodríguez-Merchán EC. Effects of hemophilia on articulations of children and adults. Clin Orthop Relat Res 1996;328:7-13.
10. Josephson N. The hemophilias and their clinical management. Hematology Am Soc Hematol Educ Program 2013;2013:261-267.
11. De la Corte-Rodriguez H, Rodriguez-Merchan EC. The role of physical medicine and rehabilitation in haemophiliac patients. Blood Coagul Fibrinolysis 2013;24:1-9.
12. Arnold WD, Hilgartner MW. Hemophilic arthropathy. Current concepts of pathogenesis and management. J Bone Joint Surg Am 1977;59:287-305.
13. Pettersson H, Ahlberg A, Nilsson IM. A radiologic classification of hemophilic arthropathy. Clin Orthop Relat Res 1980;149:153-159.
14. DiMichele D. Hemophilia 1996. New approach to an old disease. Pediatr Clin North Am 1996;43:709-736.
15. Kavakli K, Nişli G, Aydinok Y, Oztop S, Cetingül N, Aydoğdu S, et al. Prophylactic therapy for hemophilia in a developing country, Turkey. Pediatr Hematol Oncol 1997;14:151-159.
16. Federici AB. Prophylaxis of bleeding episodes in patients with von Willebrand's disease. Blood Transfus 2008;6 Suppl 2:s26-32.
17. Madhok R, York J, Sturrock RD. Haemophilic arthritis. Ann Rheum Dis 1991;50:588-591.
18. Lusher JM, Warrier I. Hemophilia A. Hematol Oncol Clin North Am 1992;6:1021-1033.
19. Gamble JG, Bellah J, Rinsky LA, Glader B. Arthropathy of the ankle in hemophilia. J Bone Joint Surg Am 1991;73:1008-1015.
20. Rodriguez-Merchan EC. Common orthopaedic problems in haemophilia. Haemophilia 1999;5 Suppl 1:53-60.
21. Dalyan M, Tuncer S, Kemahli S. Hemophilic arthropathy: evaluation of clinical and radiological characteristics and disability. Turk J Pediatr 2000;42:205-209.
22. Manco-Johnson MJ, Nuss R, Funk S, Murphy J. Joint evaluation instruments for children and adults with haemophilia. Haemophilia 2000;6:649-657.
23. Bell B, Canty D, Audet M. Hemophilia: an updated review. Pediatr Rev 1995;16:290-298.
24. Greene WB, McMillan CW, Warren MW. Prophylactic transfusion for hypertrophic synovitis in children with hemophilia. Clin Orthop Relat Res 1997;343:19-24.
25. Post M, Watts G, Telfer M. Synovectomy in hemophilic

arthropathy. A retrospective review of 17 cases. Clin Orthop Relat Res 1986;202:139-146.
26. Wiedel JD. Arthroscopic synovectomy of the knee in hemophilia: 10-to-15 year followup. Clin Orthop Relat Res 1996;328:46-53.
27. Luck JV Jr, Kasper CK. Surgical management of advanced hemophilic arthropathy. An overview of 20 years' experience. Clin Orthop Relat Res 1989;242:60-82.
28. Clark MW. Knee synovectomy in hemophilia. Orthopedics 1978;1:285-290.

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