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The Impact of HEAD-US Scoring System for Observing the Protective Effect of Prophylaxis in Hemophilia Patients: A Prospective, Multicenter, Observational Study

Kavaklı K. et al: Ultrasound and Monitoring for Hemophilia

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ABSTRACT

Objective: To observe preventive effect of prophylactic treatment on joint health in people with hemophilia (PwH) and to investigate the importance of integration of ultrasonographic examination into clinical and radiological evaluation of the joints.

Material and Methods: This national, multicenter, prospective, observational study included male patients aged ≥6 years with the diagnosis of moderate or severe hemophilia A or B from 8 centers across Turkey between January 2017-March 2019. Patients were followed-up for 1 year by 5 visits (baseline, 3rd, 6th, 9th, and 12th month visits). The Hemophilia Joint Health Score (HJHS) was used for physical examination of joints; the Pettersson Scoring was used for radiological assessment; Point-of-care (POC) ultrasonography was used for bilateral examinations of joints; and the Hemophilia Early Arthropathy Detection with Ultrasound (HEAD-US) was used for evaluation of ultrasonography results.

Results: Seventy-three hemophilic patients, of whom 62 had hemophilia A and 11 had hemophilia B, were included and 24.7% had target joints at baseline. The HJHS and HEAD-US scores were significantly increased at the 12th month in all patients. These scores were also higher in the hemophilia A subgroup than the hemophilia B subgroup. However, in childhood group increment of scores were not significant. The HEAD-US total score was significantly correlated with both the HJHS total score and Pettersson total score at the baseline and 12th month.

Conclusion: The HEAD-US and HJHS scoring systems are valuable tools during follow-up examinations of PwH and they complement each other. We suggested that POC Ultrasonographic evaluation and the HEAD-US scoring system may be integrated into differential diagnosis of bleeding and long-term monitoring for joint health as a routine procedure.

Introduction

The goal of hemophilia treatment is to prevent bleeding by replacement of factor concentrates; substitution of missing coagulation factors. Coagulation factors can be given for prophylaxis (primary and secondary prophylaxis, etc.) or for treatment, when needed [1]. Prevention of bleeding via prophylaxis is considered the gold standard treatment in severe hemophilia [1, 2]. Provision of early prophylaxis for severe hemophilic children can completely or widely prevent life-threatening bleeding, chronic joint diseases, and disabilities; thus, requirement for surgical interventions can be decreased and both health and social well-being of people with hemophilia (PwH) can be improved [1-3].

Evaluation of joint status is crucial not only for staging joint disease but also for follow-up of prophylaxis and for evaluating outcomes of replacement therapy. Joint function is assessed by The Hemophilia Joint Health Score (HJHS) is widely used for scoring. Implementation of the HJHS requires training and experience. The Pettersson scoring system, a radiological joint scoring system, gives quite reliable outcomes when performed by an experienced radiologist [4,5]. MRI is a more sensitive imaging method than plain radiogram in evaluating the joints. Nevertheless, MRI has disadvantages such as long scanning period, high cost, limited availability, and need for sedation in young children [4, 5]. However, ultrasonography may provide advantages such as appropriate cost, availability, repeatability, faster examination, no

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need for sedation while examining children, and scanning of multiple joints and dynamic examination of joints at a single session.
The present study aimed to observe preventive effect of prophylactic treatment on joint health in PwH and to investigate the importance of integration of Point of-care (POC) ultrasonographic examination into clinical and radiological evaluation of the joints.

Materials and Methods

Patients

The current study was designed as a national, multicenter, prospective, non-interventional, observational study. A total of 8 centers across Turkey were selected and the data were collected from January 2017 through March 2019. Male patients aged ≥6 years with the diagnosis of moderate or severe hemophilia A or hemophilia B (factor level <2%) were included in the study. Pediatric group (47.9%) was between age 6 and 18 years. Adult group (52,1%) were ages between 19 and 70 years (Table-1).
Patients with communication difficulties (who were unable to understand or speak Turkish) or cognitive dysfunction and patients with inhibitors were excluded. The study was approved by the Clinical Research Ethics Committee of Ege University Faculty of Medicine and written informed consents of the patients or their legal representatives were obtained.

Procedure

After enrollment in the study, the patients were followed-up for 12 months with a total of 5 visits (baseline, 3rd, 6th, 9th, and 12th month.–In the study centers, patient data concerning demographic features and hemophilia history were recorded on CRF forms at the baseline visit. Physical examination of elbow, knee and ankle joints were performed with the HJHS during each visit. ABR recordings were done in every 3 months at clinical visits.
Additionally, ultrasonographic examinations of bilateral elbow, ankle, and knee joints were performed during each visit. Ultrasonography results of the patients were evaluated with the Hemophilia Early Arthropathy Detection with Ultrasound (HEAD-US) scoring system. Evaluations were performed by expert physiotherapists and radiologists. Same experts in each centers were evaluated at different time points preventing variability.
For all patients, QoL questionnaires were administered at the baseline, 6th month, and 12th month visits.
Compliance of prophylaxis and bleeding episodes were recorded in every 3 months of clinical visits.

Measurements

The Hemophilia Joint Health Score : It is a scoring system used to assess physical joint damage in PwH and recommended for routine follow-up assessments of joint health. Using HJHS, the most commonly involved 6 joints (elbows, knees, and ankles) are evaluated in PwH and the total scores are within the range of 0-124 including gaiting. High scores indicate damage/impairment [6].
The Pettersson Scoring System: It allows detailed evaluation of radiological changes in the joints. Posterior-anterior and lateral X-ray images of the joints are evaluated. Scores range from 0-13 for a single joint and the maximum possible total score is 78 when 6 joints are evaluated [7, 8].
The Hemophilia Early Arthropathy Detection with Ultrasound (HEAD-US) Scoring System: It was developed by Martinolli *et al.* [9]. This scorring system was based on three markers for three main joints (Knees, elbows and ankles): Synovitis (score 0-2), Cartilage (score 0-4) and subchondral bone (score 0-2) with a maximum score of 8 points per joints.
The Short Form-36 (SF-36): It is a questionnaire widely used to assess health-related QoL. Based on the scores of 8 dimensions of health (physical functioning, bodily pain, role limitations due to physical health problems, role limitations due to personal or emotional problems, general mental health, social functioning, energy/fatigue or vitality, and general

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health perceptions), two component summaries (physical component summary and mental component summary) are obtained. Higher scores indicate better health status [10].
The EuroQol-5 Dimension (EQ-5D): It is one of the questionnaires frequently used to assess health-related QoL. Five parameters of health (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) are evaluated. Higher scores indicate better QoL [11]. In the present study, the three-level version (EQ-5D-3L) was used.
Patients received prophylaxis were recorded using scoring systems and quality of life parameters. Prospective evaluation of patients were provided as one year of observational period.
Bleeding frequency and target joint availability are main reasons for starting prophylaxis for moderate patients. They were mostly in secondary prophylaxis.
Children with below 10 year were in primary prophylaxis whereas older age group (10-18 yr) were in secondary prophylaxis. Most adult group was in secondary and tertiary prophylaxis.
Primary prophylaxis patients was started once weekly and then proceed to twice and thrice weekly. Most secondary prophylaxis patients was twice and thrice weekly infusions.

Sample Size

The sample size was calculated as 80 PwH with the assumptions of the rate of damaged joints would have been 8% in PwH receiving prophylactic treatment and the rate of damaged joints would have been 25% in PwH not receiving prophylactic treatment, with 80% power when the statistical significance level was presumed as 0.05.

Statistical Analysis

Data analysis was performed using the PASW Statistics for Windows, Version 18.0 (SPSS Inc., Chicago, IL, USA). In descriptive statistics, numerical variables were expressed as mean, standard deviation, median, and minimum-maximum and categorical variables were expressed as number and percentage. Student T-test was performed in comparisons of ultrasonography scores and QoL scores at each visit when the normal distribution condition was provided. The Mann-Whitney U test was used when normal distribution was not provided. In normally distributed data, repeated measures analysis was performed for the comparison of change in ultrasonography scores and QoL scores with time in the groups. When the normal distribution condition was not provided, the Friedman test was performed separately in the groups. Spearman's Rho correlation test was used for correlation analysis. Statistical significance level was set at $p<0.05$.

Results

The present study included 78 male hemophilic patients, of whom 73 received prophylactic treatment and 5 received on-demand treatment in case of bleeding. These 73 patients were included in the analyses. Of these patients, 62 had hemophilia A (58 severe and 4 moderate) and 11 had hemophilia B (10 severe and 1 moderate). General characteristics of the patients and disease-related data are presented in Table 1.
Among the included patients, 24.7% had target joints at the baseline. The most commonly affected joint was the right ankle (27.4%). Overall 31.5% of the included patients underwent major or minor surgical procedures and radioactive synovectomy was performed only in 6 patients. More than half of the patients were not being able to go to work because of hemophilia in the last 3 months (Table-1).
Annual bleeding rates (ABR) for all group, children and adults were showed in Table-2. Either in children or adult group, elevation of ABR rates was not significant.
Moreover, joint scores of all patients at the baseline and follow-ups are shown from-Table 3 to Table-6.
When the scores at the baseline and 12th month were compared, there were significant increases both in the HJHS and HEAD-US scores at the 12th month in all patients. When dividing the patients by age, no significant increase, in any of the scores, was observed in

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children, however significant increases in the HJHS, HEAD-US and Pettersson scores were seen in the adult group.
Evaluation of the patients in terms of hemophilia A and hemophilia B subgroups showed significant increases in the HJHS and HEAD-US scores at the 12th month in the hemophilia A subgroup (Table- 3and Table- 6). However, the number of included Hemophilia-B patients is much smaller in comparison to their hemophilia-A counterpart. For subgroup analysis in the Prophylaxis group were shown in the Tables 4 and 5. Significant results as elevated scores were found in the adult group than children group.
Correlation analyses were performed for the joint scores at the baseline and 12th month. In all patients, the HJHS total score was found to significantly correlate with the HEAD-US total score at the baseline and 12th month. Moreover, there was a significant correlation between the Pettersson total score and the HEAD-US total score at the baseline and 12th month (Table-7). Additionally, strong correlation was found in the three scoring systems (HJHS, Head-US and Petterson) together in the baseline and after 12th months of observation ($p<0001$).
There were no significant differences in the QoL scores between the baseline and 12th month in all patients.
Neither pediatric vs. adult group nor Hemophilia-A vs. Hemophilia-B comparisons were significant.
Comparisons of the QoL scores of the patients between the baseline and 12th month are presented in Table–8.

Discussion

In all patients, there were significant increases in the HEAD-US and HJHS scores during the one-year follow-up period, despite prophylaxis. This was consistent with the results obtained from the study by Warren *et al.* [12], in which only a small number of PwH had no damage in their joints when they reached to adolescence, in spite of early prophylaxis. In the present study, subgroup evaluation according to age revealed a significant increase in the joint scores from the baseline to the 12th month in the adult group but not in the pediatric group. In other words, prophylactic treatment slowed down the progression at the onset of arthropathy in children, but degenerative arthropatic changes persisted in adult patients. Sub-group analysis results supported the importance of early prophylaxis in the childhood.
Similarly, Warren *et al.* [12] reported that the risk of MRI osteochondral damage and ABR and joint ABR were significantly higher in the children who were started prophylactic factor VIII after 6 years of age as compared to the children in whom prophylaxis was initiated before 2.5 years of age. These results showed the importance of preventing initiation of joint damage by means of prophylaxis at an early stage in life, because the earlier the damage occurs, the more difficult it is to prevent its progression. For this reason, examination of the joints by means of regular follow-up is important for early detection and prevention of arthropathic changes in PwH. Geraghty *et al.* [13] showed that nonadherence to treatment was higher among adults as compared to children with hemophilia. Due to adolescent and adult patients are prone to inadherency in clinical practice, we had used reminders related compliance in every 3 months during clinical visits.
Early initiation of prophylactic treatment and good adherence to treatment are important factors to reduce the incidence of bleeding and to preserve joint functions in PwH [14, 15]. Hemophilic arthropathy is a progressive condition and negatively impacts QoL of patients as damage progresses. It has been reported that QoL is lower in PwH as compared to general population [16]. Earlier studies have demonstrated poorer QoL in patients with severe joint problems [16-18]. These data supports the importance of appropriate treatment to limit joint injury. In the present study, QoL was assessed using the EQ-5D-3L and SF-36 questionnaires. The QoL scores of the patients were generally high, indicating a better QoL, and the mean scores were similar at the baseline and 12th month. Assessment of QoL not only gives

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information about clinical statuses of patients but also provides an objective criterion for measuring benefit gained from treatment [19, 20]. Better adherence of patients to treatment is associated with better outcomes and is a factor that improves QoL [21-23].
During follow-up of PwH, joint function is assessed by physical examination and the HJHS is widely used for scoring. Implementation of the HJHS requires training and experience [24]. Plain radiographs have also being used for a long time to evaluate the musculoskeletal system. The Pettersson scoring system, a radiological joint scoring system, gives quite reliable outcomes when performed by an experienced radiologist [24]. MRI is a more sensitive imaging method than plain radiogram in evaluating the joints. Nevertheless, MRI has practical disadvantages such as long scanning period, high cost, limited availability, and need for sedation in young children [24]. There is a need for an easy, cost-effective, repeatable, efficient, and reliable joint scoring system. Thereby, ultrasonography has been an attractive method in the last years for objective evaluation of joint status and for early detection of changes during periodic follow-ups [25-29]. Ultrasonography provides advantages such as appropriate cost, availability, repeatability, faster examination, no need for sedation while examining children, and scanning of multiple joints and dynamic examination of joints at a single session [30]. Ultrasonography allows detection and quantitation of signs of disease activity (fluid collection in the joint, synovial hypertrophy, etc.) and degenerative patients (osteochondral changes, etc.) and it is also beneficial in discriminating inflammatory (serous) effusion from hemarthrosis. Ultrasonography, as a simple and practical tool is powerful nominate to facilitate for routine hemophilia care in close future (28).
Several scoring systems have recently been propounded to provide objectivity in ultrasonographic evaluation; the HEAD-US is one of them [28]. The HEAD-US scoring system has advantages such that it can be applied by non-imaging specialists. Even though this scoring system can be performed by non-radiologists after a short training, speed of the exam is dependent on the sonographer's experience level (24,31).
There are studies using the HEAD-US scoring to assess the joint status in PwH and evaluating its correlation with the HJHS scores. In a study evaluating joint status in children with severe hemophilia A receiving prophylaxis, 85.3% of the joints were found normal by the HJHS, whereas 79.0% of the joints were found normal by the HEAD-US scoring system [32]. While there was a correlation between the HEAD-US scores and bleeding scores, no correlation was determined between the HEAD-US and HJHS scores. Nevertheless, the HJHS and HEAD-US scores were concordant for 73.4% of the joints. Ultrasound detected minimal changes in 19.6% of the joints with normal physical functioning, whereas 12.2% of the joints that were considered normal on ultrasound showed changes on the HJHS. As the consequence, ultrasound detected higher percentage of abnormality than physical examination [32]. Jiménez-Yuste *et al.* [33] carried out a study in hemophilia B patients and concluded that using HEAD-US scoring system in routine practice provided patients with better and objective evaluation and contributed to personalization of treatment. Li *et al.* [34] determined a significant correlation between the HEAD-US and HJHS scores in the PwH receiving prophylactic treatment. Banchev *et al.* [35] reported a strong correlation between three-year joint bleeding rate and the HEAD-US total score for ankle and knee joints in hemophilia A patients receiving secondary/tertiary prophylaxis. Plut *et al.* [36] conducted a study in patients with severe hemophilia and determined very high correlation between the overall HEAD-US scores and overall International Prophylaxis Study Group MRI scores. They suggested HEAD-US protocol as a fast, reliable, and accurate method in detecting hemophilic arthropathy and determining its degree. In the present study, considering all patients, the HEAD-US total scores showed a correlation with both the HJHS total score and the Pettersson total score. Joint tissue activity and damage examination (JADE protocol) was developed for soft tissue and osteochondral measurements for POC-US scorring system in the

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USA (patented for University of California San Diego)(37). JADE protocol has similar principles, easy to learn and to administer, and ideal for use in routine practise as well as outcomes reseach tool. Both protocols (JADE and Head-US) appear feasible for quantifying hemophilic intra-articular abnormalities with lower variabilities.
The main limitation of the present study was not including more patients receiving on demand treatment and thereby not comparing the data of patients receiving prophylactic treatment with those receiving on demand treatment. Other limitation was missing some patients during prospective evaluation due to data deficiencies. Even though we were able to calculate statistical analysis, without missing patients we would have been provided better results as well.

Conclusion

The HEAD-US and HJHS scoring systems are valuable tools during follow-up examinations of patients and they complement each other. We suggested POC Ultrasonographic evaluation and HEAD-US scoring system may be integrated into differential diagnosis not only for bleeding and but also for long-term monitoring of joint health of PwH as routine procedure. Therefore, it would be possible to provide people with hemophilia with maximum benefit by means of early diagnosis of joint changes and bleedings that might be overlooked during physical examination and thereby to personalize prophylactic treatment.

Author Contribution

K. K made contributions to the design of the work and the acquisition, analysis, and interpretation of data and drafted the manuscript and substantively revised it. All authors made contributions to design and acquisition of data. All authors read and approved the final manuscript.

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Table 1: Demographics of 73 patients receiving prophylaxis			
Group	**Children**	**Adults**	**All**
PATIENTS	**35**	38	73
N (%)	(47.9%)	(52.1%)	(100%)
AGES (yr)			
Range	6-17	18-70	6-70
Median	14	36	18
Med + SD	11,3 ± 6,2	39,6±26,4	22,1±14,5
Body mass index			
Range	13,2-24,8	24,1-35,2	13,2-35,2
Median	15,9	28,6	23,8
Mean + SD	16,1±5,6	25,6±14,2	23,4±5,2
TYPE of HEMOPHILIA	All group	Hemophilia A	Hemophilia B
N	73	62	11
AGES (yr)			
Range		6-70	12-60
Median		17.5	19.0
Med + SD		21.3±14.1	26.5±16.7
SEVERİTY			
Severe	68	58	10
Moderate	5	4	1
*Presence of target joint	18 (24,3%)	15	3
*Orthopedical operation history	23 (31.5%)	20	3
*Radioisotope Synovectomy	6 (8,2%)	5	1
JOINT BLEEDING	N		
Knee-right	15	13	2
Knee-left	15	13	2
Elbow-right	18	15	3
Elbow-left	14	12	2
Ankle-right	20	17	3
Ankle-left	14	13	1
• All patients were severe HA or HB.			

Table 2: ABR rates for all group and children and adults						
	ALL GROUP		**CHILDREN GROUP**		**ADULT GROUP**	
	0th	**12th**	0th	12th	0th	12th
Median	0	3	0	3.5	1	3
Range	0-45	1-4	0-12	1-12	0-45	1-45

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Mean+SD	2.6±6.2	6.1±**8.2**	1.3±**8.0**	4.6±**3.6**	3.9±**8.0**	6.8±**9.6**
P value		>0.05		>0.05		>0.05
0th means: Retrospectively recorded one year ABR data before trial. 12th means: Prospectively Recorded ABR data by clinical visits in every 3 months.						

Table 3: Joint scores of all patients at baseline and follow-up days.

		HJHS Total Score		**HEAD-US Total Score**		**Pettersson Total Score**
	N	Mean±SD Median (min-max)	N	Mean±SD Median (min-max)	N	Mean±SD Median (min-max)
Baseline	60	9.97±12.41 3 (0-48)	61	9.70±9.25 7 (0-33)	15	15.4±15.71 11 (0-47)
3rd month	58	11.1±13.42 5.5 (0-55)	56	9.75±9.87 7 (0-36)	-	-
6th month	58	13.95±16.92 5 (0-56)	50	9.48±10.41 6.5 (0-40)	-	-
9th month	53	9.79±13.4 3 (0-50)	41	9.73±10.31 6 (0-40)	-	-
12th month	56	11.18±14.55 3 (0-57)	53	11.51±10.61 8 (0-40)	13	17.23±17.14 14 (0-48)
HJHS, Hemophilia Joint Health Score; HEAD-US, Hemophilia Early Arthropathy Detection with Ultrasound; SD, Standard deviation; Min-Max, Minimum-maximum						

Table 4: Both scoring systems and relationship with frequency of prophylaxis.

	HJHS Total Score Mean±SD Median (min-max)					**HEAD-US Total Score** Mean±SD Median (min-max)				
	N	**Receiving prophylaxis 1-2 times a week**	**N**	**Receiving prophylaxis ≥3 times a week**	**P**	**N**	**Receiving prophylaxis 1-2 times a week**	**N**	**Receiving prophylaxis ≥3 times a week**	**p**
Baseline	35	11.74±13.32 8 (0-48)	15	5.87±92 (0-29)	0.517	39	10.05±10.05 7 (0-33)	13	6.69±6.175 (0-20)	0.172
3rd month	34	12.06±13.22 6.5 (0-48)	16	5.75±6.813 (0-25)	0.973	31	10.61±11.45 7 (0-36)	16	8.19±6.967 (0-22)	0.244
6th month	29	12.14±14.55 4 (0-48)	18	11.94±15.52 5.5 (0-54)	0.410	28	9.46±124 (0-40)	13	8.38±6.059 (0-23)	0.895

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9th month	28	8.46±12.59 3 (0-48)	16	10.13±12.09 6 (0-38)	0.739	23	9.87±11.25 6 (0-40)	11	8.27±5.98 (0-22)	0.366
12th month	31	10.48±13.44 3 (0-48)	14	10.79±13.41 5 (0-41)	0.557	32	11.44±11.83 7 (0-40)	11	10.45±6.19 10 (0-22)	0.795
HJHS: Hemophilia Joint Health Score; HEAD-US: Hemophilia Early Arthropathy Detection with Ultrasound; SD: Standard deviation; Min-Max: Minimum-maximum										

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Table 5: Prophylaxis regimens and relationship with scores in pediatrics and adult group.				
	Baseline		**12th month**	
Total scores	N	Mean±SD Median (min-max)	Mean±SD Median (min-max)	**P**
Children (6-17 years)				
HJHS	29	1.86±3.07 1 (0-13)	3.17±7.07 1 (0-36)	0.166
<3 years of age	17	1.41±2.67 0 (0-11)	3.24±8.55 1 (0-36)	0.158
≥3 years of age	10	2.7±3.86 2 (0-13)	3.6±4.86 2 (0-16)	0.438
HEAD-US	29	4.03±4.59 2 (0-16)	4.69±4.35 5 (0-14)	0.322
<3 years of age	17	4.53±5.57 1 (0-16)	4.94±4.6 5 (0-14)	0.623
≥3 years of age	9	3.44±2.96 3 (0-9)	4.67±4.58 5 (0-11)	0.395
Adults (≥18 years)				
HJHS	23	17.96±12.55 17 (0-48)	22.43±15.4 22 (0-57)	**0.017**
Receiving <10 years of treatment	3	21.33±4.51 21 (17-26)	23.67±2.08 23 (22-26)	-
Receiving ≥10 years of treatment	20	17.45±13.35 13.5 (0-48)	22.25±16.55 20 (0-57)	**0.031**
HEAD-US	23	17.3±8.96 18 (0-33)	19.78±10.34 22 (0-40)	**0.006**
Receiving <10 years of treatment	4	21.25±6.29 22 (14-27)	26±4.08 24.5 (23-32)	-
Receiving ≥10 years of treatment	19	16.47±9.35 17 (0-33)	18.47±10.83 19 (0-40)	**0.023**

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Table 6: Comparison of the joint scores at the baseline and 12th month.				
		Baseline	**12th month**	
Total scores	N	Mean±SD Median (min-max)	Mean±SD Median (min-max)	**p**
All patients				
HJHS	52	8.98±11.76 3 (0-48)	11.69±14.93 3 (0-57)	**0.007**
HEAD-US	52	9.90±9.51 7 (0-33)	11.37±10.67 8 (0-40)	**0.007**
Pettersson	13	17.00±16.32 12 (0-47)	17.23±17.14 14 (0-48)	0.631
Children (6-17 years)				
HJHS	29	1.86±3.07 1 (0-13)	3.17±7.07 1 (0-36)	0.166
HEAD-US	29	4.03±4.59 2 (0-16)	4.69±4.35 5 (0-14)	0.322
Pettersson	6	3.83±4.45 2.5 (0-11)	2.67±2.66 2.5 (0-7)	0.197
Adults (≥18 years)				
HJHS	23	17.96±12.55 17 (0-48)	22.43±15.4 22 (0-57)	**0.017**
HEAD-US	23	17.3±8.96 18 (0-33)	19.78±10.34 22 (0-40)	**0.006**
Pettersson	7	28.29±13.94 32 (12-47)	29.71±13.7 32 (14-48)	**0.041**
Hemophilia A patients				
HJHS	42	8.76±11.56 2.5 (0-48)	10.95±13.61 3 (0-48)	**0.020**
HEAD-US	43	9.35±9.63 6 (0-33)	10.86±10.58 7 (0-40)	**0.010**
Pettersson	10	18.9±17.91 11.5 (0-47)	18.7±18.99 10.5 (0-48)	0.752
Hemophilia B patients				
HJHS	10	9.9±13.16 3.5 (0-36)	14.8±20.15 5 (0-57)	0.232
HEAD-US	9	12.56±8.99 13 (1-30)	13.78±11.4 11 (0-33)	0.338
Pettersson	3	10.67±8.74 13 (1-18)	12.33±9.61 14 (2-21)	0.102
HJHS: Hemophilia Joint Health Score; HEAD-US: Hemophilia Early Arthropathy Detection with Ultrasound; SD: Standard deviation; Min-Max: Minimum-maximum				

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Table 7: Petterson score and its correlation with HJHS and Head-US Scorring system*						
	BASELINE			**12 TH mo**		
	N	**RHO**	**P**	N	RHO	P
Head-US	14	0.842	**<0.001**	13	0.861	**<0.001**
HJHS	14	0.828	**<0.001**	13	0.827	**<0.001**
Spearsman's Rho correlation test						

Table 8: Comparison of the quality of life scores of the patients between the baseline and 12th month.				
	Baseline		**12th month**	
	N	Mean ± SD Median (min-max)	Mean ± SD Median (min-max)	**p**
All patients				
EQ5D	61	0.803±0.209 0.783 (0.043-1)	0.806±0.191 0.783 (0.239-1)	0.777
SF-36, Total	49	77.2±15.94 80.88 (30.75-97.25)	77.2±18.02 83.38 (31.88-98)	0.739
Children (6-17 years)				
EQ5D	31	0.913±0.123 1 (0.624-1)	0.870±0.156 1 (0.48-1)	0.154
SF-36, Total	24	84.09±10.51 85.13 (59-97.25)	87.17±6.42 87.44 (73-98)	0.331
Adults (≥18 years)				
EQ5D	30	0.689±0.22 0.713 (0.043-1)	0.740±0.203 0.78 (0.239-1)	0.381
SF-36, Total	25	70.59±17.58 75.75 (30.75-92)	67.64±20.38 69.13 (31.88-96)	0.628
Hemophilia A patients				
EQ5D	51	0.797±0.217 0.783 (0.043-1)	0.800±0.198 0.783 (0.239-1)	0.752
SF-36, Total	43	77.65±16.33 82.13 (30.75-97.25)	76.75±18.56 83.38 (31.88-98)	0.957
Hemophilia B patients				
EQ5D	10	0.835±0.171 0.806 (0.48-1)	0.839±0.153 0.783 (0.57-1)	1.000

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SF-36, Total	6	74.02±13.67 76.75 (57.88-93.38)	80.46±14.44 82.44 (53.25-96)	0.249
EQ-5D, European Quality of Life-5 Dimensions; SF-36, Short Form-36; SD, Standard deviation; Min-Max, Minimum-maximum				

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