Effect of joint range of motion on health-related quality of life in children with hemophilia

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Received 18 February 2019
Accepted 17 April 2019

Egyptian Rheumatology & Rehabilitation
2019, 46:237–243

Background
Assessment of quality of life (QOL) in patients with hemophilia is important for the disease outcome. In patients with hemophilia, repeated occurrences of hemarthrosis lead to limitations in range of motion (ROM) of major joints.
Objective
The aim of this work is to assess joint ROM and detect the presence of limitation of joint ROM in patients with hemophilia and their effect on the QOL in these patients.
Patients and methods
The study included 25 children with hemophilia recruited from Pediatric Hematology Unit, Fayoum University Hospital, during the period from June 2016 to December 2016. Their ages ranged between 4 and 16 years. Large joint examination and measurement of joint ROM were done at rheumatology clinic using goniometry by rheumatologist. QOL was assessed by using the hemophilia QOL questionnaire.
Results
The most impaired dimensions of QOL were family, treatment, and physical domains. Total health-related quality of life (HRQOL) score, physical health, view of self, and sport and school scores were found worse with increasing age. Patients who had target joints had poor QOL score. Limitation of movement (LOM) of the knee and ankle joints mainly impaired the physical and social aspects and the overall HRQOL, and LOM of shoulder joint impaired the treatment domain.
Conclusion
Age of the patient was found a factor affecting the total HRQOL score, in addition to physical, view of self, and sport and school dimensions. LOM of the knee and ankle joints mainly impaired physical and social aspects and the overall HRQOL.

Keywords:
hemophilia, joint limitation, quality of life, range of motion

Egypt Rheumatol Rehabil 46:237–243

1110-161X

Introduction

Hemophilia is a bleeding disorder of X-linked hereditary. Deficiency in coagulation factor VIII for hemophilia A and factor IX for hemophilia B is the cause of this disease [1]. Patients with severe hemophilia present with spontaneous bleeding since early childhood, chiefly in the musculoskeletal system (muscles and large joints) and, less commonly, mucosal or cerebral hemorrhages. Joint bleeding (hemarthrosis) results in synovial hypertrophy and damage of the cartilage, leading to joint destruction with recurrent bleeding episodes (hemophilic arthropathy) [2].

Overall, 85% of all bleeding events occur in joints in patients with severe hemophilia, with the ankle, knee, elbow, hip, and shoulders being the most commonly affected joints [3]. Recurrent happenings of hemarthrosis and synovitis with joint destruction and pain lead to limitations in joint range of motion (ROM). Joint ROM limitations in patients with hemophilia are increased with more advanced age, high BMI, and non-white ethnicity [4].

Quality of life (QOL) is defined – in correspondence to the WHO definition of health – as patient-perceived well-being and function in terms of physical, emotional, mental, social, and behavioral life domains [5]. Recently, the QOL of children having chronic diseases has received increasing consideration, mainly for frequent pediatric health conditions such as asthma or life-threatening conditions such as leukemia. Conversely, the QOL of young people with uncommon diseases like hemophilia has been largely ignored. It is essential to know more about QOL in this group of patients for better evaluation and improving the care these patients obtain [6]. Instruments for measuring QOL in hemophilia have been made only over the past few years. The hemophilia quality-of-life (Hemo-QOL) instrument is one of the first self-report tools, which is constructed as a set of disease-specific and

age-related questionnaires to measure QOL in children and adolescents with hemophilia, and this instrument was established in the course of the Hemo-QOL project [7].

Chen *et al.* [8] hypothesized that ROM limitations in certain major joints of adult patients with hemophilia largely affect their health-related quality of life (HRQOL). However, the effect of ROM limitations of the major joints on HRQOL in children with hemophilia has been inadequately studied before. The aim of the present study is to assess joint function and detect the presence of limitation of joint ROM in patients with hemophilia and their effect on the QOL in these patients.

Patients and methods

This is a cross-sectional study that included 25 children with hemophilia A and B, their age ranged between 4 and 16 years. All included patients were subjected to full history taking with special emphasis on age of onset of the disease, frequency of attacks, type of therapy administered, and presence of complications. General examination was done to detect pallor, bleeding from sites other than joints, and manifestations of complications. Grading of severity of bleeding into slight, moderately severe, severe, and very severe by assessing of factor activity level was as follow: mild (5–40% of normal activity), moderate (1–5% of normal activity), and severe (<1% of normal activity) [9,10].

HRQOL of hemophilic patients was assessed by newly developed disease-specific Hemo-QOL. The Hemo-QOL is a self-report specific questionnaire with three versions for different age groups: group I included younger children with ages 4–7 years and their questionnaire included 21 items pertaining to eight dimensions (physical health, feelings, view, family, friends, others, sport and school/kindergarten, and treatment). Group II included school children aged 8–12 years and the self-administered questionnaire contains two additional domains (perceived support and dealing), with overall 64 items. Group III included adolescents 13–16 years of age and their questionnaire was expanded with further additional domain (future), consisting of 77 items.

The psychometric structure of the questionnaire has acceptable psychometric properties for the three age group versions [11]. For Hemo-QOL questionnaires, a total score summarizing HRQOL for the patient and domain scores is calculated. Scores range from 0 to 100, with lower scores indicating better hemophilia-related QOL [12]. High values indicate high impairments in HRQOL. Basically high score represents low QOL and scoring involves the following steps:

Assorting numbers to the response scale, which for the age groups II and III are 1=never, 2=seldom, 3=sometimes, 4=often, and 5=all the time. Please note, for the age group I, scoring is 1=never, 2=sometimes, and 3=very often.

Measurement of ROM of 17 movements of the five major joints (bilateral hips, knees, ankles, elbows, and shoulders) was performed at the Rheumatology Outpatient Clinic, Fayoum University Hospital, by a senior rheumatology physician using the goniometry technique. Large joints assessment on examination was performed for the presence of hemarthrosis and presence of target joints (three or more spontaneous bleeds into the joint within a consecutive 6-month period). The measuring method was based on the standard technique described in the guide [13,14] (Table 1). A difference in angles between normal ROM and the participant's ROM of an individual movement was defined as deficit of ROM of the individual movement, and was obtained by subtracting the participant's ROM of the individual movement from normal ROM. Therefore, the deficit of ROM of individual movement was a positive value [8].

The study was approved through ethical committee, Fayoum University. Verbal informed assent or consent from all the study patients or their guardians respectively was taken before data collection.

Table 1 Normal angles of range of motion of major joints

Joints	Action	Degrees of motion
Shoulder	Flexion	0–180
	Extension	0–40
	Abduction	0–180
	Internal rotation	0–80
	External rotation	0–90
Elbow	Flexion	0–150
	Extension	0
Hip	Flexion	0–100
	Extension	0–30
	Abduction	0–40
	Adduction	0–20
	Internal rotation	0–40
	External rotation	0–50
Knee	Flexion	0–150
	Extension	0
Ankle	Plantar flexion	0–40
	Dorsiflexion	0–20

Statistical analysis

Data were collected and coded to facilitate manipulation of the data and double entered into Microsoft Access, and data analysis was performed using SPSS software (Milton, QLD, Australia), version 18, in Windows 7. Simple descriptive analysis was done in the form of numbers and percentages for qualitative data, and arithmetic means as central tendency measurement, SDs as measure of dispersion for quantitative parametric data, and inferential statistic tests were as follows:

(1) For quantitative parametric data:
   (a) In-depended Student's *t* test used to compare measures of two independent groups of quantitative data.
   (b) One-way analysis of variance test in comparing more than two independent groups of quantitative data.
(2) For qualitative data
   (a) χ^2 test to compare two of more than two qualitative groups.

The level *P* value less than or equal to 0.05 was considered the cutoff value for significance.

Results

All patients in the study were males, with a mean age of 8.1±0.78 years old and range between 4 and 16 years. Regarding mothers' education, 64% were educated. Positive consanguinity was present in 16% of cases and 84% had a similar condition in the family.

Overall, 76% experienced hemophilia A, and 24% experienced hemophilia B. Moreover, 60% had severe disease. Clinically hemarthrosis was present in 84% of our cases. All of our patients were on demand therapy, and only 32% of them received prophylactic treatment. The replacement therapy given was plasma in 88% of the patients, recombinant factor in 8%, and one patient received both. Age of first bleeding episode was 7.4±1.8 months, whereas age of first hemarthrosis was 3±0.22 years, and ranged between 1 and 4 years.

Limitation in joint movement was present in 52% and mainly affecting the knees (76.9%). Almost all cases belonging to the age group 13–16 years had target joints and limitation of movement (LOM). No association was found between hemarthrosis, LOM, target joint affection and disease severity, or types of replacement therapy.

There was no statistically significant difference ($P>0.05$) between severity of hemophilia and QOL dimensions. Moreover, there was no significant difference in total QOL score of patients with hemarthrosis, LOM, and the type of treatment.

However, target joint affection was associated with a higher mean±SD QOL score ($P=0.04$), indicating a poor QOL.

The treatment domain of QOL score was significantly higher in patients with LOM of the shoulder joint (31.3±18) ($P=0.04$). Moreover, the future domain was significantly higher in patients with LOM of the knee joint (60.9±4.7) ($P=0.02$). In addition, the physical activity (82.5±4.1) ($P=0.004$), view of self (73.3±6.5) ($P=0.001$), other persons (53.2±4.4) ($P=0.03$), sport and school domains (81.7±5.1) ($P=0.002$), and total QOL (56.9±3.5) ($P=0.008$) were higher in patients with LOM of the ankle joints.

The mean±SD) total QOL score of patients was 45.1 ±14.7, ranging from 10.4 to 73.4. The highest score was found for the family followed by the treatment and physical health domains 79.58±2.8, 67.64±6, and 66.86 ±3.9, respectively. The lowest score observed was that of perceived support, with 30±7.8 (Table 2).

Physical health, view of self, and sport and school scores were found worse with increasing age, where patients of the older age group had the highest scores (Table 3).

A positive correlation was found between the mean total QOL score and development of LOM in the elbow, knee, and ankle joints (*P* values of 0.01, 0.03, and 0.01, respectively) (Table 4).

Joint bleeding was analyzed, and a score was used according to the different questions of the Hemo-QOL questionnaire during the period of the past 4

Table 2 Description of different quality-of-life domains among the study group

Hemo-QOL dimensions	Mean±SD	Minimum	Maximum
Physical health score	66.86±3.9	25	96.43
Feeling score	40.71±4.2	0	89.29
View of self-score	40.27±7.1	0	94.44
Family score	79.58±2.8	37.5	100
Friend score	45.50±7.1	0	100
Perceived support score	30±7.8	12.5	56.25
Other persons score	43±4.8	0	75
Sport and school score	62.79±5.4	0	100
Dealing with hemophilia score	38.57±4.8	25	71.43
Treatment score	67.64±6	0	100
Future score	52.5±9.2	18.75	68.75
Global health score	54±1.9	50	75
Total QOL	45.1±14.7	10.4	73.4

Hemo-QOL, hemophilia quality-of-life; QOL, quality of life.

Table 3 Comparisons of different quality-of-life domains among different age groups

Hemo-QOL dimensions	Age groups			*P* value
	4–7 years (*N*=15) Mean±SE	8–12 years (*N*=5) Mean±SE	13–16 years (*N*=5) Mean±SE	
Physical health score	58.3±4.7	70.7±7.4	88.6±2.1	**0.005**
Feeling score	35.6±5.6	50±11.7	46.9±2.9	0.3
View of self-score	18.3±6.7	71.7±10.7	74.7±6	<**0.001**
Family score	80±4.4	76±3.3	81.9±4.1	0.8
Friend score	50±9.7	58.8±16.1	18.7±4.4	0.2
Perceived support score	–	46.3±5.8	30±7.8	0.1
Other persons score	35±6.8	56.7±8.2	53.3±4	0.1
Sport and school score	50±6.7	80.6±7.9	83.3±5.9	**0.009**
Dealing with hemophilia score	–	46.4±8.4	30.7±2.1	0.1
Treatment score	73.3±9.3	65.7±5.4	52.5±8.1	0.4
Future score	–	–	52.5±9.2	–
Global health score	50±0	65±6.1	55±5	**0.003**
Total quality of life	37.5±3.2	57.3±5.6	55.7±3.7	**0.003**

Hemo-QOL, hemophilia quality-of-life. Bold values are significant at p<0.05.

Table 4 Correlation between bleeding score, domains of quality of life with degree of limitation of movement among study group

LOM	Bleeding	PS	FS	VOS	FaS	FrS	PS	SS	DH	TS	FS	TQOL
Shoulder												
r	0.48	0.18	–0.09	0.19	–0.24	–0.27	0.27	0.09	–0.22	–.38	0.31	0.07
P value	0.02	0.4	0.7	0.4	0.3	0.2	0.4	0.7	0.5	0.07	0.6	0.7
Elbow												
r	0.63	0.15	0.38	0.53	–0.02	–0.05	0.19	0.35	0.18	–0.08	0.75	0.49
P value	**0.002**	**0.02**	0.06	**0.007**	0.9	0.8	0.6	0.08	0.6	0.7	0.1	0.01
Hip												
r	0.34	0.16	0.03	0.14	–0.12	–0.08	0.38	0.16	–0.22	–0.25	–0.07	0.10
P value	0.1	0.4	0.9	0.5	0.6	0.7	0.3	0.5	0.5	0.2	0.9	0.6
Knee												
r	0.62	0.49	0.18	0.47	0.01	–0.23	–0.16	0.36	0.07	0.006	0.81	0.42
P value	**0.002**	**0.01**	0.4	**0.01**	0.9	0.3	0.7	0.07	0.8	0.9	0.1	0.03
Ankle												
r	0.80	0.52	0.1	0.59	–0.04	–0.18	0.17	0.49	–0.07	–0.22	0.30	0.50
P value	**0.001**	**0.007**	0.6	**0.002**	0.9	0.4	0.6	**0.01**	0.8	0.3	0.6	0.01

DH, dealing with hemophilia score; FaS, family score; FrS, friend score; FS, feeling score; FS, future score; LOM, limitation of movement; OP, other persons score; PS, perceived support score; PS, physical health score; SS, sport and school score; TQOL, total quality of life score; TS, treatment score; VOS, view of self-score. Bold values are significant at p<0.05.

weeks before the study. Regarding the frequency of bleeding events, it was found that three patients did not bleed, 10 patients were exposed to bleeding more than two times. Experiencing bleeding attacks was found sometimes in 13 patients. Regarding the severity, eight patients had slight bleeding, five patients had moderately severe bleeding, 10 patients had severe bleeding, and two patients had very severe bleeding attacks. As for the strange feeling in joints, we found eight patients could not predict the bleeding before it occurred, nine patients rarely could get that feeling, and four always could predict the bleeding before it happened. According to staying quiet in bed, it was found that 13 patients seldom lied quiet in bed during the bleeding attack.

The mean bleeding score was 50.86±4.8 and was significantly higher with increasing age (79.04±3.6) (*P*<0.001). The bleeding scores of shoulder, elbow, knee, and ankle joints were 74.6±11.1, 72.1±5, 67.1 ±5.3, and 74.6±3.1, respectively.

Besides joint bleeding, all cases had history of bleeding from other sites: 40% during circumcision, 76% had epistaxis and bleeding gums, 8% bleeding from injection sites, 8% hematemesis, 4% for hemoptysis, 76% had ecchymosis, intracranial hemorrhage in 12%, hematuria in 12%, and 4% after dental procedure. When comparing the different sites of bleeding among different age groups, mucosal bleeding and ecchymosis were more prevalent among cases of

younger age (4–7 years) than other age groups, with a statistically significant difference ($P<0.05$).

A positive correlation was found between the bleeding score and LOM of shoulder, elbow, knee, and ankle joints ($P=0.02$, 0.002, 0.002, and 0.001, respectively), indicating that a higher score was associated with worsening of the LOM of the joints affected (Table 4).

There was a statistically significant positive correlation, with *P* value less than 0.05, between LOM of elbow joint score and physical and view domains, between knee joint score and physical and view domains, and between ankle joint score and physical, view, and sport domains, which indicates that higher LOM score is associated with an increase in the domains' score (Table 4).

Discussion

Joint disease in hemophilia resembles arthritis as the damage of joint, tendons, ligaments, and soft tissue is getting worse with time, resulting in pain, restricted movement, muscle atrophy, and reduced ROM [3].

Hemarthrosis has been found to be the most common (84%) presenting feature in this study followed by mucosal bleeding and skin bleeds (76%). Karim *et al.* [15], reported that hemarthrosis (82%) and skin bleeds (72%) were the most common clinical manifestations. Target joints were present in 36% of the studied hemophilic patients. The knee joint was the predominant target joint in 90% of cases and the ankle joint in 60%. Moreover, Payal *et al.* [16], reported that 37.5% of hemophilic patients developed target joint, and the knee joint was the principal target joint in 28.57% of cases and ankle joint in 8.92%.

In the present study, it was found that the first hemarthrosis was at the age of 3±0.22 years and ranged between 1 and 4 years. This was in agreement with Abdel Ghany *et al.* [17], who found that the mean age of first hemarthrosis in severe hemophilic patients was 2.22±1 years and ranged from 0.5 to 4.0 years.

LOM was present among 52% of patients; the most commonly affected joints were the knee in 76.9% followed by the ankle in 69.2%. It was found that the target joints and LOM were higher among older age groups mainly in group III (age 13–16 years) with significant difference. As joint damage becomes progressive, the symptoms get worse with increasing age of patients with hemophilia. Moreover, another study reported that functional joint impairments were detected in nearly only one-tenth of European patients with a significant increase in the group III (age 13–16 years) [11].

However, Tantawy and colleagues, reported no differences between the three age groups regarding hemarthrosis and LOM. In addition, they stated that in the majority of the young age group (age 4–7 years) and in all patients with older age (age 13–16 years) at least one target joint was present [18]. Bullinger and Von Mackensen [5] reported that target joint and limitation were present in only half of the children: 61% of the old age group (age, 13–16 years) in contrast to young age group (age, 4–7 years).

The present work revealed that there was no significant association between hemarthrosis, target joints, and limitation of joints movement and different degrees of disease severity. However, another reported that the risk of developing a target joint was more in patients with severe hemophilia compared with those with moderate or mild hemophilia (33.1 vs. 18.8% and 5%, respectively) [19].

Moreover, Prejs and colleagues, reported that the initial hemarthrosis occurs during the first year of life in patients with severe hemophilia, and 90% of youths with severe factor VIII or factor IX deficiency had at minimum one joint hemorrhage before the age of 4.5 years and more were exposed to develop hemophilic arthropathy with limitation of joint movement more than the other degrees of hemophilia [20].

Recently, HRQOL for different diseases had received increasing concern, but factors that may positively or negatively affect the QOL of children with hemophilia and the differences in these factors among different countries were not studied on a large scale [21].

The findings of the present study revealed that the mean total QOL score was 45.1±14.7, ranging from 10.4 to 73.4. The most impaired dimensions of QOL were family, treatment, and physical domains and less impairment in support, dealing, and view of self-domains. Physical health, view of self, and sport and school scores were found worse with increasing age ($P=0.005$, 0.001, and 0.009, respectively), which indicates a poor QOL with increasing age. This is in agreement with that described in a study in Italy by Scalone *et al.* [22], in which the overall QOL was found to be negatively associated with age in both

questionnaires. In addition, this is in agreement with a previous study in Egypt by Tantawy *et al.* [18], in which HRQOL was assessed by Hemo-QOL questionnaire. However, it is in contrast to a study in Iraq by Taha and Hassan [6] in which HRQOL was not affected by age of the patients.

Young children are mainly impaired in family and treatment dimensions, whereas older children have impairment in physical, sport, view of self, family, feeling, friend, and future scores. This is in agreement with that reported by Gringeri *et al.* [11] and Remor *et al.* [23]. This can be explained by the overprotection of parents for their young children, reflected in the family dimension, whereas older children had higher impairments in the social and physical dimension.

The present study showed that patients with target joints had a poor QOL compared with those without (P=0.04). Moreover, patients with hemarthrosis and LOM had a poor QOL score compared with those without, but this did not reach significance. Karin and Berntop [24] stated that patients' QOL was severely affected hemarthrosis, recurrent joint bleeding, and LOM.

There was no significant difference in total QOL score regarding prophylactic treatment; this could be explained by small number of prophylactic treatment patients in the study and short time of study to show the effect of regular prophylaxis on QOL. However, Royal *et al.* [25], suggested that hemophilic patients who were treated prophylactically have a better QOL when compared with those who were treated on demand.

Results of the present study revealed that LOM of the knee and ankle joints mainly affected physical and social aspects and the overall HRQOL. The knee LOM made a significant effect on the future dimension; the ankle LOM had a significant effect on physical health, sport and school, view of self, other persons dimension, and the total QOL score; and shoulder LOM affected the treatment dimension. None of our patients had hip joints LOM. Chen *et al.* [8], in his study group (mean age, 36.9 years) showed that the deficit in ROM of the major joints in adults lead to diminished HRQOL in physical, mental, and social aspects, where limitation of the hip and ankle joints mainly affected the physical health dimension, whereas limitation of elbow and shoulder joints chiefly affect emotional and mental health.

Conclusion

Hemophilia like any other chronic disease affects different aspects of patients' life and also causes variable degrees of disability. Age of the patient was found as a factor affecting the total HRQOL score, in addition to physical, view of self, and sport and school dimensions, which indicated more affection of QOL with increasing age. LOM of the knee and ankle joints mainly impaired physical and social aspects and the overall HRQOL.

The limitations of this study is the small sample size and that most patients were on demand therapy.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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