Haemophilia

Haemophilia (2012), 1–5 DOI: 10.1111/j.1365-2516.2012.02765.x

ORIGINAL ARTICLE

Quality of life in adult patients with haemophilia – a single centre experience from Sweden

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Summary. Increased or maintained health and quality of life (HRQoL) are essential goals in health care among patients with a chronic disease. To gain an understanding of HRQoL in patients with haemophilia at the Haemophilia Treatment Centre in Malmö, Sweden, patients seen from 2004–2008 were asked to complete the Short form Health Survey, SF-36, also answering to what extent haemophilia, physically and mentally, interferes with their daily life at their annual check-up. Data were extracted from the UMAS Haemophilia Database. Interference of haemophilia in daily life was estimated using a Visual Analogue Scale. A total of 105/144 haemophilia patients were included in the study (73%); 28 mildly, 21 moderately and 56 severely affected. The median age of patients at study entry was 44.0 years (range 18–84 years). The comparison of SF-36 data of Swedish haemophilia patients with the general Swedish male population yielded no significant differences in age groups 15–24, 25–34 and 65–74 years. Patients in age groups 35–44 years, 45–54 years and 55–64 years were significantly impaired in some of their HRQoL domains. For severely affected patients who filled in SF-36 over a period of 5 years no statistical differences in HRQoL were found. For patients undergoing orthopaedic surgery HRQoL increased in most SF-36 domains. Patients reported in general on the VAS that they feel 'somehow' interfered in their daily life due to haemophilia. The results indicate a need for continuous monitoring of HRQoL to identify an increased need of care in the ageing haemophilia population.

Keywords: adult patients, haemophilia, health-related quality of life, severity, Sweden

Introduction

Health is defined by the World Health Organization (WHO) as 'a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity' [1]. The direct perception of the patient plays an important role. Improved or maintained health and health-related quality of life (HRQoL) are essential goals in health care among patients with a chronic disease and those who are disabled.

Haemophilia is an x-linked recessive bleeding disorder affecting men. According to the residual plasma coagulation factor activity, i.e. factor (F)VIII or FIX it is possible to distinguish different types of severity: haemophilia A and B are defined as '*severe*' with the representative factor activity below 0.01 IU mL^{-1} (<1%), '*moderate*' with a factor activity between 0.01 and 0.05 IU mL^{-1} (1–5%) and 'mild' with a factor activity between 0.05 and 0.40 IU mL^{-1} (5–40%) [2]. Studies have demonstrated an impact of severity on the HRQoL of haemophilia patients [3,4].

Prophylactic treatment in Sweden was widely implemented during the 1960s and the early 1970s. In the beginning limited supplies of factor concentrate were available and furthermore most of the boys were quite old and had already developed haemophilia arthropathy when they started prophylactic treatment ('secondary prophylaxis') [5]. Treatment is nowadays started in patients with severe haemophilia at the age of 1 year, before the joints become affected. This so-called 'primary prophylaxis' [6] is instituted as a long-term continuous treatment prior to any clinically evident joint bleeding and continuously ideally for 52 weeks annually but at a minimum of 45 weeks per years. At the Malmoe centre in Sweden, the prophylactic treatment is given continuously throughout adulthood. Patients with severe haemophilia who start prophylactic treatment before the age of 3 years have significantly better joint outcomes [7] and several studies have reported an increased HRQoL in patients who started prophylactic treatment at an early

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Accepted after revision 18 January 2012

age [8,9]. An affected joint causes severe pain in many patients and an option for these patients to diminish pain is orthopaedic intervention such as ankle arthrodesis or knee/hip replacement. Total joint replacement has improved HRQoL in these patients and has reduced spontaneous haemarthroses [10].

Due to plasma contamination many patients have been infected until the early 1990s with blood-borne viruses such as HIV [11] and Hepatitis C [12]. However, at the Malmoe centre the last infection with HCV is dated to 1986. Even though treatment for Hepatitis C is available, some patients refuse treatment due to side effects of the medication. Both HIV and Hepatitis C have been demonstrated to be associated with decreased HRQoL in many patients [3,7,13].

The objective of the present study was to assess patients' HRQoL and to compare it with the norm data of the general population of Swedish males in the according age groups. In addition we wanted to analyse the change of HRQoL over time and after orthopaedic interventions.

Materials and methods

This was a quantitative longitudinal study with a 5 year follow-up performed at the Haemophilia Treatment Centre in Malmö, Sweden.

Study population

A total of 325 patients with severe (n = 136), moderate (n = 46) and mild haemophilia (n = 143) were registered at the Malmoe centre. One hundred and forty-four patients aged >18 years who had filled in the SF-36 and VAS scale during their annual check-ups between 2004 and 2008 were asked whether they would agree that their data could be analysed in this ancillary study comparing their HRQoL data with the general population. The study was approved by the Ethics Committee at Lund University, Sweden and informed consent was obtained from the patients.

Instruments

Data were extracted from the UMAS Haemophilia Database, which is a centre based registry containing data of patients with congenital bleeding disorders [14]. The database has been in operation since 1986 and is continuously developed. It contains information on clinical data such as diagnoses, treatment, bleedings, joint score and HRQoL issues (SF-36, VAS) as well as socio-demographic information such as employment status and education. The main purpose of the database is to facilitate daily routine work for the haemophilia nurse and to extract data for scientific studies.

The Short Form Health Survey (SF-36) is a self-administered generic HRQoL questionnaire for adults [15] allowing the comparison of a specific disease such as haemophilia with norm data of the general populations related to gender and age groups. It consists of 36 items pertaining to eight dimensions of HRQoL (PF, physical functioning; RF, role physical functioning; BP, bodily pain; GH, general health perception; VT, vitality; SF, social functioning; RE, role emotional functioning; and MH, mental health). Each of the eight domains can be transformed into scores ranging from 0 (worst quality of life) to 100 (best quality of life); two summary scores can be calculated for physical component score (PCS) and mental component score (MCS) respectively. The SF-36 has been translated, psychometrically tested, and normed in over 30 countries and is available in most European languages. A manual with Swedish norm data [16,17] for different age groups and gender is available.

Visual Analogue Scales (VAS) have been used in psychological assessment since the early years of the 20th century and are often used for measuring pain and have also been incorporated into health-related quality of life instruments [18]. VAS is a line that represents the continuum of the symptom which has to be rated. The distance of the respondent's mark from the lower end of the scale, measured in millimetres, forms the basic score, ranging from 0 to 100. In this study, 0 was considered as no interference of haemophilia with daily life (physically and mentally) and 100 as maximum interference.

Data analysis

Statistical analyses were performed using SPSS Inc., Chicago, IL, USA version 17.0. The study population has been grouped into men in similar age groups according to the Swedish SF-36 manual to compare our results with the general population of Swedish males according to SF-36 norms i.e., 15–24 years, 25–34 years, 35–44 years, 45–54 years, 55–64 years, 65–74 years and >75 years respectively. In this study only patients ≥18 years of age were included. The age was calculated for the year the patient filled in for the first time the SF-36 and VAS.

Clinical and socio-demographic data were presented as frequency distribution in percentage or as mean (M) ± standard deviation (SD) and range (min-max). Data for SF-36 and VAS were reported for M ± SD and correlations were analysed with Pearson correlations. Differences in HRQoL across patients with different severities were calculated using ANOVA. Testing for variables having an impact on patient's Physical Component Score, PCS, a multiple linear regression stepwise model was performed.

For comparison of HRQoL between patients with haemophilia and the Swedish general male population the Student's t-test was used.

When calculating the GLM (General Linear Model) for repeated measures for data collected over 5 years only those patients who had values in all domains of the SF-36 were included.

For measuring differences before and after orthopaedic surgery the paired Student's *t*-test for repeated measures was used, considering the year before the surgery and the last HRQoL assessment after the surgery. Four patients were not considered in this analysis, since they had neither a HRQoL assessment the year prior the surgery nor a HRQoL assessment the year after the surgery; in total this comparison was performed for nine patients.

Results

A total of 105/144 (73%) patients gave their permission to use their data for this ancillary analysis and were included in the study after obtaining written informed consent; two patients could not give their consent, because one patient died and one patient moved to another centre. Thirty-seven patients decided not to participate in the study; they were comparable with the participants in their socio-demographic and clinical data. Fourteen patients out of 105 filled in the questionnaire over the complete period of 5 years (2004–2008), of whom 10 had severe haemophilia.

The median age for included patients at study entry was 44.0 years (range 18–84 years). The majority of the patients were living with a partner (65.6%). Fifty-seven per cent of the cohort had a high school education and 82.5% were in a full-time position. Three per cent of the patients were unemployed and 8.3% had early retirement due to haemophilia.

The distribution of haemophilia patients with regard to their disease severity was as follows: mild (26.7%) moderate, (20%) and severe (53.3%). Clinical data including replacement therapy, presence of inhibitor, viral infection and orthopaedic surgery of the study population are shown in Table 1.

Patients across different severities showed different impairments in their HRQoL. Severely affected patients were more impaired in their 'physical functioning' than moderate or mild patients. By contrast moderate patients reported more impairment in 'general health' and 'mental health' compared to severe and mild patients (see Fig. 1). Patients with HCV infections reported almost in all domains of the SF-36 higher impairments compared to patients without HCV infections (see Fig. 2). Patients diagnosed with current or previous inhibitors reported higher impairments in their 'physical functioning' (PF), $P \leq 0.027$ than patients without inhibitors. No differences in HRQoL were found for HIV infection and living situation in the cohort.

Patients reported in general on the VAS that they feel 'somehow' interfered in their daily life due to haemophilia ($M = 30.44$, SD = 26.3); patients with mild haemophilia were less impaired ($M = 23.43$, SD = ;27.0) compared to moderate ($M = 34.33$, SD = 23.5) or severe haemophilia patients ($M = 32.48$, SD = 26.7).

High correlations were found for patients who reported high interference of haemophilia with their daily life on the VAS and Physical Component Score (PCS), ($r = -0.793$, $P = 0.000$); the correlation is negative since a high value in the PCS means a good HRQoL, while a high value in the VAS means a high interference with daily life. No significant correlation was found with the Mental Component Score (MCS), ($r = 0.076$, $P = 0.570$).

The comparison of SF-36 data of Swedish haemophilia patients with the general Swedish male population revealed that there were no significant differences for the age groups 15–24 years, 25–34 years and 65–74 years. By contrast patients in the age group 35–44 years (ER: $t = 2.421$, $P < 0.0252$) (Fig. 3a),

Table 1. Clinical data of the study population.

	Severe haemophilia ($n = 56$)	Moderate haemophilia ($n = 21$)	Mild haemophilia ($n = 28$)	Total population ($n = 105$)
Clinical data	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Age in years	39.0 (14.9)	44.8 (16.3)	48.8 (16.5)	42.8 (16.1)
	n (%)	*n* (%)	*n* (%)	*n* (%)
Type of Haemophilia				
A	41 (73.2)	17 (81)	23 (82.1)	81 (77.1)
B	15 (26.8)	4 (19)	5 (17.9)	24 (22.9)
Treatment				
Prophylaxis	54 (96.4)	10 (47.6)	1 (3.6)	65 (61.9)
On-demand	2 (3.6)	11 (52.4)	27 (96.4)	40 (38.1)
Inhibitor				
Current	2 (4)	0 (0)	0 (0)	2 (2)
Previous	3 (9)	0 (0)	0 (0)	3 (3)
HCV RNA positive	24 (43)	7 (33)	9 (32)	40 (38)
HIV positive	6 (11)	4 (19)	0 (0)	10 (10)
Orthopaedic surgery (2004–2008)	10 (17.9)	2 (9.5)	1 (3.6)	13 (12)

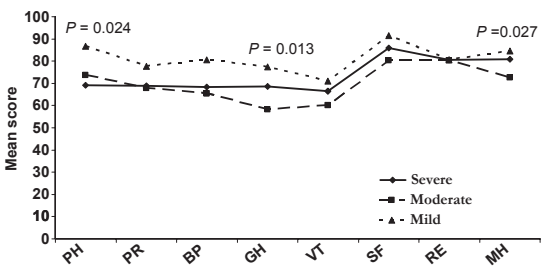

Fig. 1. Comparison of HRQoL across patients with different severities.

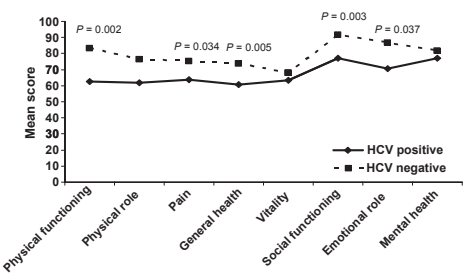

Fig. 2. Comparison of HRQoL between patients with and without HCV infections.

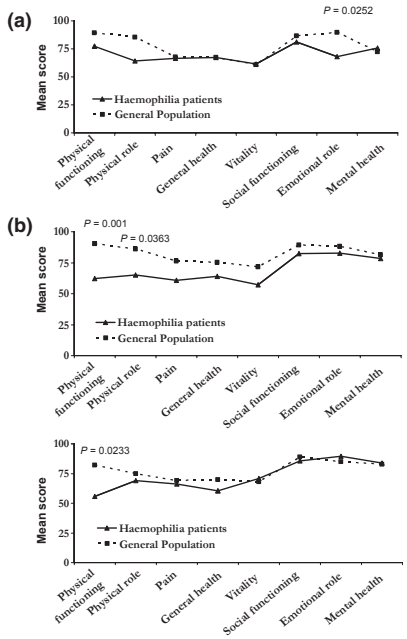

Fig. 3. a,b,c - Comparison of SF-36 of haemophilia patients compared with the general population of age group 35–44 years (n = 24), 45–54 years (n = 23) and 55–64 years (n = 13) respectively.

45–54 years, (PF: t = 4.854, P < 0.001; PR: t = 2.261, P < 0.0363) (Fig. 3b) and 55–64 years, (PF: =2.622, P < 0.0233) (Fig. 3c) were significantly impaired in some of their HRQoL domains. For the age group >75 years only two patients filled in the questionnaire.

Regression analysis showed that 30.8% of the variance in HRQoL for the Physical Component Score (PCS) of the SF-36 could be explained by age of start of prophylaxis, bleeding frequency and orthopaedic joint score independently (P < 0.001). The earlier the patient started prophylaxis, the higher was the HRQoL. By contrast the Mental Component Score (MCS) was not associated with these variables.

A significant negative correlation between orthopaedic joint score (high value indicates negative orthopaedic status) and PCS (high value indicates good HRQoL) was found (Year 2004: r = −0.667 (P = 0.000), 2005: r = −0.462 (P=0.001), 2006: r = −0.567 (P=0.000) and 2007: r = −0.415 (P = 0.007), but no significant correlation with MCS.

A total of 10 out of 56 severely affected patients filled in the SF-36 over the complete period of 5 years (2004–2008); no statistical significant differences in the HRQoL domains were found over the years 2004–2008 (data not shown).

Thirteen patients had orthopaedic interventions in the period from 2004 to 2008, of which five patients underwent surgery with ankle arthrodesis, four had knee replacement (one patient both knees at the same time), two had hip replacement and two patients were documented to have had minor surgery, i.e. Ulnaris transposition and resection of Capitulum Radii. For all

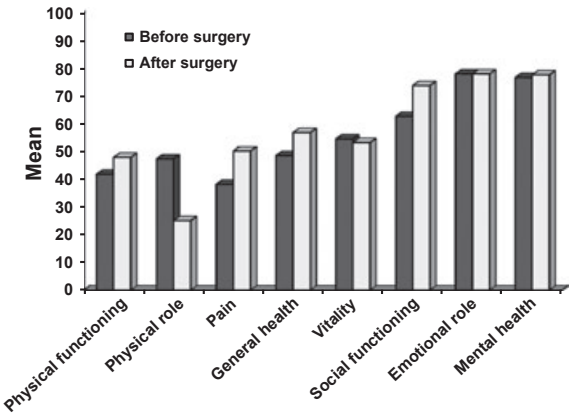

Fig. 4. Comparison of HRQoL before and after orthopaedic intervention (n = 9).

nine patients for which a HRQoL assessment the year prior and after the orthopaedic surgery was available HRQoL increased in almost all SF-36 domains after orthopaedic intervention, but decreased in 'physical role' (PR). These differences were not significant (Fig. 4).

Moreover, in patients who underwent prosthesis surgery (n = 5) 'physical functioning' (PF) increased significantly after surgery ($P \leq 034$).

Discussion

Patients with haemophilia reported almost as high HRQoL as the Swedish general population.

Differences can mainly be seen in the domains 'Physical Functioning' and 'Physical Role' in the age groups 45–54 and 55–64 years. Patients in these age groups did not start prophylactic treatment at an early age and had developed haemophilia arthropathy due to bleedings, especially in knees and ankles. Several studies have shown the importance of an early start of prophylactic treatment to avoid development of haemophilia artropathy [3,7,13]. In Sweden, most patients continue their prophylactic treatment when they are adults but some patients increase the interval between treatments and few patients switch to on demand treatment. The question whether prophylactic treatment throughout adulthood should stop or not, is being discussed intensively. There is an ethical dilemma to increase the interval between treatments or even stop prophylactic treatment that has been going on since an early age to eliminate the risk of bleedings and increase HRQoL when the severity of the patient's haemophilia is the same. On the other hand, as people grow older they are generally less physically active and therefore less likely to get traumatic bleeds. But elderly patients will have age-related co-morbidities such as balance dysfunction and falling tendency with an increased risk of intracranial haemorrhage [19]. Another aspect that must not be neglected is economy. Prophylactic treatment is more expensive than on demand treatment despite the fact that

patients with prophylactic treatment have less bleeds, are absent fewer days from school or work, spend fewer days in hospital and have a higher HRQoL [20,21].

Patients in the current study were asked to estimate on the VAS scale to what extent haemophilia interfered in their daily lives, both physically and mentally. As the question covered both the physical and the mental health of the patients, it did not allow the VAS instrument to measure the difficulties differentiated for both aspects. The question should perhaps have been divided into two separate ones to measure to what extent the patient's physical and mental health, respectively, is impaired by haemophilia since the physical and mental well-being of the patient does not necessarily correlate with each other. On the other hand, the HRQoL questionnaire SF-36 provides information on both physical (Physical Component Score – PCS) and mental (Mental Component Score – MCS) parameters.

Patients with hepatitis C reported lower HRQoL in most of the domains of SF-36. It seems obvious that hepatitis C has a major effect on HRQoL. In addition to side effects of the treatment, patients also fear having to be on the sick list for a longer period of time and to inform their employer about haemophilia, especially patients with a mild form of the disease [22].

Although many old patients with a severe form of haemophilia are severely impaired by haemophilia arthropathy, no statistical significance showing improvement of HRQoL after orthopaedic surgery was seen, however, a trend towards improvement could be shown in patients undergoing knee or hip replacement where PF (Physical Functioning) increased. We have not found any previous studies where QoL had been measured before and after orthopaedic interventions and the number of patients who had undergone orthopaedic interventions in this study is small, which makes the result vague, as the study certainly is underpowered.

Conclusion

Prophylactic treatment has improved HRQoL and life expectancy in adult patients with haemophilia. With adequate treatment the patient with haemophilia will face co-morbidity in the same extent as in the general population but patients who started prophylactic treatment later in life also have to cope with disability due to haemophilia arthropathy. To maintain a high HRQoL in the haemophilia patient the results from this study indicate a need for continued monitoring of HRQoL parameters to identify an increased need of care in the ageing haemophilia patient and his family.

Disclosures

The authors stated that they had no interests which might be perceived as posing a conflict or bias.

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