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– ORIGINAL PAPERS –

Is Quality of Life Better in Hemophilia Patients with or Without Prophylactic Treatment? Using Haemo-SYM to Answer the Question

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Abstract

Hemophilia A is a bleeding disorder that is caused by a clotting factor VIII deficit. For years the research in Hemophilia was focused on new therapies, but since novel treatments brought a longer span of life for patients, the question of how greatly these treatments improved patients QoL arose. In Romania prophilactic treatment has been approved only in 2017. Until then our main focus was the life span of patients, but since the introduction of the prophilactic program we started to ask ourselves the same question. Therefore we collected data from 100 patients, 50 with prophylactic treatment and 50 without prophilactic treatment and applied the Haemo-SYM questionnaire and a selfevaluation tool. We found that QoL life has been improved slighlty by the recent introduction of prophylaxis in our country and that the Haemo-SYM has proven once again as a useful tool in assessing QoL.

Keywords: *quality of life, Haemo-SYM, hemophilia, bleeding*

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Introduction

Hemophilia A is a genetically transmitted bleeding disorder which manifests with a factor VIII deficiency. Patients can present with prolonged bleeding with or without trauma and should be given treatments that stimulates the production of clotting factor VIII, treatments that were first introduced in the 1990's, until then only supportive treatments being available. [1] More recently, since the discovery of effective treatments, bleeding episodes are not so often encountered in hemophilia patients, hence the focus has shifted a bit in

assessing not only the objective efficacy of the drugs but also the subjective progress, which can be assessed by QoL. The tool chosen for this study was Haemo-SYM seeing that it's focus on symptom severity, which consequently impacts QoL2. We aimed to compare the subjective autoevaluation done by patients with the objective assessment done by our orthopedic colleagues regarding patients mobility. The limitations of this study are represented by the fact that at the time of data collection, most patients were on prophylactic treatment only for 1-2 years prior to data collection; the introduction of prophylactic treatment protocols in Romania was done only as late as 2017, being available to a majority of patients in 2018-20193-4. We believe it is important to mention that some of the patients included in this study were on prophylaxis treatment for a longer period of time, due to them buying the coagulation factor from other countries until it was accessible in our country. Consequently, not all patients were at that moment, and some are not yet undergoing prophylaxis, which results in hemorrhagic episodes more often than in other countries.

Objectives

Our aim was to prove that this tool can be used in correctly assessing QoL in hemophilia patients, and might be used in clinical practice to monitor and personalize patient treatment.

Materials and method

Inclusion criteria in the study were selected as male adult patients, which in Romania is over 18 years, with the diagnosis of inherited Hemophilia A, which were seen from 01.11.2021- 30.04.2022 in the inpatient unit of the Hematology Clinic in the Emergency Municipal Hospital Timişoara and from Medical Center for Young Adults and Children "Cristian Serban" from Buzias, Romania. Exclusion criteria were represented by children, other bleeding disorders, such as Hemophilia B, von Willebrand disease and acquired hemophilia, etc. From the study were also excluded patients that could not understand and consent the study. This was done having in mind the research ethics, our peers demonstrated the need for it in their paper[5]. The group was divided into two categories: prophylaxis treatment group that consisted of 50 patients, and the on-demand group, that consisted of 50 patients. Each patient was given a consent form to sign prior to completing the questionnaire. All patients completed the Haem-SYM autoevaluation questionnaire and were asked to give an autoevaluation mark from 0-100 on how good they feel in the day of the assessment. Moreover, data such as age, marital status, residence (rural or urban), number of children, comorbidities, medication and paraclinical determinations were collected from patient charts. We measured the level of factor VIII activity at the moment of data collection, and compared it with those at diseases diagnosis. Even though are fully aware that the form of disease does not change throughout a patient's life, we have named this parameter as current evolutionary stage. We did this in an attempt to measure both from a clinical and paraclinical perspective, the evolution of our lot. The data was centralized using an Excel table. The statistical analysis was done using Epi Info 7.2.5.0. The categorical variables were described using frequency and percentages. The continuous variables were described using standard deviation and media. Difference in distribution of two categorical variables was tested using the chi square test, and the Fisher exact test was used when the number of frequencies within a category was very low. For continuous variables, the group homogeneity was appreciated using the Bartlett test. For semnificative differences ($p<0.05$), the Mann-Whitney test was used to study the meaning of the differences. When we found insignificant homogeneity differences ($p>0.05$) the difference significance was tested with t-Student test. Significant differences were considered when $p<0.05$. The correlations between continuous variables were tested using the Pearson coefficient (r) with significance (p). Significance was considered at $p<0.05$ with 95% confidence interval. The Anova analysis was used to test the differences between the media of more than one group.

The Haemo-SYM questionnaire, permission for use and scale interpretation was provided by Anne Rentz, research scientist for Evidera. The questionnaire was validated by dr. Rentz in a study done in 2009 and was used in other studies where the aim was to evaluate QoL when giving on-demand and prophylactic treatment to patients such was done by Barbara A. Konkle at all in 2015[6].
The Haemo-SYM consists of 17 items and 2 additional questions which patients need to assess how severe the symptom was in the last month, 0 being absent, 1-very mild, 2- mild, 3-moderate, 4-severe, 5-very severe. The results might vary between 0 and 95, 0 being the best QoL and 95 representing the worst QoL. The autoevaluation mark ranged from 0 being the worst state of health ever encountered and 100 being the best state of health ever

felt. The data obtained from both tools was centralized in an Excel sheet and analyzed using the Epi-Info7.2.5.0.

Results

Homogeneity factors

For a correct assessment of the lot we have designed table 1, which paints a clear picture of our patients.

	Lot A (without prophylactic treatment/ on demand)	Lot B (with prophylactic treatment)	The meaning of the difference
Median age	m=42.33; d.s.=10.41	m=39.98; d.s.=11.65	p=0.29
Living - rural	58.82%	54.00%	p=0.69
Education level – superior level	54.90%	72.00%	p=0.10
Employment status – employed population	25.49%	38.00%	p=0.20
Marital status: 1. Bachelor 2. Married 3. Divorced/ widowed	 33.33% 50.98% 15.69%	 38.00% 56.00% 6.00%	p=0.29
Number of children	m=0.82; d.s.=0.87	m=0.72; d.s.=0.76	p=0.52
Family with hemophilia	49.02%	40.00%	p=0.43
Severe forms of disease	78.43%	82.00%	p=0.80

Table 1. *Homogeneity factors of our patient lot*

QoL favoring factors

Our initial expectation was that when compared the on-demand and prophylaxis groups we would find a significant difference, but while viewing the scores of Haemo-SYM and self-evaluation mark based on the presence of prophylaxis, we seem to have found a lack of statistical significance between the on-demand and prophylaxis (self-evaluation mark: t=0.69, p=0.49; Haemo-SYM: t=0.44, p=0.66), difference that is not impacted by careful analysis of the prophylaxis and by taking into account the number of years since start of prophylaxis (self-evaluation mark: t=1.17, p=0.25; Haemo-SYM: t=1.55, p=0.13).

The existence of comorbidities impacts the QoL when assessed by the self-evaluation mark (mo=71.77, d.s.=14.04; m1=63.81, d.s.=17.55; Bartlett's test: χ^2=1.48, p=0.22; t=1.96, p=0.05); but that is not the case for Haemo-SYM (mo=34.05, d.s.=17.53; m1=41.71, d.s.=18.63; Bartlett's test: χ^2=0.12, p=0.73; t= -1.73, p=0.09).The cardiovascular pathologies associated to hemophilia impact QoL of patients when compared to both self-evaluation mark (t=2.49, p=0.01) and Haemo-SYM scores (t= -2.43, p=0.02), situation which is similar when referring to infectious diseases (self-evaluation mark – t=2.74, p=0.007; Haemo-SYM – t= -2.09, p=0.04). In regards to hematological (self-evaluation mark – p=0.18, Haemo-SYM – p=0.71) and neuropsychiatry comorbidities (self-evaluation mark – p=0.16, Haemo-SYM – p=0.41) the significance is not found. When taking into account other comorbidities, these have a significant influence on QoL on the self-evaluation mark, where we find a better QoL in patients without comorbidities (p=0.05), meanwhile the results from the Haemo-SYM scale are influenced in the sense of a higher score in patients with comorbidities, therefore a lower QoL, but without this difference reaching a statistical significance (p=0.19).

The distribution between groups of case with or without comorbidities does not have a significant difference for overall comorbidities (χ^2=0.29, p=0.59), cardiovascular (χ^2=0.03, p=0.88), infectious (χ^2=0.08, p=0.78), hematological (χ^2=0.13, p=0.72), neuropsychiatry (χ^2=0.08, p=0.78), nor for other comorbidities (χ^2=0.89, p=0.35).

In the lot without prophylaxis the scores obtained at the self-evaluation scales are quite high, while on the Haemo-SYM are quite low, therefore patients quote a better QoL on those without comorbidities contrary to those with comorbidities (self-evaluation: m0=71.70, d.s.0=10.10; m1=62.59, d.s.1=17.37; Haemo-SYM:m0=31.10, d.s.0=15.91; m1=43.22, d.s.1=20.17), but without the difference reaching a statistical significance (self-evaluation: t=1.59, p=0.12; Haemo-SYM: t= -1.77, p=0.08). The results are similar when looking at cardiovascular comorbidities (t=1.96, p=0.06), infectious

(t=1.60, p=0.12), hematological (t=0.45, p=0.65) and other comorbidities (t=1.73, p=0.09) in the case of self-evaluation assessment. In regards to neuropsychiatry comorbidities, the trend for self-evaluation mark median is reversed (m0=63.60, d.s.0=15.99; m1=70.17, d.s.1=20.90), but without it reaching a statistical significance (t= -0.91, p=0.37). When looking at Haem-SYM, the trend is similar when it comes to cardiovascular, infectious, neuropsychiatry and other comorbidities, but we can see a slight inversion of trend regarding hematological complications, but without a statistical significance (t=0.11, p=0.91).

In the lot with prophylaxis we encounter the same logical tendency, of a better QoL in absence of comorbidities, for overall comorbidities (m0=71.83, d.s.0=17.12; m1=65.13, d.s.1=17.87), also for cardiac, infectious, hematological and other comorbidities, the neuropsychiatry comorbidities present a reversed trend (self-evaluation: m0=65.82, d.s.0=16.69; m1=75.00, d.s.1=26.45; Haemo-SYM: m0 = 40.22, d.s.0 = 17.17; m1 = 30.20, d.s.1 = 18,20), but,again, without it reaching a statistical significance (self-evaluation: t= -1.10, p=0.27; Haemo-SYM: t=1.23, p=0.23).

From table 2 we can clearly see that there is significant difference between way of life and the scores obtained from the two tools that we used in this study. On both scales the differences between the groups are highly significant.

	Lifestyle	Medie	Standard deviation	Variance	Bartlet test	The meaning of the difference
Selfevaluation	Pasive	61.52	17.35	300.96	χ^2=3.19	t-test Student
	Active	74.22	13.03	169.66	p=0.07	t=-3.68 p<0.001
Haemo-SYM	Pasive	44.16	18.47	341.14	χ^2=1.06	t-test Student
	Active	31.16	15.71	246.72	p=0.30	t=3.44 p<0.001

Table 2. *Scale score in regards to patient lifestyle*

As we can observe in table 3, the correlation between age at onset of disease and the results obtained at present time regarding QoL is negligible, with the exception of years of evolution without prophylaxis, where the rise of this item is correlated with the rise of Haemo-SYM scores (median correlation r=0.331).

	Self-evaluation	Haemo-SYM
Age at onset	0.082	-0.043
Years of evolution	-0.251	0.231
Years of evolution without prophylaxis	-0.292	0.331
Years of evolution with prophylaxis	0.180	-0.241

Table 3. *Correlation coefficient(r) between age at disease onset and scale results*

The number of hemorrhagic events are not significantly different between the two lots, nor as total number (t=0.80, p=0.43), nor as number of events/year of evolution (t=0.15, p=0.88), but we can observe a different number of events if we take into account of the duration of prophylaxis, in patients with prophylaxis under 10 years (m=41.69, d.s.=20.97) the value being closer to patients with an on-demand treatment plan (m=44.80, d.s.=33.06), than that of patients with prophylaxis for over 10 years (m=35.91, d.s.=18.55). Nevertheless, for the

entire sample of patients we could not find a statistical relevance, but could find it when directly comparing between the 2 subgroups of patients with prophylaxis (Mann-Whitney test χ^2-3.60, p=0.05)

Complications

In our study, the patients that did not have chronic hemophilic arthropathy(CHA) also did not present other complications, therefore patients without CHA are without complications. We did not find any differences between the complications distribution between the two lots (Fisher test χ^2=0.59, p=1.00). The number of hemorrhagic events is significantly higher in patients with CHA (m0=17.81, d.s.=13.03; m1=47.31, d.s.=27.02; χ^2=20.26, p<0.001); for other osteo-articular complications the difference is slightly smaller, not being statistical significant (m0=41.22, d.s.=25.94; m1=47.44, d.s.=32.39; t test=-0.95, p=0.34).

Muscular complications are present in 70% of patients with prophylaxis, while 52.94% of patients without prophylaxis. Nevertheless the difference is not statistically significant (χ^2=3.10; p=0.12). The number of hemorrhagic events are higher in patients with muscular complications rather than in those without (m0=25.51, d.s. 0=17.28; m1=53.40, d.s.1=27.35; Mann-Whitney =28.45, p<0.001). The most common complication, CHA, significantly affects QoL and the intensity of symptomatology, as shown in table 4, as do other osteoarticular complications (arthrosis and ankylosis of limbs, septic arthritis, bone demineralization, kyphoscoliosis, chronic osteomyelitis, chronic synovitis), findings shown in table 5

	CHA	Median	Standard deviation	Variance	Bartlet test	The meaning of the difference
Selfevaluation	No	80.06	13.99	195.80	χ^2=0.54	t-test Student
	Yes	62.81	16.30	265.54	p=0.46	t=3.96
						p<0.001
Haemo-SYM	No	24.63	14.37	206.52	χ^2=1.09	t-test Student
	Yes	42.94	17.90	320.56	p=0.30	t=-3.86
						p<0.001

Table 4. *CHA and scale scores*

	Other osteo-articular complications than CHA	Median	Standard deviation	Variance	Bartlet test	The meaning of the difference
Selfevaluation	No	69.90	15.44	238.30	χ^2=0.24	t-test Student
					p=0.62	t=5.31
						p<0.001
	Yes	50.78	14.16	200.45		
Haemo-SYM	No	35.86	17.73	314.41	χ^2=1.66	t-test Student
					p=0.20	t=-4.56
						p<0.001
	Yes	54.22	14.06	197.54		

Table 5*. Scale score when looking at other oseto-atricular complications than CHA*

We found there is a significantly different distribution (χ^2=12.31, p<0.001), where we can find a smaller number of severe cases in the prophylaxis lot (16%), rather than in the on-demand group (50.98%). There are no significant differences (p between 0.20-0.32) of case distribution with complications when viewing the present disease stage. The number of bleeding events according to the current evolutionary stage differs significantly between patients in a mild or moderate evolutionary stage and those with a severe evolutionary stage (m=37.18, d.s.=23.23, vs. m=53.38, d.s.=32.12; Mann-Whitney χ^2=6.22, p=0.01). The scale results for QoL are majorly influenced by the current evolutionary stage of disease, as shown in table 6.

	Current evolutionary stage of disease	Median	Standard deviation	Variance	Bartlet test	The meaning of the difference
Selfevaluation	Mild/moderate	67.99	15.16	229.89	χ^2=3.21 p=0.07	t-test Student t=2.04 p=0.04
	Severe	60.74	19.76	390.63		
Haemo-SYM	Mild/moderate	36.97	17.40	302.91	χ^2=0.63 p=0.43	t-test Student t=-2.38 p=0.02
	Severe	46.09	19.60	384.08		

Table 6: *Scale scores in comparison to current evolutionary stage of disease*

From the perspective of functional deficit, patients without functional deficit and those with mild functional deficit are in equal proportions in the two groups. Significant differences (χ^2=3.95, p=0.05) appear at the distribution of patients with moderate and severe deficit in the on-demand group versus patients with severe deficit in the prophylaxis group. There is a direct relation between the number of bleeding events and the grade of functional deficit, which is illustrated in table 7. The difference between scores holds a high statistical significance, therefore we can assume that the level of functional deficit is in direct correlation with QoL. When comparing scores obtained from the selfevaluation tool and Haemo-SYM, we find a highly significant reverse relationship (r= -0.729), which means that when the Haemo-SYM scores are high, the selfevaluation scores will be low.

	Median	Standard deviation	Variance	Bartlet test	The meaning of the difference
Without functional deficit	18.93	13.61	185.30	χ^2=9.76 p=0.02	Kruskall-Wallis χ^2=24.63 p<0.001
Mild functional deficit	39.43	23.46	550.25		
Moderate functional deficit	43.68	23.05	531.08		
Severe functional deficit	64.05	31.92	1019.05		

Table 7: *Bleeding events in regards to functional deficit*

Discussions

We expected that when comparing the two lots we will find a significant statistical difference, at least when looking at the subgroup with a longer prophylaxis duration. This was expected due to clinical information and information from literature also7-9, but when using these tools there was no significant difference found. Taking into consideration that when evaluating the functional deficit and some of the complications suffered by patients we did find a significant difference we might assume that this might be due to the tools being quite specific to bleeding and pain therefore disregarding the other attributes that comprise QoL. The selfevaluation mark is quite subjective and our results did show that the lower QoL was felt by patients with comorbidities and a severe functional deficit, therefore disregarding the other attributes that comprise QoL.

We did ask ourselves, especially in the case of Haemo-SYM, if the high scores obtained at this scale lead to a passive lifestyle for patients, or if the passive lifestyle leads to higher scores. In both the prophylaxis group and on demand treated patients, there is a significantly higher quality of life (increased self-rating scale score) and significantly lower Haemo-SYM scores when subjects have an active lifestyle. The presence of complications significantly influences the quality of life and the intensity of symptoms[10]. These findings along with the study done by Ferreirra et all 1[1], suggest that the answer might be that a passive lifestyle leads to higher scores, therefore and active lifestyle, which is achievable by having a prophylactic regimen, as proved quite recently in 2021 by

Lassandro el all1[2], will greatly improve QoL in hemophilia patients. In Romania, this might not be feasible in the near future, because we found that the number of bleeding events is directly corelated with scores from Haemo-SYM and reversed corelated with the selfevaluation scale. Among the factors that favor the reduced bleeding events is also the prophylactic regimens, with a duration of over ten years for it to be of statistical significance, we can state that a longer duration of prophylaxis is required to see a difference in our patients. This is also backed by the fact that we found a lack of statistical significant difference on the overall lots, which are comprised by a large number of patients with prophylaxis under 10 years, difference which was significant when analysing the smaller subgroup of patients with prophylaxis for over 10 years and by the observational study done by Manco-Johnson et all from 1999-20101[3].

The efficacy of prophylaxis treatment on direct disease symptoms was proven in our study by the current evolutionary stage, which showed a lower number of severe cases(16%) in the prophylaxis group, in comparison to the on-demand group which presented with a higher percentage(50.98%) of severe cases. Our findings are supported by studies done by Konkle et all[6] and Miesbach et all1[4].

We do believe that the lack of significance when analysing the case distribution of patients with complications regarding current disease stage can be explained by the introduction of prophylaxis after the occurrence of complications, which lead to the imperious necessity of starting prophylaxis as earlier as possible. Santagostino et all1[5] and Coppola et all1[6] came to the same conclusions as we did. We did find that even in the first years of treatment there are fewer bleeding events, as we know also from Burke et all17. Moreover, our data proved that the presence of CHA, other musculoskeletal and osteoarticular complications lead to a moderate and severe functional deficit.

This paper is part of a larger study we did18, but when focusing our attention on only Haemo-SYM and paraclinical, objective findings we did manage to obtain some of the results we were expecting, but we did obtain a significant difference from when using other tools as well, such as the lack of statistical significance in the overall groups, whereas in our previous work the overall lot did have a significant statistical difference. This leads us to believe that the main cause for these inconsistent results might be the tardiness of introducing prophylaxis in our lot of patients. When looking at the results of studies done on children with hemophilia19 we are made to believe that our lot of patients would have had a much different result if they would have undergone prophylaxis before CHA appeared, since the pain and suffering of CHA will not disappear with prophylaxis, therefore introducing it before it appears should be our main goal.

Conclusion

Indeed QoL is better when undergoing prophylaxis in our lot, and the Haemo-SYM questionnaire can be used in clinical practice, alongside factor VIII activity in customising patient treatment, by giving an easy and clear assessment of symptoms, but our main goal should be introducing prophylaxis as early as possible, since childhood, to obtain a good QoL for our patients.

Author Contributions

Conceptualization: Ionita Hortensia-Marioara; methodology: Calamar Popovici-Despina; software: Hategan Mieta Gabriela; validation: Ionita Ioana and Ionita Claudiu; formal analysis: Ionita Ioana; investigation: Guran Catalina; resources: Guran Catalina; data curation: Hategan Mieta Gabriela; writing-original draft preparation: Guran Catalina; writing-review and editing: Ionita Ioana and Ghilezan Florica; visualization: Oros Dacian Nicolae; supervision: Hategan Mieta Gabriela; project administration: Guran Catalina; funding acquisition: Ghilezan Florica. All authors have read and agreed to the published version of the manuscript."

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Institutional Review Board Statement

The study was conducted in accordance with the Declaration of Helsinki, and approved by the Ethics Committee of the University of Medicine and Pharmacy "Victor Babes" Timisoara.

Informed Consent Statement

Informed consent was obtained from all subjects involved in the study.

Data Availability Statement

The data for this paper is available from the corresponding author, by e-mail request.

Conflicts of interest

The authors did not receive funding for this research, and are not employed by any pharmaceutical company, but

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