What is the role of prophylaxis in the improvement of health-related quality of life of patients with hemophilia?

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A 32-year-old male with severe hemophilia presents for his annual evaluation. He has a history of multiple joint bleeds that he has always treated on-demand, that is, after they occur. You have recommended prophylaxis, that is, preventively, before they occur, to decrease his episodes of bleeding; however, he had been reluctant to comply in the past. He is having difficulty keeping up at work because of interruptions, pain, and lost time at work. He is willing to consider a trial of prophylaxis. You discuss the impact of hemophilia on his health-related quality of life (HRQOL) and consider measuring his HRQOL over time using a generic measure of HRQOL to determine whether prophylaxis will reduce interruptions, pain, and lost time from work and improve his HRQOL.

Introduction

Hemophilia is a chronic disorder that can negatively affect health-related quality of life (HRQOL). This can be due to a variety of hemophilia-related issues such as bleeding episodes, pain, decreased functional capacity, and impaired performance at school, work, or recreation. Current management recommendations for severe hemophilia include the use of prophylaxis for prevention of bleeding episodes and hemophilia-related complications. Prophylaxis has been shown to reduce bleeds and joint limitation. In addition to clinical measurements such as frequency of bleeds and joint range of motion, it is recognized that the measurement of HRQOL serves as an important outcome in the comprehensive evaluation and care of hemophilia patients. The purpose of this evidence-based mini-review is to answer the question: "In pediatric or adult patients with hemophilia A or B, is prophylaxis associated with improvements in HRQOL?"

Methods

To examine the current best evidence for the use of prophylaxis in the improvement of HRQOL among patients with hemophilia, we conducted a PubMed search. Keywords that were used for the search included: "quality of life" and "hemophilia." Inclusion criteria for articles included were: (1) studies that focused on the use of prophylaxis and its impact on HRQOL (measured using standardized generic and disease-specific instruments) of patients with hemophilia; (2) year of publication: studies published between 1970 and 2013; (3) methods: studies that used empiric study designs including only quantitative methods; and (4) language: studies that were written in English. Reference lists of reviews identified from the search above focusing on "prophylaxis" or "quality of life" in their title were also searched for additional studies.

Of the 432 titles identified, 413 did not fulfill the inclusion criteria and were excluded due to a lack of prophylaxis-specific analyses, a lack of hemophilia-specific analyses, a lack of HRQOL measurements by standardized instruments, or exclusively qualitative or psychometric or cost-effectiveness analytic approaches. Based on the inclusion criteria, a total of 21 studies met the inclusion criteria.[1-21]

Results

Study details and participant characteristics

The study designs, sample characteristics, and results of the studies are provided in Table 1. Most of the studies were multi-institutional studies conducted within the United States (4 studies)[2,3,10,15] or multi-institutional studies conducted across the United States and multiple European countries (13 studies).[6,7,9,11-14,16-21] Four single institutional European studies were also represented.[1,4-5,8] Of the 21 studies, 14 were cross-sectional observational studies.[2-6,8,10,11,13,15,17,18,20,21] Seven studies used more robust study designs (ie, randomized prospective trials).[1,7,9,12,14,16,19] Several studies were limited in their diagnostic representation, including 3 studies that included only hemophilia patients with inhibitors.[10,12,16] The age of the patients with hemophilia also varied, with 7 adult-only studies,[1,4-6,8,9,19] 3 pediatric-only studies,[7,11,17] and the remaining 11 combination adult-pediatric studies.[2,3,10,12-16,18,20,21]

Measures of HRQOL

A total of 9 different measures were used to assess the HRQOL of hemophilia patients across the 21 studies. The instruments used to measure HRQOL included generic and disease-specific measures of HRQOL. The most frequently used generic HRQOL measure was the Short Form 36 (SF-36) in 9 studies,[4,5,8,13,15,18-21] the EQ5D (a measure of HRQOL from the EuroQoL Group) in 5 studies,[1,6,12,14,16] and the Short Form 12 (SF-12) in 3 studies.[2,3,10] Pediatric-specific generic HRQOL measures included the Pediatric Quality of Life Inventory (PedsQL), which was used in 2 studies.[2,3] The German Children's Quality of Life Questionnaire (KINDL) and the Child Health Questionnaire (CHQ) were also used as pediatric-specific generic HRQOL measures in single studies.[11,15] Only 2 adult-focused, disease-specific HRQOL measures were used: MedTap QoL and HaemoQOL.[1,9] Pediatric disease-specific HRQOL measures included the HaemoQOL, which was used in 2 studies.[11,17]

Use of prophylaxis and HRQOL

Among adult patients with hemophilia, the impact of prophylaxis on HRQOL is mixed. Duncan et al studied 64 adults and Noone et al

Table 1. Study designs, sample characteristics, measures utilized, and outcomes of studies (N = 21)

Reference	Study type	Patients	Prophylaxis	Measures	Outcomes
Studies combining adult and pediatric patients					
Duncan et al[2]	Cross-sectional observational	N = 64 (adult), mean age 37.9 y	PRO (adult) 50% (9.4% always PRO, 31.2% on-demand → PRO)	SF-12	(adult) Highest HRQOL (all domains) in adults reporting always PRO. Physical function and PCS better in always PRO.
		(peds) N = 53, mean age 10.5 y	PRO (ped) 96% (22.6% always PRO, 73.6% on-demand → PRO)	PedsQL	(peds) Always PRO not significantly different from other categories.
Poon et al[3]	Cross-sectional observational	(adult) N = 164, mean age 33.5 y	PRO (adult) 25.5%	SF-12	(adult) No differences for PRO.
		(peds) N = 165, mean age 9.7 y	PRO (ped) 55.2%	PedsQL	(peds) No differences for PRO.
Tagliaferri et al[14]	Retrospective cohort	N = 84 N = 30 (adolescents) N = 54 (adult)	On-demand → PRO during adolescence (>10 y) or during adulthood (≥ 18 y)	EQ-SD	Regardless of age, HRQOL better among PRO for all domains. Most improvement noted among domains of mobility, usual activities, and pain/discomfort.
du Treil et al[15]	Cross-sectional observational	N = 47	N = 18 high intensity (PRO or IT)	SF36	(adult) "high intensity" regimens more bodily pain than those on-demand.
		N = 28 (adults) N = 19 (peds)	N = 29 on-demand	Child Health Questionnaire (self-report)	(peds) more bodily pain when receiving on-demand therapy.
Royal et al[20]	Cross-sectional observational	N = 1013, mean age 35.8 y	PRO (N = 313)	SF-36	PRO associated with less bodily pain, better general health and physical function.
			On-demand (N = 590)		PRO and HIV negative same as above and better mental health and social function PRO and HIV positive only decreased vitality.
Molho et al[21]	Cross-sectional observational	N = 118, mean age 23 y	At least one PRO course (48.2%) N = 39 pts ≥ 1 course PRO (≤ 3 mnts) N = 24 pts ≥ 1 course PRO (3-12 mnts)	SF-36	Patients who had at ≥ 1 course of PRO had better HRQOL relating to restriction of activity due to physical problems.
Studies focusing on adult patients					
Noone et al[6]	Cross-sectional observational	N = 80, mean age 27.5 y (20-35)	Grp 1 PRO 100% of life Grp 2 PRO 50%-100% of life Grp 3 PRO 1%-50% of life Grp 4 PRO 0% of life	EQ-5D	Highest mean EQ-5D utility value in Grp 1 patients. On-demand associated with lower scores in dimension of self-care.
Collins et al[9]	Prospective crossover	N = 20, mean age 36.4 y (30-45)	On-demand for 6 mo followed by PRO for 7 mo	HaemoQOL	PRO not associated with significant differences in total HRQOL scores or domain specific scores.
Fischer et al[19]	Retrospective cohort	N = 49 PRO mean age 22.3 y (18.5-24.5) N = 106 On-demand mean age 22.3 y (18.9-25.4)	PRO group 98% (history of PRO) On-demand 48% (history of PRO)	SF-36	PRO associated with higher HRQOL scores across all physical domains except for role limitations due to physical health. No differences for mental health domains.
Studies focusing on pediatric patients					
Gringeri et al[7]	Randomized prospective	N = 45, median age 4 y (1-7), N = 23 randomized to PRO, median age 49.7 mo	N = 21 PRO analyzed	HaemoQOL	Child/adolescent ratings noted "Family" dimension more impaired and overprotected with on-demand. No differences for parent ratings. Feelings parental imposed limits on work/leisure time in on-demand group.
		N = 19 randomized to on-demand, median age 48.8 mo	N = 19 On-demand analyzed		
Bullinger et al[11]	Cross-sectional observational	N = 298, mean age 10 y (8-16)	PRO N = 217	HaemoQOL	Variance in HRQOL not explained by PRO versus on-demand in any county.
			Germany 93.2%, Italy 56.7%, France 50%, Spain 62.7%	KINDL-R	
Gringeri et al[17]	Cross-sectional observational	N = 339, mean age 10 y (4-16) Grp I 4-7 y, N = 95 Grp II 8-12 y N = 118 Grp III 13-16 y N = 105	PRO 66.7% (19.8% primary, 78.8% secondary)	HaemoQOL	Grp I PRO more impaired in "feeling" subscale. Grp III PRO less impaired in "sport/school" subscale and less impairment in total HRQOL.
Studies focused on timing and dosing of prophylaxis					
Lindvall et al[4]	Cross-sectional observational	N = 105, median age 44.0 y (18-84)	PRO 61.9%	SF-36	Age of start of PRO significant association with PCS. Earlier PRO start associated with higher HRQOL. Age of start of PRO not associated with MCS.
Khawaji et al[5]	Cross-sectional observational	N = 81 Grp A median age 27 y (18-45) Grp B median age 50 y (22-78)	Grp A (N = 30), PRO before 3 y Grp B (N = 51), PRO after 3 y	SF-36	Grp A better HRQOL (physical function, physical role, general health, social function, PCS), but non-significant after age adjusted. No significant differences for other domains or MCS.
Lindvall et al[1]	Randomized prospective crossover	N = 10, median age 26.5 y	PRO (standard vs. daily)	EQ-5D	Decreased HRQOL (pain/discomfort and mobility) with daily PRO, but not significant. Largest difference in pain/discomfort.
				MedTap QoL	MedTap with more problems with physical activity in daily prophylaxis group and more stressful.
Khawaji et al[8]	Cross-sectional observational	N = 39 Grp A median 26 y (19-35) Grp B median 42 y (33-56)	Grp A (N = 21), PRO before 3 y Grp B (N = 15) PRO after 3 y	SF-36	Grp A improved HRQOL (physical function, social function, and PCS) compared to Grp B. No significant differences for other domains or MCS.
Plug et al[13]	Cross-sectional observational	N = 721, ages 16-64 y Severe N = 279 Moderate N = 114 Mild N = 328	PRO in 53% severe, 9% moderate, 0.4% mild (born prior to PRO 31-64 y) PRO in 81% severe, 19% moderate, 2% mild (born after PRO 16-30 y)	SF-36	Severe patients born after PRO demonstrated higher HRQOL (physical function, role physical, pain, and general health) compared to older patients born after PRO. No differences in moderate or mild patients.

Table 1. (continued)

Reference	Study type	Patients	Prophylaxis	Measures	Outcomes
Fischer et al[18]	Cross-sectional observational	N = 128 pts, median age 16.8 y	high-dose PRO start median 2 y	SF-36	The mean scores for the HRQOL domains were higher in the high-dose PRO group, but differences were not statistically significant.
		N = 42 pts, median age 15.2 y (high-dose PRO)	inter dose PRO start median 5 y		
		N = 86 pts, median age 17.9 y (inter mediate dose PRO)			
Studies focused on inhibitor patients					
Brown et al[10]	Cross-sectional observational	N = 53, mean age 20.7 y	PRO (adult) 28.6%	SF-12	On-demand negative associated with PCS and bodily pain, regardless of inclusion of age in the model.
			PRO (peds) 62.1%		
Hoots et al[12]	Randomized prospective	N = 37 (entered pre-PRO observation)	N = 11, low-dose PRO followed by post-PRO observation	EQ-5D	Trend of improvement in pain and mobility domains at end of PRO period and post-PRO period compared to pre-PRO period.
		Low-dose PRO median age 13 y, (5.1-50.5)	N = 11, high-dose PRO followed by post-PRO observation		
		High-dose PRO median age 17.8 y (10.6-56.1)			
Konkle et al[16]	Randomized prospective	N = 37 (entered pre-PRO observation)	N = 11, low-dose PRO followed by post-PRO observation	EQ-5D	Trend of improvement in pain and mobility domains at end of PRO period and post-PRO period compared to pre-PRO period.
		Low-dose PRO median age 13 y, (5.1-50.5)	N = 11, high-dose PRO followed by post-PRO observation		
		High-dose PRO median age 17.8 y (10.6-56.1)			

PRO indicates prophylaxis; PCS, physical component summary; and MCS, mental component summary.

studied 80 adults and each found the highest HRQOL in those using prophylaxis.[2,6] Among the domains of HRQOL, physical health was noted to be better among adults on prophylaxis.[2,14,19-21] With respect to pain, the use of prophylaxis among adults was associated with greater pain as reported by Du Triel et al[15] compared with less pain reported by Royal et al and Tagliaferri et al.[14,20] Tagliaferri et al studied 30 adolescent and 54 adult patients receiving prophylaxis in comparison to on-demand therapy and found better HRQOL across all domains with the greatest differences in mobility, usual activities, and pain/discomfort.[14] Noone et al also noted that the use of on-demand therapy was associated with lower scores "self-care."[6] Poon et al studied 164 adults and found no association between the use of prophylaxis and HRQOL.[3] Collins et al studied 20 adults and also found no significant differences among adults treated with prophylaxis compared with on-demand therapy.[9]

The impact of prophylaxis on HRQOL among pediatric patients with hemophilia demonstrates mixed results. In 2011, Gringeri et al studied 45 randomized pediatric patients and found that patients treated on-demand demonstrated impairment in the "family" domain of the HaemoQOL and felt overprotected and less able to participate in work and leisure time.[7] In 2004, Gringeri et al studied 339 child and adolescents using the HaemoQOL and found that prophylaxis was associated with impaired HRQOL ("feeling" subscale) among children, with less impairment in sport/school subscales in adolescents receiving prophylaxis.[17] Du Treil et al found greater pain in children on on-demand therapy compared with prophylaxis.[15] Bullinger and von Mackensen, in a study of 298 children, found no association between the use of prophylaxis and HRQOL,[11] confirmed in studies by Duncan et al and Poon et al.[2,3]

The timing of the start of prophylaxis and the schedule of prophylaxis may play a role an important role in HRQOL. Khawaji et al noted that adults starting prophylaxis before 3 years of age was associated with greater HRQOL across several domains (physical and social health); however, these differences became nonsignificant after age adjustment.[5] Lindvall et al studied 105 adults and noted that the earlier use of prophylaxis was associated with higher HRQOL with a specific focus on physical health.[4] Plug et al noted that being born after the introduction of prophylaxis was associated with better physical health compared with those born before the introduction of prophylaxis.[13] Lindvall et al also assessed the schedule of prophylaxis among 10 pediatric and adult patients and found that daily prophylaxis was associated with diminished HRQOL in the domains of pain and mobility compared with standard prophylaxis, although these findings were not statistically significant.[1]

The use of prophylaxis in adult and pediatric hemophilia patients with inhibitors was also the subject of evaluation. Hoots et al[12] and Konkle et al[16] provided reports of a randomized prospective trial of high-dose recombinant FVIIa compared with low-dose recombinant FVIIa prophylaxis in inhibitor patients and demonstrated improvements in HRQOL within the domains of pain and mobility. In a pooled data analysis from the 22 patients, the improvement was not statistically significant. Brown et al also studied the use of prophylaxis in 53 adult and pediatric hemophilia patients with inhibitors and noted that on-demand therapy was negatively associated with physical health and pain,[10] but baseline physical health and pain is known to be poor in this group.

Conclusion

Given the available evidence, we recommend against the use of prophylaxis compared with on-demand therapy to improve HRQOL among adult or pediatric patients with hemophilia (Level 3). This recommendation is based largely on observational and cross-sectional studies assessing the relationship between prophylaxis and HRQOL. Small sample sizes, limited age representation of hemophilia patients in individual studies, and the limited use of both generic and disease-specific HRQOL instruments are also important limitations in the extant literature. Further, the degree to which the intervention itself, such as frequent, invasive intravenous infusions several times weekly, contributes to poorer HRQOL is not quantified. Future studies should use large patient samples and robust study designs, including longitudinal assessments of HRQOL. In addition, these should assess the degree to which prophylaxis itself affects HRQOL and the sample size should be large enough to capture differences among adults, adolescents, and children. Analyses should also include not only generic HRQOL measures, but also disease-specific measures of HRQOL, to provide a rich description of the experiences of living with hemophilia. Given the importance of HRQOL assessment in hemophilia care and the future changing

landscape of hemophilia prophylaxis anticipated with the availability of long-acting factors, ongoing data collection comparing current and newer factors will be needed to address the question of for which patients and with which products prophylaxis improves HRQOL among patients with hemophilia.

Disclosures

Conflict-of-interest disclosure: D.B. declares no competing financial interests. M.V.R. is on the board of directors or an advisory committee for Biogen Idec and NHF-MASAC; has received research funding from Baxter, Bayer, Biogen Idec, CSL Behring, and Novo Nordisk; and has consulted for Baxter and Biogen Idec. Off-label drug use: None disclosed.

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References

1. Lindvall K, Astermark J, Bjorkman S, Ljung R, et al. Daily dosing prophylaxis for haemophilia: a randomized crossover pilot study evaluating feasibility and efficacy. *Haemophilia.* 2012;18(6):855-859.
2. Duncan N, Shapiro A, Ye X, Epstein J, et al. Treatment patterns, health-related quality of life and adherence to prophylaxis among haemophilia A patients in the United States. *Haemophilia.* 2012;18(5):760-765.
3. Poon JL, Zhou ZY, Doctor JN, Wu J, et al. Quality of life in haemophilia A: Hemophilia Utilization Group Study Va (HUGS-Va). *Haemophilia.* 2012;18(5):699-707.
4. Lindvall K, Von Mackensen S, Berntorp E. Quality of life in adult patients with haemophilia–a single centre experience from Sweden. *Haemophilia.* 2012;18(4):527-531.
5. Khawaji M, Astermark J, Berntorp E. Lifelong prophylaxis in a large cohort of adult patients with severe haemophilia: a beneficial effect on orthopaedic outcome and quality of life. *Eur J Haematol*. 2012;88(4):329-335.
6. Noone D, O'Mahony B, Prihodova L. A survey of the outcome of prophylaxis on-demand or combined treatment in 20-35 year old men with severe haemophilia in four European countries. *Haemophilia.* 2011;17(5): e842-3.
7. Gringeri A, Lundin B, von Mackensen S, Mantovani L, et al. A randomized clinical trial of prophylaxis in children with hemophilia A (the ESPRIT Study). *J Thromb Haemost*. 2011; 9(4):700-710.
8. Khawaji M, Astermark J, Von Mackensen S, Akesson K, et al. Bone density and health-related quality of life in adult patients with severe haemophilia. *Haemophilia.* 2011;17(2):304-311.
9. Collins P, Faradji A, Morfini M, Enriquez MM, et al. Efficacy and safety of secondary prophylactic vs. on-demand sucrose-formulated recombinant factor VIII treatment in adults with severe hemophilia A: results from a 13 month crossover study. *J Thromb Haemost*. 2010;8(1):83-89.
10. Brown TM, Lee WC, Joshi AV, Pashos CL. Health-related quality of life and productivity impact in haemophilia patients with inhibitors. *Haemophilia.* 2009;15(4):911-917.
11. Bullinger M, von Mackensen S. Psycho-social determinants of quality of life in children and adolescents with haemophilia–a cross cultural approach. *Clin Psychol Psychother*. 2008;15(3): 164-172.
12. Hoots WK, Ebbesen LS, Konkle BA, Auerswald GK, et al. Secondary prophylaxis with recombinant activated factor VII improves health-related quality of life of haemophilia patients with inhibitors. *Haemophilia.* 2008;14(3):466-475.
13. Plug I, Peters M, Mauser-Bunschoten EP, de Goede-Bolder A, et al. Social participation of patients with hemophilia in the Netherlands. *Blood.* 2008;111(4):1811-1815.
14. Tagliaferri A, Franchini M, Coppola A, Rivolta A, et al. Effects of secondary prophylaxis started in adolescent and adult haemophiliacs. *Haemophilia.* 2008;14(5):945-951.
15. du Treil S, Rice J, Leissinger CA. Quantifying adherence to treatment and its relationship to quality of life in a well-characterized haemophilia population. *Haemophilia.* 2007;13(5): 493-501.
16. Konkle BA, Ebbesen LS, Erhardtsen E, Bianco RP, et al. Randomized, prospective clinical trial of recombinant factor VIIa for secondary prophylaxis in hemophilia patients with inhibitors. *J Thromb Haemost*. 2007;5(9):1904-1913.
17. Gringeri A, von Mackensen S, Auerswald G, Bullinger M, et al. Health status and health-related quality of life of children with haemophilia from six West European countries. *Haemophilia.* 2004;10(Suppl 1):26-33.
18. Fischer K, Astermark J, van der Born JG, Ljung R, et al. Prophylactic treatment for severe haemophilia: comparison of an intermediate-dose to a high-dose regimen. *Haemophilia.* 2002;8(6):753-760.
19. Fischer K, van der Bom JG, Molho P, Negrier C, et al. Prophylactic versus on-demand treatment strategies for severe haemophilia: comparison of costs and long-term outcome. *Haemophilia.* 2002;8(6):745-752.
20. Royal S, Schramm W, Berntrop E, Giangrande P, et al. Quality-of-life differences between prophylactic and on-demand factor replacement therapy in European haemophilia patients. *Haemophilia.* 2002;8(1):44-50.
21. Molho P, Rolland N, Lebrun T, Dirat G, et al. Epidemiological survey of the orthopaedic status of severe haemophilia A and B patients in France. *Haemophilia.* 2000;6(1):23-32.