UNRAVELLING ADHERENCE AND FLOURISHING ACCEPTANCE IN PEOPLE WITH HAEMOPHILIA

Anne Hoefnagels

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Unravelling adherence and flourishing acceptance in people with haemophilia door Johanna Wilhelmina Hoefnagels
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Het ontrafelen van therapietrouw en het laten opbloeien van acceptatie bij mensen met hemofilie

(met een samenvatting in het Nederlands)

PROEFSCHRIFT

ter verkrijging van de graad van doctor aan de Universiteit Utrecht op gezag van de rector magnificus, prof.dr. H.R.B.M. Kummeling, ingevolge het besluit van het college voor promoties in het openbaar te verdedigen op donderdag 15 juli 2021 des middags te 4.15 uur

door

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geboren op 14 december 1988
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A tree is such a rich metaphor in a million beautiful ways.
You can consider a tree growing and consider its
connectedness to all things above (visable)
and under the ground (unvisable).

Ann Brashares

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GENERAL INTRODUCTION

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Haemophilia

Haemophilia is a rare congenital bleeding disorder generally affecting men[1]. It is characterised by a deficiency of the biological active coagulation factor VIII (haemophilia A) or IX (haemophilia B)[1]. With an estimated incidence of approximately 1:10,000 births, currently there are ±1,600 people affected in The Netherlands[2] who can be divided amongst three severities based on the percentage baseline clotting factor activity: severe (<1%), moderate (1-5%) and mild (6-40%). The lack of clotting factor is correlated with an increase in spontaneous or traumatic bleeding[1] (figure 1). Bleeds mainly occur in joints and muscles, but can also be intracranial or gastrointestinal[1] with major consequences on physical as well as psychosocial health[3,4]. Repeated joint bleeds can eventually lead to arthropathy[5] with chronic pain[6], disability and loss of work or school, leading to a reduced quality of life[7,8].

Bleeding can be prevented and treated with intravenous clotting factor concentrate (CFC)[1]. In patients with severe haemophilia, this treatment is prescribed as a prophylactic replacement therapy[1]. Prophylactic CFC treatment is usually administered three times a week or every other day[1]. Patients are perform the intravenous injections themselves (i.e., self-infusion or home-infusion), preferably in the morning due to the limited half-life of CFCs and the need to achieve optimal protection during the day[1].

Life-long treatment

The majority of children with severe haemophilia are diagnosed in the first year of life and begin prophylactic treatment after the first joint bleed (around the age of 2 years)[1,9]. In young children, parents perform the intravenous injection (through a central venous access device or a peripheral vein). Around the age of 13 years, children learn to perform self-infusion and take over responsibilities for their prophylactic treatment from their parents. This includes self-infusion, ordering medication, recognising and handling bleeds, and discussions with their haemophilia treater[10,11].

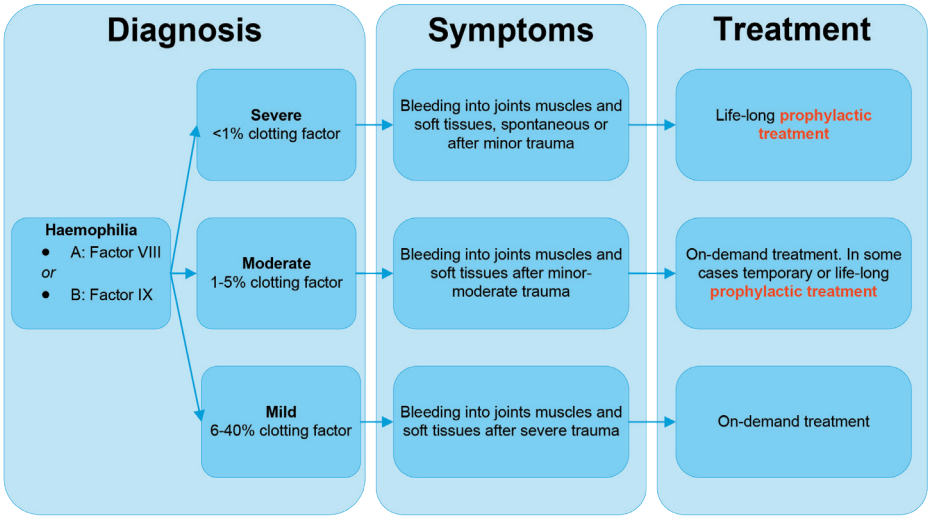

Figure 1 Clinical information of haemophilia

The fact that treatment consists of life-long intravenous self-infusion contributes to the burden of this disease and makes its management demanding[1,11,12]. Furthermore, non-adherence is frequent in adolescents and remains a persistent problem in adulthood[13,14].

High adherence is needed to prevent bleeding

Adherence to the prescribed treatment is essential to prevent bleeding and for joint preservation[3,15]. However, it is estimated to be between 50%[16,17] and 80%[13,14]. Non-adherence was defined as missing >15% of infusions, changing >10% of the doses without consultation of the treated, or taking <30% of infusions in the morning[18]. In one study, a group of patients with severe haemophilia who discontinued prophylaxis on their own initiative were followed for ten years; despite their reported low bleeding rates, significant joint deterioration was observed on physical examination and X-ray[3].

In haemophilia, it is known that patients underestimate[19,20] their adherence levels whereas clinicians overestimate patients' adherence levels[21,22]. Promoting adherence to treatment requires a multidisciplinary effort from clinicians, nurses and pharmacists[23]. Dutch nurses stated that they discuss adherence and provide practical solutions improving adherence[22,23]. The current prophylactic treatment

only works when the patient demonstrates high adherence[24]. To provide better patient-centred care resulting in higher adherence and better patient outcomes, it is important to understand the reasons for non-adherence and to invest in interventions that improve treatment adherence in the case of haemophilia.

Aim

Therefore, the aim of this thesis is to clarify and improve adherence to prophylaxis in patients with haemophilia. This outline is visualised in figure 2.

Outline

The first part of this thesis is focused on unravelling (non-)adherence in children, adolescents and adults. **Chapter 1** explores adherence and its relation to treatment attitude and treatment satisfaction. **Chapter 2**, assessed adherence related to age and bleeds. **Chapter 3**, the perspectives of adolescents and young adults are evaluated in a qualitative study. **Chapter 4** explores whether patients are more adherent if they perform (high risk) sports.

The second part of this thesis is focused on flourishing, consisting of improving adherence to life-long treatment in adults. **Chapter 5** reports on the development and pilot testing of two interventions. **Chapter 6** describes the effectiveness of the 'Living with haemophilia' training in a larger group.

Figure 2 Image represent the outline of this thesis

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.

Unravelling

CHAPTER 1

Adherence to prophylaxis and its association with attitude and treatment satisfaction

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ABSTRACT

Introduction

Prophylactic replacement therapy (prophylaxis) in patients with haemophilia (PWH) requires lifelong, frequent (self)infusions. Prophylaxis effectiveness depends on adherence, and the drivers of treatment adherence among PWH are unclear.

Aim

To quantify prophylaxis adherence and associations between adherence and patients' treatment attitudes and satisfaction in a large cohort of children and adults with haemophilia.

Methods

In a nationwide, cross-sectional, questionnaire-based study, PWH with complete information currently using prophylaxis were selected. Validated Hemophilia Regimen Treatment Adherence Scale-Prophylaxis (VERITAS-Pro; normalised score range: 0–100, optimum 0) measured treatment adherence; the Patient Activation Measure (PAM-13; total score range 0–100, optimum 100) measured patient attitude; Hemophilia Patient Satisfaction Scale (Hemo-Sat; range 0–100, optimum 0) measured treatment satisfaction. Groups were compared according to age (children: <12 years; adolescents: 12–18 years; adults >18 years) and adherence levels using non-parametric tests, and correlations were assessed using Spearman's rho.

Results

Among 321 participants (median age 33 years, interquartile range [IQR]= 15–54 years), adherence was high (median VERITAS-Pro total score 17, 89% adherent) but worsened with age, with median scores of 5, 14, and 20 in children, adolescents, adults, respectively (P≤ 0.001). Attitudes toward treatment (median 66 vs 68) participants and treatment satisfaction (12 vs 10) were similar between adherent and non-adherent patients. The VERITAS-Pro total score was not correlated with the PAM-13 score (r=0.41) or the Hemo-Sat score (r=−0.11).

Discussion

Prophylaxis adherence was high (89%) but decreased significantly with age and was not correlated with treatment attitude or treatment satisfaction.

INTRODUCTION

Repeated bleeding events in the joints and soft tissues are hallmarks of haemophilia. Especially in patients with severe haemophilia (clotting factor VIII or IX activity ≤1%) are at high risk for these spontaneous bleeds[1]. Prophylactic treatment is recommended for these specific groups, consisting of intravenous, self-infusions approximately 2–3 times per week[1]. This demanding treatment typically starts before the age of three years[2]. In young children, parents administer this injection at home, and by 12 years, children begin learning to administer the injections themselves (known as self-infusion)[3]. Adherence to prescribed treatment regimens is necessary to prevent bleeds in all age groups[1].

In a previous Dutch study, 57% of patients with severe haemophilia (N= 241 patients) were reported as adherent to their prescribed treatment[4]. Other studies have reported adherence levels between 53%[5] and 76% among haemophilia patients using other evaluation methods[6,7]. Adherence was determined by evaluating infusion logs, applying a cut-off score for the Validated Hemophilia Regimen Treatment Adherence Scale-Prophylaxis[8,9] (VERITAS-Pro), using the adherence definition described by Schrijvers et al.[10] or performing short interviews. Most studies have been performed with limited datasets, varying from 31[7] to 78[5] patients. Some have reported decreased adherence levels starting at puberty[11,12], whereas others have not[5].

Several adherence definitions exist, depending on the evaluation method. Using a consensus process, Schrijvers et al.[10] defined adherence to prophylaxis as missing less than <15% of infusions, experiencing <10% dose changes, and <30% time changes (hours). Two qualitative studies explored the reasons for non-adherence in patients with haemophilia (PWH) [13,14]. Among adults, the perception of adherence and the ability to perform prophylaxis were the primary contributors to (non)-adherence[13]. Among adolescents and young adults, the level of treatment responsibility and the estimated risk per activity had strong influences on adherence[14]. A European study (N= 180) demonstrated that the treatment centre visit duration and good relationships with the treatment centre were associated with better treatment adherence[15]. To date, whether adherence and treatment satisfaction [measured using the Hemophilia Patient Satisfaction Scale (Hemo-Sat)] are related remains unknown. Some studies have suggested that patients'

treatment attitudes [measured using the Patient activation measure (PAM-13)] might impact health conditions, including adherence[16,17]. Based on these reports, we hypothesised that 1) non-adherent patients would be distributed over all 4 PAM levels and 2) adherent patients would be more satisfied with their treatment than non-adherent patients. The aim of this study was to quantify prophylaxis adherence and associations between adherence, treatment attitude, and treatment satisfaction in a large cohort of children and adults with haemophilia.

METHODS

A cross-sectional, web-based survey was conducted among all Dutch PWH. The 'Haemophilia in the Netherland's (HIN-6) nationwide survey is repeated every 6–9 years and is comprised of various questionnaires[18]. Medical ethical approval was obtained from the Medical Ethical Committee Leiden, Den Haag, Delft number: NL59114.058.17.

Population

Male PWH from all six Dutch treatment centres were invited to participate in a national, multi-centre, cross-sectional study. In 2019, patients received an e-mail (and reminder e-mails) containing a link to the HIN-6 survey (paper version available on request). Participants who did not sign informed consent for blood and urine collection but did complete the questionnaire were treated as consent to participate (opt-in inclusion). For this particular study, patients with prescribed prophylactic treatment who completed at least one domain of the VERITAS-Pro questionnaire were included from the HIN-6 database.

Data collection

The HIN-6 study questionnaire is comprised of several validated questionnaires (e.g. adherence, quality of life, sport, work, satisfaction). The questions were adapted to the respondent ages: 1) the parents of children with haemophilia (0–11 years), adolescents (12–18 years), and adults (>18 years). The parent version included the Hemo-Sat questionnaire, and the adult version included both the PAM-13 and Hemo-Sat questionnaires. Completing all questionnaires took approximately 30–60 minutes, and intermediate pausing or stopping was allowed. Data were collected as pseudonymised and coded. Additionally, research nurses obtained the treatment characteristics from medical files for a pre-defined

number of patients (e.g. age, diagnoses, treatment details, concomitant infections). All data were collected using an online case report form (via Castor EDC); paper version available on request. For this study, the following variables were collected: demographic characteristics, the adherence[12] questionnaire, patient treatment attitude questionnaire[16,17], and the treatment satisfaction questionnaire[19].

Adherence

The Dutch version of the validated VERITAS-Pro was used to assess prophylaxis adherence over the past two weeks[9]. This haemophilia-specific questionnaire consists of 24-items, generating a total score and six domain scores: Time (e.g. scheduled days and times per week), Dose (e.g. increase or decrease in dose), Plan (e.g. supplies at home), Remember (e.g. forgot or remember infusions), Skip (e.g. skip or postpone infusions), and Communicate (e.g. contacting the treatment centre in case of bleeds or medical interventions). The VERITAS-Pro can be used as a continuous variable (normalised to 0–100, optimum 0) or as a categorical variable (adherent, non-adherent, cut-off normalised score ≥34[8]). Cronbach's alpha for the VERITAS-Pro was α 0.70.

Adherence, as defined in haemophilia

Adherence was assessed according to the consensus definition reported by Schrijvers et al. [10] Based on this definition, three VERITAS-Pro questions were selected and separately analysed. VERITAS-Pro question 2 represents the domain of missed infusions, question 5 represents dose changes, and question 3 represents time changes.

Patient treatment attitude

The Dutch version of the validated generic PAM-13 was used to assess motivators, attitudes, behaviours and outcomes towards the patients' illness, referred to as treatment attitudes[16]. The questionnaire consists of 13-items resulting in a 0–100 (optimum 100) score. In addition, patients can be categorised into four levels; (i) disengaged and overwhelmed; (ii) becoming aware, but still struggling; (iii) taking action; and (iv) maintaining behaviours and pushing further[17,20]. Cronbach's alpha for the PAM-13 was 0.87[16]. Only adult participants completed the PAM-13.

Patient satisfaction

The Dutch version of the Hemo-Sat[19] was designed to assess patient satisfaction. The Hemo-Sat is a haemophilia-specific instrument consisting of a total score and

six domains: Ease and Convenience, Efficacy, Burden, Specialist/Nurse, Centre Hospital, and General Satisfaction. The questionnaire consists of 32 questions, measured on a scale of 0–100 (optimum 0). Cronbach's alpha for the Hemo-Sat was 0.85[15]. Only parents of children and adult patients completed the Hemo-Sat.

Data analyses

All data analyses for each questionnaire were performed according to the following age groups: children (0–11 years), adolescents (12–18 years) and adults (>18 years). Missing data were excluded from the analysis. The VERITAS-Pro total and domain scores were normalized [(total score − 24) / 96 × 100% and (domain score − 4) / 16 × 100%]. In the HIN6 study questionnaire for children, one question for the domain 'Communicate' was erroneously omitted. Normalised total scores for children were calculated for the remaining questions (23 questions instead of 24). Patients were divided into adherent or non-adherent groups based on the VERITAS-Pro total score (normalised cut-off value for non-adherence: ≥34)[10]. The data were not normally distributed; therefore, the differences between 3 groups were tested using the Kruskal–Wallis test.

To assess adherence according to the consensus definition of Schrijvers et al., three questions were selected from the VERITAS-Pro: 1) 'I infuse the recommended number of times per week'; 2) 'I use the doctor-recommended dose for infusions'; and 3) 'I perform prophylaxis infusions in the morning, as recommended'. Patients were categorised as adherent (always), suboptimal (often), or non-adherent (Sometimes, Rarely, and Never) based on the response to each question. To analyse patient activation, adult patients who completed the entire PAM-13 questionnaire were selected. The PAM-13 total scores and corresponding levels were calculated by 'Insignia Health', the developers of the PAM-13[16]. Patient characteristics were analysed using descriptive statistics and presented as the median and interquartile range (IQR, 25th percentile–75th percentile). The relationship between adherence and the PAM-13 or Hemo-Sat scores was analysed using the Mann–Whitney U test and the relationship between the PAM-13 levels (1–4) and adherence was analysed using Pearson's Chi-square test. Additionally, the correlations between the VERITAS-Pro and PAM-13 or Hemo-Sat scores were analysed using Spearman's rho. Significant correlation coefficients above 0.4 were considered clinically relevant[40].

RESULTS

The study included 61 children, 29 adolescents, and 231 adults. Patient characteristics are shown in table 1. The median overall age was 33 years (IQR: 15–54 years), for children was 6 years (IQR: 4–9 years), for adolescents was 14 years (IQR: 13–16 years), and for adults was 47 years (IQR: 31–59 years). Most patients were diagnosed with haemophilia A (87%), distributed equally across all age groups. The majority had a severe phenotype (90%). Overall, patients with haemophilia B were prescribed higher doses per injection (median 25 IU/kg vs 16 IU/kg in haemophilia A) with lower frequencies per week (median 2×/week versus 3×/week in haemophilia A).

Table 1 Patient characteristics (self-reported)

	All N= 321	Children (0–11 year) N= 61	Adolescents (12–18 year) N= 29	Adults (>18 year) N= 231
	Median (IQR) or N (%)			
Age (years)	33 (15–54)	6 (4–9)	14 (13–16)	47 (31–59)
Weight (kg)	74 (56–87)	23 (17–32)	56 (48–64)	82 (72–90)
Haemophilia A	279 (87%)	52 (84%)	23 (80%)	204 (88%)
Severe (A and B)	290 (90%)	54 (87%)	28 (97%)	208 (90%)
Moderate (A and B)	20 (6%)	6 (10%)	1 (3%)	13 (6%)
Dose per infusion (IU/kg)				
Haemophilia A	16 (13–24)	28 (22–40)	17 (13–22)	14 (12–20)
Haemophilia B	25 (16–38)	43 (29–56)	28 (23–41)	23 (14–30)
Infusion frequency per week				
Haemophilia A	3 (2–3)	3 (2–3)	3 (3–3)	3 (2–3)
Haemophilia B	2 (1–3)	2 (1–2)	2 (1–2)	3 (1–4)
Self-infusion	222 (69%)	3 (5%)	22 (76%)	197 (85%)
Positive inhibitor history	49 (15%)	12 (19%)	2 (7%)	35 (15%)
HIV history	21 (7%)	*	*	21 (9%)
HCV history	125 (39%)	*	*	125 (54%)

* Not applicable for this age group. HIV: human immunodeficiency virus; HCV: hepatitis C virus; IQR: interquartile range.

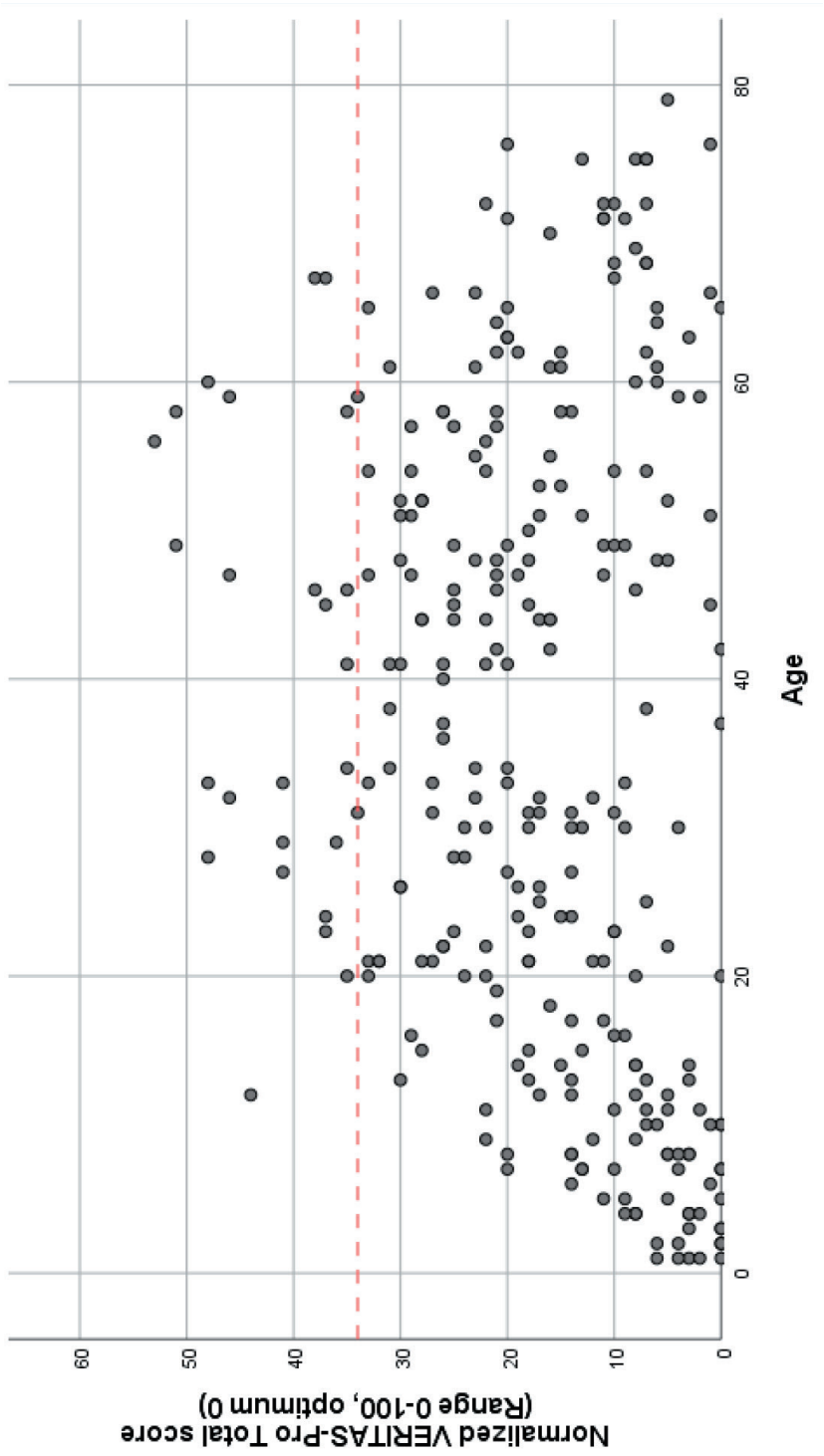


Figure 1 Adherence distribution according to age (red dotted line indicates the cut-off score for adherence). VERITAS-Pro: Validated Hemophilia Regimen Treatment Adherence Scale-Prophylaxis.

Adherence

Adherence scores, according to age, are shown in table 2. Overall, prophylaxis adherence was high (89% adherent, median total score of 17, IQR= 8–25), and only 11% were defined as non-adherent. Participants with haemophilia B (N= 42, 13%) showed a trend towards better adherence than participants with haemophilia A (score: 17 vs 13, p=0.34). Figure 1 shows a non-linear association between adherence and age group: adherence was best (lowest score) among the very young and deteriorated with increasing age (p=≤0.01). In children, 0% were non-adherent, in adolescents 3%, and in adults 15%. The top 3 domains with the highest non-adherence were Communicate (39% non-adherent), Plan (32%), and Dose (23%).

Adherence, as defined in haemophilia

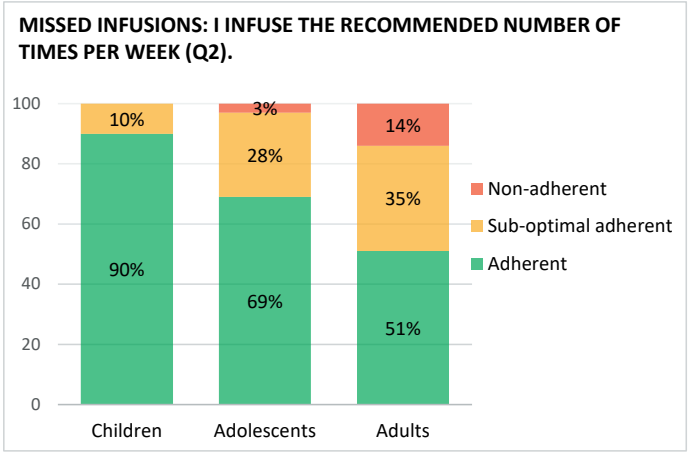
Adherence was evaluated based on three questions selected from VERITAS-Pro. In response to 'I infuse the recommended number of times per week', 0% of children, 3% of adolescents, and 14% of adults were non-adherent, which was comparable to the non-adherence percentages determined using the VERITAS-Pro total score (0%, 3%, and 15%, respectively). In response to 'I use the doctor-recommended dose for infusions', 2% of children, 0% of adolescents, and 2% of adults were non-adherent, which was lower for adolescents and adults than their respective VERITAS-Pro total scores. In response to 'I perform prophylaxis infusions in the morning, as recommended', 13% of children, 41% of adolescents, and 37% of adults were non-adherent. Figure 2 shows adherence, evaluated based on the answers to these 3 VERITAS-Pro questions. For all subgroups, the percentages of non-adherence were higher than the percentages suggested by the VERITAS-Pro total score.

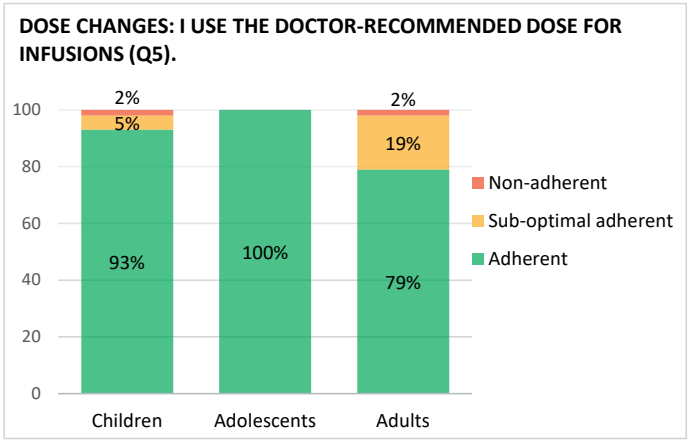
Table 2 Adherence measured using the VERITAS-Pro (range 0–100, optimum 0)

	All N= 321	% Non-adherent†	Children N= 61	% Non-adherent†	Adolescents N= 29	% Non-adherent†	Adults N= 231	% Non-adherent†	P-value
	Median (IQR) or (%)								
Total score	17 (8–25)	11%‡	5 (2–10) §	0%	14 (8–19) §	3%	20 (11–28)	15%	≤0.00
Time	19 (0–31)	12%	6 (0–19)	0%	18 (0–25)	7%	25 (6–39)	16%	≤0.00
Dose	6 (0–13)	23%	0 (0–6)	7%	0 (0–13)	10%	6 (0–19)	29%	≤0.00
Plan	25(6–38)	32%	19 (0–25)	23%	25 (14–25)	21%	25 (13–38)	36%	0.02
Remember	19 (0–31)	15%	0 (0–6)	3%	19 (6–31)	17%	18 (6–38)	18%	≤0.00
Skip	6 (0–25)	9%	0 (0–6)	0%	0 (0–13)	7%	13 (0–25)	11%	≤0.00
Communicate	38 (19–50)	39%	*	*	25 (6–38)	28%	38 (19–56)	52%	0.02

†percentages are based on the total group. For example (‡) 11% of the N= 321 patients were non-adherent (above the cut-off score), based on total VERITAS-Pro score. *Not able to analyse because ≥25% missing data.
Total score significantly different between all age groups, and significant differences between children and adults were observed for all domains.
IQR: interquartile range; VERITAS-Pro: Validated Hemophilia Regimen Treatment Adherence Scale-Prophylaxis.

Figure 2 Adherence, as evaluated using three questions selected from the VERITAS-Pro questionnaire





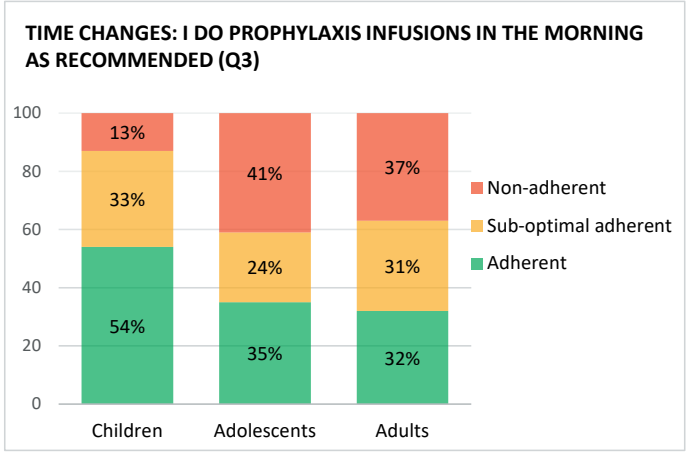


Table 3 Patients' treatment attitude and treatment satisfaction according to adherence

	Total	Adherent	Non-adherent	Diff between score and crosstabs* (P-value)
	Median (IQR) or N (%)			
Patients' treatment attitude (PAM-13)	N= 181 (100%)	N= 151 (100%)	N= 30 (100%)	
PAM-13 Score[$] (median, IQR)	66 (53–75)	66 (53–78)	68 (57–73)	0.83
Increasing level of Activation				
Level 1: Disengaged and overwhelmed (N, %)	12 (6%)	2%	10%	0.40*
Level 2: Become aware, but still struggling (N, %)	37 (20%)	22%	13%	
Level 3: Taking action (N, %)	66 (37%)	34%	47%	
Level 4: Maintaining behaviours and pushing further (N, %)	66 (37%)	38%	30%	
Treatment Satisfaction (median, IQR)	N= 208	N= 180	N= 28	
Total score	12 (6–21)	12 (5–20)	10 (5–21)	0.57
Ease and Convenience	15 (15–28)	15 (5–27)	10 (5–23)	0.37
Efficacy	21 (8–33)	21 (8–33)	17 (13–33)	0.91
Burden	13 (5–31)	13 (6–31)	6 (0–31)	0.33
Specialist/Nurse	0 (0–13)	4 (0–14)	0 (0–31)	0.31
Centre Hospital	0 (0–13)	0 (0–13)	7 (0–13)	0.39
General Satisfaction	0 (0–13)	0 (0–13)	0 (0–13)	0.79

[$] Interpretation of PAM-13: Each point increase in the PAM-13 score correlates to a 2% increase in medication adherence. PAM-13: Patient Activation Measure; IQR: Interquartile range.

Adherence and patients' treatment attitudes

In total, 181 (78%) adults completed the PAM-13 questionnaire. The median PAM-13 score among the total population was 66 (IQR= 53–75). Patients who were scored as adherent were primarily classified into Levels 3 (34% taking action) and

4 (38% maintaining behaviours and pushing further). Unexpectedly, non-adherent patients were also primarily classified into Levels 3 and 4 (level 3: 47%; level 4: 30%; Chi-square p=0.40). Patient activation, according to adherence, is shown in table 3, and a correlation table can be found in the appendix. The PAM-13 scores (0–100) were similar between adherent and non-adherent groups (66 vs 68, p=0.83) and were not correlated (r=0.41, p=0.6) with the VERITAS-Pro total scores. No VERITAS-Pro domain scores correlated with the PAM scores (r values between −0.12 and 0.11, all p=>0.05. The correlation table can be found in Appendix 1.

Adherence and treatment satisfaction

Overall, patients reported high treatment satisfaction (median Hemo-Sat: 12, IQR= 6–21). In particular, the domains Specialist/Nurse, Centre Hospital, and General Satisfaction had maximum scores (median= 0; IQR= 0–13). Treatment satisfaction was similar between adherent and non-adherent groups for both total score (median= 12 vs 10) and the domain scores. Treatment satisfaction, according to adherence, is shown in table 3. Adults were significantly more satisfied with their treatment than children (median= 16 in children vs 10 in adults, p=0.01). No correlation between VERITAS-Pro total scores and Hemo-Sat total scores was observed (r=−0.11), nor between any VERITAS-Pro domain scores and Hemo-Sat total scores (r between −0.13 and 0.08). The correlation table can be found in Appendix 1.

DISCUSSION

The aim of this study was to quantify prophylaxis adherence and examine the association between adherence and patients' treatment attitudes or satisfaction in a large cohort of children and adults with haemophilia. We hypothesised that 1) non-adherent patients would be distributed over all 4 PAM-13 levels and 2) adherent patients would be more satisfied with their treatment than non-adherent patients. Overall, Dutch PWH reported high adherence to prescribed treatment (89%). Adherence levels decreased significantly among older patients. The attitude towards treatment (PAM-13 score) was similar between adherent and non-adherent patients. Both groups showed high levels of patient activation: with the majority categorised as Level 3 (taking action) or 4 (maintaining behaviours and pushing further), which indicated that non-adherent patients make conscious

choices regarding their treatment. Overall treatment satisfaction was high and showed no association with adherence.

The HIN-6 is a repeated nationwide study associated with several limitations. First, the potential risk of selection bias exists, as the selection of patients on prophylaxis may potentially result in the selection of more adherent patients who took the time to complete the questionnaires. However, this potential bias is not expected to affect the association between adherence with treatment attitude. All outcomes were self-reported, which could be associated with a risk of under- or overreporting[6,22]. Underreporting by patients is a well-known phenomenon, particularly for adherence[6,22]. Therefore, actual adherence levels could be higher than those reported.

Overall, the VERITAS-Pro scores reported in the present study were similar to those in earlier reports by Duncan et al.[8] (mean score 18), who examined 67 patients with a mean age of 15 years [standard deviation (SD)= 12.7]. The domain with the best adherence was Dose (mean= 9, range= 0–63) and the domain with the worst adherence was Time (mean= 22, range= 0–75)[8]. The VERITAS-Pro total and domain scores reported for the Dutch validation study were comparable to the those reported in our sample for similar age groups (children and adolescents) Lock et al. reported a median total score of 13 (IQR= 5–18) among 60 children with a mean age of 10 years (SD= 4)[9]. Patients were reported to be most adherent for the domain Skip (median= 0, IQR= 0–13) but the least adherent for the domain Plan (median= 19, IQR= 0-31)[9].

This current study reported a significant difference in adherence between all age groups: children, adolescents, and adults. Other studies have previously reported a significant difference between young children and adolescents[11,21], which may be associated with the finding that patients begin learning how to infuse themselves starting around the age of 12 years to manage self-treatment[3]. To the best of our knowledge, this study is the first to evaluate patient treatment attitudes using the PAM-13 questionnaire in PWH. Overall, in the present study, both adherent and non-adherent patients were primarily categorised to Levels 3 and 4. In addition, this current study failed to identify any correlation between adherence and PAM-13 scores (r=0.41; p=0.56). These results are not comparable with those reported for several other studies that examined the association between PAM-13 scores

and adherence in other chronic disorders[22–24]. Only one study used a comparable study design as our study. Jie Gao et al.[24] studied adults with cystic fibrosis (N= 64) who were categorised into two levels of adherence. Non-adherent patients were typically categorised to Levels 3 (41%) and 2 (32%), whereas adherent patients were categorised to Levels 3 (64%) and 4 (27%)[24]. Other studies have reported low correlations between adherence questionnaire and PAM-13 scores (r= −0.18[23] and r= 0.15[25]).

Two qualitative studies examining PWH (adults and adolescents) described a relationship between non-adherence and self-management or the ability to exert prophylaxis[13,14]. We hypothesised that some patients are intentionally non-adherent, making the conscious choice not to administer prophylaxis. Based on the descriptions for the PAM-13 questionnaire levels, this hypothesis would be compatible with Levels 3 (taking action) and 4 (maintaining behaviours and pushing further). Others are unintentionally, subconsciously non-adherent, which would be compatible with Levels 1 (disengaged and overwhelmed) and 2 (becoming aware but still struggling). However, these study results showed that most non-adherent patients were classified as Levels 3 and 4 rather than Levels 1 and 2. Therefore, most haemophilia patients appear to be making a conscious choice to be non-adherent to their treatment regimen. Based on previous qualitative research[14], we hypothesised that this non-adherence might be caused by not experiencing bleeds after skipping or forgetting prophylaxis, which impacts patients' estimations of the risks associated with skipping prophylaxis.

This study results showed that adherence among Dutch PWH is high and that both adherent and non-adherent patients have a high treatment attitude and satisfaction regarding their treatment. However, some patients were non-adherent to their prescribed treatment regimens, with high treatment attitudes, which suggested that they were making the conscious choice to be non-adherent. Haemophilia nurses and treaters might overestimate their patients' adherence levels. Therefore, haemophilia nurses and treaters should be aware that even knowledgeable patients with an high treatment attitude can be non-adherent and at risk for bleeds and joint damage. An open and non-judgmental conversation should be performed to assess the patient's reasons for adherent or non-adherent behaviours. Motivational interviewing can be applied as a useful conversation technique, characterised by open questions, affirmation, reflective listening, and summary

reflections[30,31]. If non-adherence is associated with disease acceptance (in terms of prophylaxis or related complication), support through a cognitive behavioural intervention may be appropriate[26–28]. Preliminary reports on haemophilia-specific acceptance and commitment training have shown promising results[29]. The present study used quantitative research methods to test a hypothesis based on the findings of qualitative research. Contrary to expectations, the hypothesis was not confirmed.

CONCLUSION

This paper describes high prophylaxis adherence levels among children, adolescents, and adults with haemophilia. Overall, adherence decreased among older patients. Both adherent and non-adherent patients were generally categorised as PAM-13 scale Levels 3 and 4, indicating that patients generally have high treatment attitude, and non-adherence likely represents a deliberate choice. No correlations between the adherence questionnaire (VERITAS-Pro) scores and the scores for the attitudes towards treatment (PAM-13) or treatment satisfaction (Hemo-Sat) questionnaires were observed.

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APPENDIX

Appendix 1 Spearman's rho correlations between adherence (VERITAS-Pro) and treatment attitude (PAM-13) or treatment satisfaction (Hemo-Sat)

		Patient attitude		Treatment satisfaction
		Pam-13 score (0–100)	Pam-13 Level (1–4)	Hemo-Sat Total score
		Correlations		
Adherence	Total score	0.41	−0.00	−0.11
	Time	0.03	−0.00	0.01
	Dose	−0.12	−0.14	0.03
	Plan	0.04	0.02	0.08
	Remember	0.11	0.05	−0.13
	Skip	0.09	0.06	−0.6
	Communicate	−0.02	−0.03	−0.02

None of the correlations reached significance at the 0.05 level (2-tailed) VERITAS-Pro: Validated Hemophilia Regimen Treatment Adherence Scale-Prophylaxis; PAM-13: Patient Activation Measure; Hemo-Sat: Hemophilia Patient Satisfaction Scale

Unravelling

CHAPTER 2

Adherence to prophylaxis and bleeding in children: Significant drop during puberty but no correlation with bleeding

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ABSTRACT

Introduction

Adherence is crucial to the effectiveness of prophylactic replacement therapy in (severe) haemophilia. Adherence varies according to age and is expected to affect bleeding frequency. This study explored the associations between adherence to prophylactic treatment and age and bleeding frequency in children and adolescents with severe haemophilia.

Methods

In a single-centre retrospective study, routine data was collected during outpatient visits. Children with severe haemophilia on prophylaxis with an available adherence questionnaire (VERITAS-Pro, range 0-100, optimum 0) were studied. Three-year data on treatment and bleeding were extracted from electronic patient medical records. Data were analysed for the age groups 0-13 years and 14-18 years using the Mann-Whitney U and Spearman's rank tests.

Results

In total, 62 children with severe haemophilia were included in the study. They had a median age of 12 years old (IQR= 9-14 years old). The overall adherence (total score) was high: the median was 17 points (IQR= 13-25); 95% of the children adhered to their prescribed treatment. Young children were significantly more adherent than older children (delta of 5 points, p=0.04). The overall annual bleeding rate was low, with a median of three per year (IQR= 1.6-4.3), including one joint bleed/year. (IQR= 0.3-2). Adherence (total score) was not correlated with bleeding (r= -0.15) or joint bleeding (r= -0.09).

Conclusion

The children in this study had very high adherence. Older children (14-18 years old) reported significantly lower adherence. There was no correlation between adherence and bleeding.

INTRODUCTION

Individuals with severe haemophilia or Von Willebrand disease type 3 lack a clotting factor and are at risk of experiencing spontaneous bleeds in the joints, muscles, or soft tissues[1]. To prevent bleeding, patients must inject themselves with prophylactic clotting factor concentrate, which is a demanding treatment consisting of intravenous infusions 3 to 3.5 times each week, starting before the age of three years[2]. In Dutch children with haemophilia or Von Willebrand disease, parents generally perform these injections at home until children learn to self-administer, which generally occurs during early adolescence, at an average age of 12 years old[2]. Around the age of 14 years old, children slowly start to take responsibility for their infusions[2], which coincides with the normal physical, cognitive, and psychosocial changes that occur at this age.

In addition to normal developmental changes, children with haemophilia or Von Willebrand disease must manage an additional burden: adherence to the treatment and self-management of their disease[3]. In haemophilia and other chronic conditions, reduced adherence is often reported during adolescence. Previous studies have reported adherence differences between children (younger than 18 years) and adults (older than 18 years)[3]. Low adherence to prophylaxis could result in more frequent bleeding events and subsequently negative effects on joint status[4]. The adherence age cut-off of 18 years used in previous studies is too crude to identify the optimal age for adherence interventions. This study aimed to explore the associations between adherence to prophylactic treatment and age and the frequency of bleeding events in children and adolescents with severe haemophilia.

METHODS

This study was performed as a cross-sectional study. Data were collected during regular outpatient visits in The Netherlands (Utrecht). Adherence was measured using the 'Validated Haemophilia Regimen Treatment Adherence Scale-Prophylaxis' (VERITAS-Pro) questionnaire. Demographics and bleeds were extracted from electronic patient medical records. The Medical Ethics Review Committee of University Medical Center (UMC) Utrecht approved the use of data

collected during regular patient care for this study, and informed consent was waived.

Population

A convenience sample of patients from the Van Creveldkliniek Utrecht, The Netherlands was used. Patients younger than 18 years were included if they had been diagnosed with severe haemophilia or Von Willebrand Disease type 3, had been prescribed prophylactic treatment, and had a VERITAS-Pro questionnaire filled out between 2011 and 2016. Additionally, bleeding data for three years prior to the completion of the VERITAS-Pro questionnaire had to be available.

Data collection

The following demographic variables were extracted from electronic medical records: age, diagnosis, mode of venous access (intravenous (IV) or central venous access device (CVAD)), who administered the prophylactic treatment (parent, child, or both), dose and treatment frequency, 3-year bleeding history, as well as joint status, defined as the presence of synovitis and arthrosis (defined as a Haemophilia Joint Health score of >3 points or abnormal Pettersson score) registered by a clinician in the patient record. Extraction of bleeding data from medical records was performed by two independent researchers (LH and JH) and crosschecked.

All patients visiting the outpatient clinic are asked to complete the VERITAS-Pro[5]. The questionnaire is completed by the individual (parent or patient) who administers the prophylactic treatment. The VERITAS-Pro includes 24 questions answered on a 5-point Likert scale and produces a total score and six domain scores: Time, Dose, Plan, Remember, Skip, and Communicate. All scores in this study were normalized to a 0-100 scale, (total score-20/96*100 or domain score-4/16*100); the optimal total score and domain scores were 0, with higher scores representing non-adherence. Additionally, the following cut-off scores were applied to categorize adherent and non-adherent individuals[5]: total score above 34, Time above 44, Dose above 19, Plan above 31, Remember above 44, Skip above 44, and Communicate above 38.

Analyses

Based on the literature, the data were analysed according to two categories of treatment responsibility[2]: before taking responsibility for prophylaxis (< 14 years) and after taking responsibility (≥ 14 years). Due to the skewed distribution, the Mann-Whitney U test was used to compare differences between groups, and Spearman's Rank Correlation Coefficient was used to identify potential correlations between VERITAS-Pro scores and bleeding levels. All analyses were performed using SPSS version 25.

RESULTS

In total, N= 97 patients had completed the VERITAS-Pro questionnaire; however, only 62 patients were included in our analyses. Twenty-four patients were excluded due to incomplete questionnaires (N= 13), missing date of questionnaire completion (N= 2), or missing bleeding data (N= 9). Patient characteristics are shown in table 1. The median age was 12 years old [interquartile range (IQR)= 9-14 years old], most patients were diagnosed with haemophilia A (77%), and four patients (8%) used a CVAD. Overall bleeding rates were low at a median of 3/year (IQR= 1.6-4.3), including one joint bleed (IQR= 0.3-2). Furthermore, eight patients (1.5%) did not report any joint bleeding in the last three years. Administration of prophylaxis changed with age: self-infusion was reported less frequently in children (10% vs 61%, $p<0.01$). Adolescents reported significantly more joint bleeds (1 vs 0.7, $p<0.01$) compared to (younger) children.

Adherence: Total population

Table 2 and figure 1 show the group differences related to the VERITAS-Pro total score and domains. The median total VERITAS-Pro score was 17 (IQR= 13-25), but only 5% of the total population was categorized as non-adherent based on the previously established cut-off scores. Two patients had the optimum domain score of 0. The three domains with the lowest adherence were Plan (median= 25, IQR= 6-31, 37% non-adherence), Communicate (median= 25, IQR= 19-25, 37% non-adherence) and Time (median= 19, IQR= 5-25, 11% non-adherence).

Adherence: Children versus adolescents

When comparing adherence levels in children according to age (≥ 14 years of age vs. younger than 14 years old), the younger group had a 3% non-adherence rate, with a

median score of 16 (IQR= 11-20), whereas the older group had a 10% non-adherence rate, with a median score of 21 (IQR= 16-30) (p=0.04). Children had significantly better adherence in three of the four domains that are crucial to the consensus definition of adherence reported in Schrijvers et al.[6] (Timing p=0.05, Remembering p=0.02, and Skip p=0.04). Only adherence to dose remained constant with increasing age. However, no significant correlation between age, as a continuous variable, and the total VERITAS-Pro score was identified (Spearman's r=0.10).

Table 1 Patient and treatment characteristics by age group

	Total N= 62	*Children (4- <14 years old)* N= 39	*Adolescents (≥14 -18 years old)* N= 23	*Group diff* (p=)*
	Median (IQR) or %			
Age (years)	12 (9-14)	10 (8-12)	15 (14-17)	0.00
Diagnosis				
Haemophilia A	77%	82%	70%	0.23
Haemophilia B	21%	18%	26%	
Von Willebrand type III	2%	0%	4%	
Central Venous Access Device	7%	8%	4%	0.31
Who is performing infusion				
Patient	29%	10%	61%	0.00
Parent	52%	77%	9%	
Together	18%	10%	30%	
Unclear	2%	3%	0%	
Prophylactic infusions/week	3 (3-3.5)	3 (3-3.5)	3 (3)	0.18
Prophylaxis dose/infusion, IU	1000 (750-1000)	750 (500-1000)	1000 (1000-1500)	0.01
Total bleeds/year	3 (1.6-4.3)	3.3 (2-5)	2 (1.3-3)	0.59
Joint bleeds/year	1 (0.3-2)	0.7 (0.3-2.3)	1 (0.3-1.3)	0.00
No joint bleeds in last year	13%	10%	17%	0.86

* Mann–Whitney U test

Table 2 Group differences and correlations for adherence and prophylaxis (range 0-100, optimum 0)

	Total sample (N= 62)			*Children (N= 39)*			*Adolescents (N= 23)*			*Total bleeds**	*Joint bleeds**
	VERITAS-Pro norm score		*Non-adherent*	*VERITAS-Pro norm score*		*Non-adherent*	*VERITAS-Pro norm score*		*Non-adherent*	*Group diff. (p=)*	*r*	*r*
	Median (IQR) or %											
Total scale	17	(13-25)	5%	16	(11-20)	3%	21	(16-30)	10%	**0.04**	-0.15	-0.09
Time	19	(5-25)	11%	13	(13-19)	5%	25	(6-38)	22%	**0.05**	-0.26	-0.11
Dose	0	(0-13)	10%	0	(0-13)	11%	0	(0-13)	9%	0.41	0.03	-0.02
Plan	25	(6-31)	37%	25	(0-31	33%	25	(6-31)	44%	0.55	0.06	-0.09
Remember	13	(0-25)	10%	6	(0-25)	3%	19	(13-34)	24%	**0.02**	0.12	0.06
Skip	6	(0-25)	10%	3	(0-25)	8%	22	(0-31)	14%	**0.04**	-0.15	-0.10
Communicate	25	(19-50)	37%	25	(19-41)	27%	38	(24-58)	55%	0.12	0.02	0.02

* Group differences are significant at the 0.05 level (significant results are indicated in bold), correlations above r=0.5 are considered relevant.

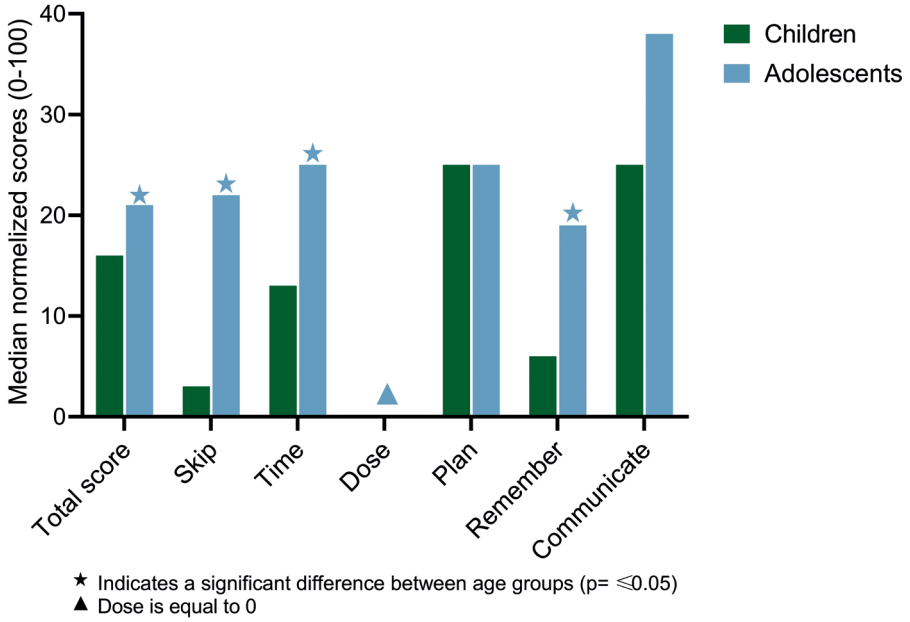

Figure 2 Group differences in adherence to prophylaxis (range 0-100, optimum 0)

Association of adherence with bleeds

With the increased self-infusion rates and lower adherence in the older age group, the annual number of joint bleeds increased slightly, but significantly, from 0.7 to 1 (p=0.00). The proportion of patients with an absence of joint bleeding was comparable between children and adolescents (10% vs 17%, p=0.86). Contrary to our expectations, the VERITAS-Pro total score and domain scores did not correlate with total bleeds (r=0.02-0.26) or joint bleeds (r=0.02-0.11).

DISCUSSION

This study aimed to explore the relationships between adherence to prophylactic treatment and age and the frequency of bleeding events in children and adolescents with severe haemophilia. A correlation between adherence and bleeds was expected. Contrary to our expectations, the VERITAS-Pro total score and domain scores did not correlate with total bleeds (r= 0.02-0.26) or joint bleeds (r=0.02-0.11). Adolescents had a significantly higher VERITAS-Pro median total score (p=0.04) and median domain scores for Time (p=0.05), Remember (p=0.02), Skip (p=0.04) compared with the children.

There are some strengths and limitations to this study that must be discussed. All data was collected by two researchers (JH and LH) and crosschecked. The majority of the patients were assigned to one specific paediatric haematologist (KF). When doubts or uncertainties arose, this clinician was consulted, thus minimalizing the risk of collection bias. This study had a cross-sectional design, data were collected during regular care, and patient characteristics and bleeds were extracted from medical records. Bleeding data were collected retrospectively, going 3 years back from the moment patients completed the VERITAS-Pro. Bleeding was routinely recorded in the patient files at 6-12 month intervals by the consulting haematologist. Demographic data were collected a few years after completion of the VERITAS-Pro.

The overall high degree of adherence identified in children in this study is in line with previous reports[3,7]. This study observed an important drop in adherence around 14 years of age. Despite this well-known, age-related drop in adherence, we must be aware that the age at which children assume the responsibility for their prophylaxis treatment could be country-dependent. Previous studies performed on adults with severe haemophilia have reported contradictory results regarding the association between bleeding and adherence, with some studies reporting an association[8] between adherence and bleeds, while others found no association[9]. Nijdam et al.[4] reported deterioration in joint status after discontinuation of prophylaxis treatment despite low bleeding rates. A recent qualitative study reported that adherence behaviour in adolescents and young adults with severe haemophilia was dependent on: 1) the level of treatment responsibility, and 2) the risk estimation (short-term) of prophylaxis per activity[10]. This risk assessment included a continuous balancing act between two arguments: doing what they prefer and feeling safe. This finding implies that adherence is continuously influenced by bleeding. A potential reason for the lack of association of bleeds with adherence is a short adherence feedback-loop: a patient was non-adherent, experienced a bleed, and became adherent again[11]. In this situation, bleeds are associated with adherence, but this association is difficult to capture.

The results of the present study confirmed the risk of non-adherence among teenagers after they assume treatment responsibility. An open, non-judgmental conversation regarding non-adherence, bleeding risks, and the preferences of the adolescent is recommended[10]. Regardless of the lack of a noted association

between reported bleeds and non-adherence in this study, it is very important to be aware of the risks associated with subclinical bleeds and potential joint damage in non-adherent children[4].

CONCLUSION

The present study reported a drop in adherence between children after 14 years of age. No correlation between adherence and the number of bleeds was observed. In our opinion, this result may be explained by the (short-term) risk assessments made by adolescents and young adults that influence their decision-making regarding adherence.

Note
A minor adjustment in the normalization formula of the VERITAS-Pro was made in comparison with the original letter to the editor.

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Unravelling

CHAPTER 3

The perspectives of adolescents and young adults on adherence to prophylaxis in haemophilia: A qualitative study

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ABSTRACT

Purpose

Adolescents and young adults (AYAs) with severe hemophilia use prophylaxis that requires a high level of adherence. The present study aimed to explore the underlying reason for adherence and non-adherence to prophylaxis in hemophilia from the perspective of AYAs.

Patients and Methods

A qualitative study in Dutch AYAs with hemophilia (14–25 years) using prophylaxis was executed. Focus group interviews and individual interviews were recorded, transcribed, coded and analyzed using an iterative process. Member checking in three respondents was used to validate the potential model.

Results

A total of 21 interviews were performed. Parental support decreased when AYAs gained more treatment responsibilities, which resulted in a higher risk for non-adherence. AYAs were weighing their potential bleeding risk per activity based on the wish to do what they prefer while also wanting to simultaneously feel safe. When bleeding with low impact on their daily life occurred, or when bleeding remained absent, AYAs felt safe and the perceived need for prophylaxis decreased.

Conclusion

The level of treatment responsibility per AYA and estimated risks per activity were the two main underlying reasons for (non-)adherence. Clinical implications: We suggest using a conversation technique to discuss adherence, especially during bleeding assessment visits.

INTRODUCTION

Adolescents and Young Adults (AYAs) struggle with 'normal' changes in biological, physical and emotional wellbeing[1]. Adolescents with a chronic illness are exposed to additional challenges such as accepting responsibility for their disease and its treatment. The physical and emotional changes of AYAs can result in difficulties in imagining the future and the rejection of parents or medical professionals[1]. Potential peer pressure and AYAs' desire to be normal can easily lead to non-adherence to their chronic treatments[2]. Notably, self-management skills must be learned during adolescence. These skills are defined as "the individual's ability to manage the symptoms, treatment, physical and psychosocial consequences and lifestyle changes inherent in living with a chronic condition[3].

Hemophilia is a rare X-linked congenital bleeding disorder affecting ±1/10.000 males[4]. People with hemophilia A lack clotting factor VIII, those with hemophilia B lack clotting factor IX. Bleeding tendency in hemophilia A and B is similar. People with severe hemophilia (clotting factor VIII/IX <1%) need prophylactic factor replacement therapy[4]. Prophylactic treatment consists of intravenous injections twice weekly to every other day (i.e. 2-3.5 injections/week) to maintain minimal clotting factor activity levels and prevent bleeding[5]. Prophylaxis is initiated at the onset of bleeding, usually between 2 and 4 years, and continued for life As soon as possible, parents are taught to perform intravenous injections at home[5]. Using disposable needles, the injections are performed manually in 2-3 minutes and can be performed in a home setting. Just before puberty, around the age of 13 years, boys are taught to infuse themselves[5]. This continuous intensive intravenous treatment is very demanding for both parents and children.

Despite this treatment are AYAs with severe hemophilia continuously at risk for bleeding in their joints, muscles, and soft tissue[6]. Such bleeding can occur spontaneously and lead to irreversible damage, especially in the joints. Multiple instances of bleeding in the joints can lead to severe arthropathy and disability at a young age[7,8]. To prevent this bleeding, AYAs with severe hemophilia require continuous and life-long intravenous prophylactic replacement therapy[6]. A high level of adherence is crucial to maintain the factor levels and prevent bleeding[7]. During adolescence, adherence drops in hemophilia (range 13% to 17% non-adherence[9,10]), which is comparable to that of other chronic diseases[11,12]. Non-

adherence in hemophilia leads to significantly more breakthrough bleedings, target joints, more days missed at school and work, and subsequently a lower quality of life[13,14].

Little remains known about the underlying reasons for non-adherence to prophylaxis from the AYA perspective. In adults, adherence to prophylaxis was associated with acceptance, feeling and fearing symptoms, as well as understanding and planning and infusion skills[15]. Brand et al.[10] studied the reasons for non-adherence during the transition from paediatric care to adult services. Notably, they defined social (e.g. lower family and peer support), emotional and developmental (e.g. rebellion against prescribed treatment), practical (e.g. lack of time) and educational (e.g. lack of knowledge) issues[10]. We hypothesized that the underlying reason for (non)adherence in AYAs depends on factors other than care transition.

Understanding the underlying reasons for non-adherence, as experienced by AYAs, could help healthcare providers to begin patient-centered conversations and provide patient-tailored care. Therefore, the present study aimed to explore the underlying reasons for (non)adherence to prophylaxis in hemophilia from the perspective of AYAs.

MATERIAL AND METHODS

This present study comprises a qualitative exploration using a grounded theory approach[16]. This approach is designed for developing a theoretical understanding of a subjective process that continues over a known period of time[16]. Data was collected using focus group interviews and individual interviews. Institutional review board (IRB) of the University Medical Centre Utrecht, The Netherlands approval was obtained before the study, written consent was obtained from participants before the interviews and the COREQ guideline[17] was used for reporting qualitative research.

Sampling

Dutch AYAs (age 14-25 years) with hemophilia that were prescribed prophylactic treatment for at least two consecutive years at a minimum frequency of two times a week were invited to participate in the present study. To ensure sufficient

experience and variability with decision making regarding the administration of routine prophylaxis in daily life, it was decided to include only patients who used prophylaxis for a minimum of two years. AYAs were excluded when they were unable to read or understand Dutch. Under qualitative sampling strategies, purposeful sampling was applied to create a diverse sample. Therefore, maximum variation was sought for age, adherence levels and bleeding frequency in the sample[18]. Predefined definitions were used to assess adherence levels[19], bleeding frequency and education level (Table 1).

Table 1 Pre-specified definitions used for sampling variation.

Characteristic	Definition		
Adherence level [18]	Adherent	missed infusions changes in dosing changes in timing	0-15% 0-10% 0-30%
	Sub optimally adherent	missed infusions changes in dosing changes in timing	15-25% 10-25% 25-100%
	Non adherent	missed infusions changes in dosing	25-100% 25-100%
Bleeding history	Occurrence of a bleeding in the last year (diagnosed by physician)		
Education	High school (HS), Vocational education (VE), Higher vocational education (HVE), University (U)		

Eligible AYAs, participating were informed about the study by phone. If they were interested in participating, they received an information letter by e-mail. The information letter contained information about the reason for this study and research aim. After providing potential participants with one week to consider participation (and their parents of young adults between the age of 14–18 years old), they were called to determine whether they were interested in participating. AYAs, and if they were younger than 18 years both parents and AYA, signed written informed consent.

Data collection and study procedures

A total of three face-to-face focus groups were conducted. The focus group interviews included a fun activity in advance (an 'escape room') to create a relaxed atmosphere between participating AYAs and to stimulate discussions among

them. Individual interviews were subsequently performed to generate more in-depth exploration about barriers, motivators and facilitators of prophylaxis and decision making regarding adherence. Three respondents were then interviewed a second time to present them with the emerged conceptual figure and to accomplish this (member checking). All interviews were face-to-face and each interview took between 30-90 minutes in total. According to the AYAs' preferences, interviews were conducted either in their homes or at the hemophilia treatment center (HTC). Following interviews, AYAs answered three questions to determine their adherence level and checked with diaries or pharmacy data.

The interviews were guided by a topic list based on the literature[15,20] and the clinical expertise of the research team (JH, MK, KF, LS). The topics were converted to open questions and adapted (when necessary) after each round of interviewing (details in Box 1 and appendix 2). Interview topics included perceptions regarding hemophilia, self-monitoring and decision-making, barriers, motivators and facilitators of adherence, and the integration of prophylaxis in daily life. All interviews were audiotaped, transcribed verbatim and anonymized. Transcriptions were not returned to the respondents for comments, yet the conceptual figure was discussed and verified by respondents (member checking). The focus group interviews were executed by two (female) hemophilia nurses (JH and LS), both with formal interviewing training. Memos were made during the focus group by the second interviewer (LS) and used to evaluate the focus group. The individual interviews were conducted by one interviewer (JH or LS). Both interviewers had no current healthcare provider relationship with the respondents. The interviewers attempted to create a non-judgmental atmosphere and they emphasized the importance of learning from the AYAs. Further medical and treatment baseline characteristics (age diagnose and prescribed medication) were extracted from the medical record.

Qualitative data analyses

According to qualitative guidelines[21], data were analyzed using open, axial, and selective coding[18,22]. After each interview, the process started with a thorough reading of the interview followed by summarizing and conceptualizing the content[21].

Box 1 Topic list

- Experiences with prophylaxis
- Integration of prophylaxis in daily life
- Hemophilia related skills
- Perception and expectations about hemophilia, prophylaxis and adherence
- Barriers, motivators, and facilitators of prophylaxis
- Decision making
- Self-monitoring
- Social environment
  - o Parental influence
- Patient characteristics

Open coding of meaningful fragments was performed and categorized guided by their content into a more conceptual category (axial coding). Codes and themes were derived from the data and not specified in advance. Interviews were coded by JH and verified by LS. After each round of approximately 3 to 4 interviews, the (new) results were discussed among the study team (JH, MK, KF, and LS). Selective coding was used to compare new data with existing themes, leading to the strengthening of existing themes or the establishment of new themes (Appendix 1; additional details can be provided on request). The analysis process was supported by the qualitative software package NVivo 11®.

RESULTS

Overall, 18 of the 38 AYAs approached agreed to participate in the present study (response rate: 47%), with 21 interviews being obtained (three respondents were interviewed twice). The main reasons for refusal included limited time and lack of interest. A total of nine AYAs joined one of the three focus groups (N= 2, N=4, N= 3 per group), while nine AYAs were interviewed individually. Data saturation was reached on the main components, meaning that no new themes or meaningful fragments were identified for addition into the current structure of the model[18,23].

The majority of AYAs was interviewed at home in the absence of family members, though one was interviewed in the presence of some family members by their request. Patient characteristics are presented in table 2. The median age was 18 years (range 14-24 years). A total of 11 AYAs were classified as adherent, while four were sub-optimally adherent and three were non-adherent to their prophylactic regimen[19].

Adherence behavior in AYAs: Varying treatment responsibility and estimating risk

Based on the obtained data, the present study revealed that adherence behavior was dependent on 1) the level of treatment responsibility and 2) the risk estimation of prophylaxis per activity. The first underlying reason was explained by the varying levels of parental support regarding treatment responsibility that AYAs experienced. Notably, three consecutive phases related to growing up with hemophilia were observed. In these three consecutive phases, the treatment responsibilities increased while the parental support decreased and the risk of non-adherence increased. The second underlying reason was explained by AYAs weighing their potential bleeding risk by day and activity. They explained that this risk assessment was based on the desire to do what they prefer while simultaneously feeling safe. Feeling safe was described by AYAs as the absence of bleeding impacting on their (daily) life. Doing what they prefer was described as acting like their healthy peers. A schematic overview of this process is shown in figure 1, while table 3 presents the underlying themes.

Varying treatment responsibility

AYAs mentioned varying levels of parental support, which resulted in various responsibilities for each AYA regarding prophylaxis. With increasing age, we identified three consecutive phases in the AYAs' responsibility for treatment, with concomitant changes in adherence (see figure 1 for a conceptualization of this description).

First phase of treatment responsibility

In the first phase, AYAs felt able to infuse themselves; however, parents performed the infusions most of the time. AYAs mentioned that their parents took responsibility for their prophylactic treatment and performed bleeding management. Most of the AYAs were unaware of their treatment schedule. They told us that their parents never skipped or missed prophylaxis, which enabled them to rely on their parents. AYAs explained that they felt comfortable with the support of their parents. AYAs in this phase informed us they experienced minimal or no bleeding at all. Moreover, AYAs described short discussions with their parents regarding the necessity of prophylaxis, and they mostly agreed with the opinion of their parents. Due to the high level of parental support, most AYAs in this phase adhered to the prescribed dose and frequency of prophylaxis.

Table 2 Demographic and background characteristics (N= 18 patients with severe hemophilia).

Age	Interview	Prescribed frequency (times a week)	Prescribed dose (IU)	Adherence level[1]	Bleeding last year	Education	Daily activity
14	Focus	3.5	1000	+	Yes	High school	School
14	Focus	3.0	750	+	Yes	High school	School
14	Focus	3.0	1500	+	No	High school	School and work
14	Individual	3.0	1000	+	No	High school	School
15	Focus	3.0	1000	±	No	High school	School
15	Focus	3.5	1000	±	Yes	High school	School and work
16	Focus	3.5	1500	+	No	High school	School and work
17	Individual	3.5	1500	+	Yes	Voacational	School and work
19	Focus	2.0	1000	+	No	Voacational	School and work
19	Individual	3.5	1000	+	Yes	Advanced vocational	School
19	Individual	2.0	2000	+	Yes	Advanced vocational	School and work
19	Individual	3.0	1000	+	No	Advanced vocational	School and work
19	Individual	2.0	1000	-	Yes	Voacational	School and work
21	Focus	2.5	1000	±	Yes	Advanced vocational	School and work
21	Individual	2.0	1000	±	No	Voacational	School and work
21	Individual	3.0	2000	-	Yes	Advanced vocational	Work
22	Individual	3.5	1250	+	No	University	School and work
24	Focus	3.0	1000	-	No	Voacational	Work

[1.] + = adherent, ± = sub-optimal adherent, - = non-adherent

Second phase of treatment responsibility

During the second phase, most AYAs explained that they prepared and infused the prophylaxis independently. Sometimes they skipped or forgot their infusion despite reminders from their parents. AYAs in this phase mentioned that they sometimes experienced bleeding. While they informed us that they recognized bleedings, decision making concerning bleedings varied per AYA. Some AYAs made their own decisions, while others asked their parents for advice. AYAs mentioned that they gradually became more responsible for their treatment by taking over the preparation and infusion, and eventually remembered and performed infusions independently. It was unclear whether the AYAs or their parents initiated the process of becoming more responsible. AYAs explained that they sometimes estimated the need for prophylaxis, which resulted in discussions between parents and the AYAs. Notably, AYAs experienced their parents being too careful. In this second phase, the combination of more responsibilities and estimated the need for prophylaxis resulted in a variety of adherence levels.

Third phase of treatment responsibility

In the third phase, AYAs felt entirely responsible for preparing and administering prophylaxis, as their parents were no longer involved. Some AYAs mentioned that they would rarely forget their prophylaxis, and, if they did, they took it as soon as possible. On the other hand, some AYAs told us that they purposefully skipped prophylaxis because they did not feel the need to take it. AYAs explained that they were weighing arguments in favor of and against prophylaxis. As such, AYAs were making their own decisions concerning their prophylactic treatment. Nearly all AYAs had experience with bleeding. AYAs told us that they only contacted their parents for advice in the case of an emergency and that discussions about this with their parents were out of the question. In this phase, the increased independence and weighing arguments related to prophylaxis resulted in various adherence levels.

Estimating risk

All AYAs mentioned that they were weighing treatment decisions based on the desire to do what they prefer while simultaneously feeling safe. These decisions were affected by the estimated bleeding risk. All AYAs stressed the importance of wanting to live like their healthy peers, without the presence of bleeding. Some AYAs reported that they felt safe when no bleeding occurred or when bleeding

did not affect their daily activities. Other AYAs weighed the perceived need for prophylaxis per activity ('Is this activity safe without prophylaxis?'). Meanwhile, all AYAs mentioned skipping activities when they did not feel safe (even with prophylaxis). Therefore, AYAs mentioned that feeling safe was more important than doing what they preferred.

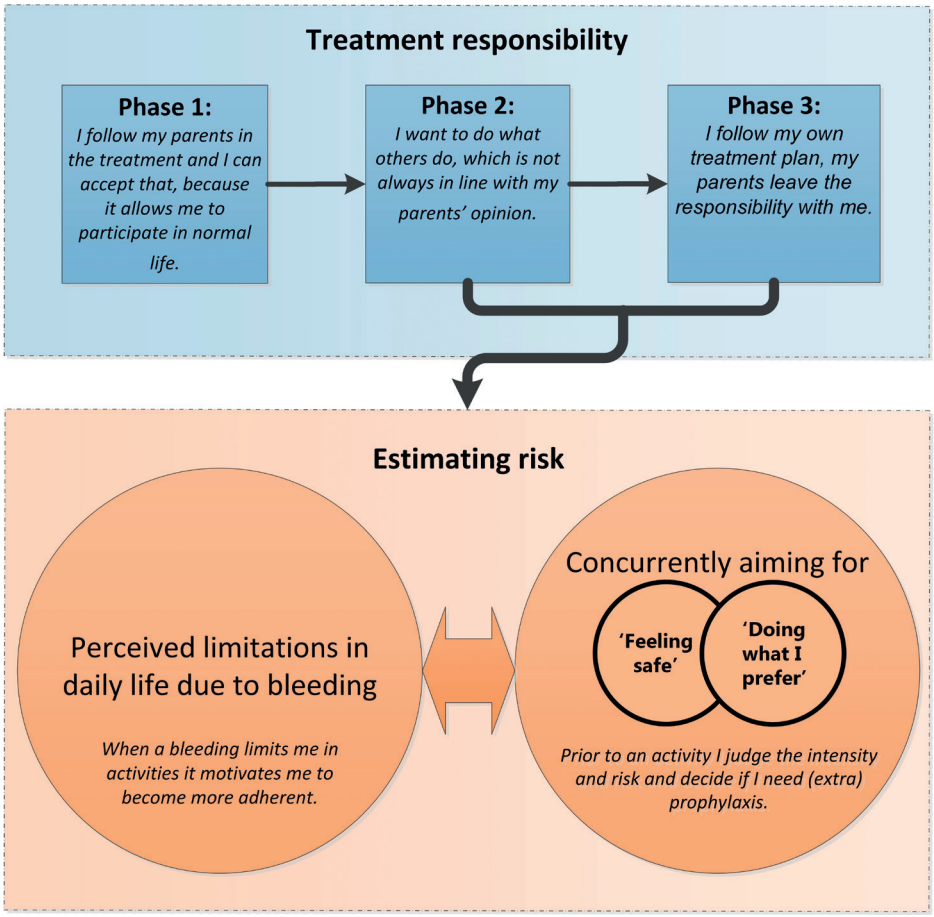

Figure 1 Decision making concerning prophylaxis adherence among AYAs: Treatment responsibility and estimating bleeding risk. Phase 1: parents took responsibility for their prophylactic treatment and performed bleeding management phase 2 and 3 increased self-management causing considerations concerning adherence

The impact of bleeding influenced the balance between feeling safe and doing what they preferred. AYAs mentioned that bleeding with a substantial impact on daily life motivated them to behave more adherently. When this bleeding occurred

Table 3 Quotes explaining adherence to prophylactic treatment in adolescents with hemophilia.

Treatment responsibility			
	Phase 1	Phase 2	Phase 3
Varying treatment responsibilities	· I'm able to perform self-infusion, yet my parents help me most of the time. · My parents take care of any bleeding. · I feel that my parents are still responsible for prophylactic treatment. I rely on my parents.	· I prepare and infuse myself, yet sometimes my parents remind me or prepare the prophylaxis. · I recognize bleeding, yet decision making varies for each bleed. · I am gradually taking over the prophylactic treatment or my parents are gradually transferring the prophylactic treatment to me.	· I prepare and infuse myself; my parents are no longer involved. · I perform bleeding management myself. I ask advice from my parents only in case of an emergency. · I feel fully responsible for prophylactic treatment.
Discussion about adherence with parents	· I prefer that my parents support me in adhering to prophylaxis; we sometimes discuss the necessity for prophylaxis, and mostly I agree with my parents.	· I have regular discussions with my parents about prophylaxis. My parents are too 'careful' with me.	· I have no discussions with my parents because they do not know what I am doing or see it as my responsibility.
Adherence level	**The AYA is fully adherent because of parental supervision.**	**Adherence levels vary among AYAs: AYA could be adherent or non-adherent.**	**Adherence levels vary between AYAs: AYA could be adherent or non-adherent.**
Estimating risks			
Doing what I prefer and feeling safe at the same time	· When no bleeding occurred after skipping, it doesn't motivate me to regularly use prophylaxis. · Before engaging in an activity, I judge its intensity and bleeding risk and decide if I require (extra) prophylaxis for that activity. · If an activity doesn't feel safe, even with (extra) prophylaxis, I skip that specific activity.		
Bleeding	When bleeding limits me in activities, it motivates me to become more adherent.		

after a missed infusion, it was more motivating to take prophylaxis the next time. On the other hand, AYAs who experienced minimal bleeding or minimal bleeding impact were more non-adherent.

DISCUSSION

The present study aimed to explore the underlying reasons for non-adherence to prophylaxis in hemophilia from an AYA perspective. The results revealed that adherence behavior was dependent on the 1) level of treatment responsibility and 2) AYAs risk estimation of prophylaxis per activity. We identified three consecutive phases in growing up with hemophilia that reflected changes in treatment responsibility: the treatment responsibilities increased, parental support decreased and adherence levels decreased. Notably, AYAs were estimated the need for prophylaxis by activity (risk estimation). They explained that this risk estimation was based on their desire to feel safe and do what they prefer.

Various strategies were used to optimize internal validity and minimize bias[24]. Interviewer bias was reduced by using formally trained interviewers specializing in hemophilia that did not have a treatment relationship with the patients. Three interview methods (focus group, individual and respondent validation) were used to establish general knowledge and more in-depth insights as well as to verify themes that emerged. Purposeful sampling[22] was used to improve external validity, while data saturation[25] for the main components was reached during the final two interviews. The distribution between adherence and non-adherence to prophylaxis among AYAs was approximately equal, although the inclusion of more non-adherent AYAs could create a more detailed understanding.

All eligible AYAs were approached, and a total of 47% were willing to participate. We experienced that AYAs (especially non-adherent AYAs) were difficult to recruit due to their busy lives and lack of interest in research. Other qualitative studies reported comparable difficulties in recruiting AYAs[20,26]. This probably resulted in sampling bias. The results of the present study are supported by previous studies in the literature.Namely, our findings concerning treatment responsibility are supported by two studies[27,28] that both described a gradual process of adolescents achieving self-management in three consecutive phases. Both studies mentioned AYAs taking over illness-related activities during adolescence (e.g. remembering

medication, taking medication, conversations with clinicians) and decreased parental support between early, middle and late adolescence[27,28]. In our opinion, this development is in line with the normal psychological development of puberty. This is supported by Casey at al. in their statement that "adolescence is the period in which independence skills are acquired to increase the success of separating from the protective influence of the family[29].

In 2015, a comparable qualitative study in adults with hemophilia was performed[15], which identified four factors influencing adherence to prophylaxis: 1) acceptance of hemophilia, 2) feeling and fearing symptoms, 3) understanding hemophilia and prophylaxis, and 4) planning and infusing skills. The 'feeling and fearing symptoms' in adult corresponds with 'feeling safe', which was identified in the present study. In both adults and AYAs, this factor affects treatment decisions concerning adherence. AYAs did not report difficulties concerning understanding hemophilia and prophylaxis, or any difficulties in planning and infusing. This might be explained by the fact that their parents served a major role in administering the prophylaxis during the first two phases of adolescence and that these two factors are more expected in elderly people.

In the present study, the identified barriers to adherence resonate with findings in AYAs with cystic fibrosis (CF-AYA). Gregory et al.[30] performed a qualitative study exploring barriers to adherence among adolescents with cystic fibrosis. One of the barriers reported was interpreted as CF-AYA wishing to be 'normal' instead of different or disabled. This is comparable to our findings ('to do what I prefer'). The second reported barrier was a lack of perceived consequences, which was explained as not recognizing the impact or not seeing the need for treatment. CF-AYA stated that the therapy "makes no difference", which was congruent with hemophiliac AYAs that experienced minimal or no bleeding.

The present study has implications for clinical practice. Several interventions to improve adherence in AYAs with a chronic disease were studied. Most interventions were focused on reminders[31], interactive smartphone apps[31–33], text messaging[31,32] and motivational interviewing (MI)[34]. Two reviews on implementing reminders or interactive applications showed only short-term effects[34,35]. In the present study, AYAs reported that they learned from bleeding events and did not mention using reminders. Motivational interviewing is a patient-centered communication

technique[34] that has shown promising results in 11 out of 12 studies in AYAs with asthma, diabetes and human immunodeficiency virus (HIV). For example, the adherence levels of AYAs with asthma increased from 32% to 62% after using MI[34,36]. In the present and previous studies, most boys with hemophilia learned through experiential learning instead of individualized education or expert patient programs[37]. AYAs did not consider the route of administration as a reason for non-adherence, our data may be compared with asthma, diabetes and human immunodeficiency virus (HIV). As such, we believe that patient education combined with MI should be applied during a bleeding assessment visit rather than a regular visit since the AYA could is more open to learning. Future research should be focused on individualized patient education per phase (as defined in this study) as well as interventions using MI in AYAs with hemophilia to improve adherence.

CONCLUSION

This study explored the underlying reasons for adherence to prophylaxis in hemophilia from an AYA perspective. The level of treatment responsibility and (short-term) risk estimation per activity influenced adherence positively or negatively.

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Unravelling

CHAPTER 4

Sports participation is not associated with adherence to prophylaxis in Dutch participants with haemophilia

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ABSTRACT

Introduction

The standard treatment for people with severe haemophilia is regular clotting factor replacement therapy to prevent bleeds and joint damage. Though it is demanding, prophylactic treatment is very effective at reducing bleeding risk, enabling people with severe haemophilia to lead an active life, including playing sports. Involvement in sports may be a reason to be more adherent to prophylaxis.

Aim

To assess the association between adherence to prophylaxis and participation in sports among men with haemophilia on prophylaxis.

Methods

A nationwide cross-sectional questionnaire study was performed. Participants (children, adolescents, and adults) with haemophilia using prophylaxis and who completed questionnaires on prophylaxis adherence and sports were selected. Adherence was measured using the 'Validated Hemophilia Regimen Treatment Adherence Scale-Prophylaxis' (VERITAS-Pro, range 0-100, optimum 0). A score >34 points was considered non-adherent. Sports participation was evaluated using the 'Modifiable Activity Questionnaire' (MAQ), and high risk sports were defined as categories 2.5-3 according to the National Hemophilia Foundation (NHF)[83]. VERITAS-Pro scores were compared by sports participation using the Mann-Whitney U test.

Results

In total, 266 participants (median age 34 years, P25-P75= 15-53) were included in the study. Overall, adherence to the prescribed prophylaxis was high (89% adherent), especially among children <12 years (100%). Most participants were involved in sports (71%), but children (<12 years) played significantly more sports (93% vs. 55%) and more high-risk sports than adults (67% vs. 27%). VERITAS-Pro scores were similar between those who did and did not play (high-risk) sports.

Conclusion

Most participants were active in sports, and young children were especially involved in high-risk sports. Contrary to our expectation, prophylaxis adherence was not associated with sports participation.

INTRODUCTION

People with severe haemophilia (PWH) lack clotting factor VIII or IX activity (<1 IU/dl) and are at risk for spontaneous bleeds in joints, soft tissue, and muscles[2]. In The Netherlands, standard treatment for haemophilia is regular replacement therapy to prevent bleeding (i.e. prophylaxis), with the aim of preventing joint damage due to repeated bleeding[2]. This replacement therapy consists of intravenously self-administered clotting factor concentrate 2-3 times/week, usually initiated before the age of three[2,3]. For young children, parents generally perform these injections. Around the age of 12 years, children are taught self-infusion and gradually take on more responsibility for their prophylaxis[4]. While effective, this treatment, which involves frequent infusions for life, is very demanding. Maintaining minimum levels of clotting factor activity requires continuous adherence to prophylaxis[2].

With early prophylaxis, participants are able to lead an active life, including participation in (high-risk) sports. Today, regular sports participation among young Dutch people with haemophilia (PWH) is high and comparable to that of the general population (77% vs. 74%)[5]. Non-adherence to prophylaxis is associated with increased bleeding, increased absence from school and work, and reduced quality of life[6]. A person is considered non-adherent to prophylaxis if they regularly deviate from the prescribed dose, take prophylaxis in the evenings, or skip infusions[7]. Depending on age, non-adherence among PWH is estimated around 57%[8].

Over the past decades, recommendations regarding participation in sports among people with haemophilia have changed. Before the introduction of prophylactic treatment, PWH were advised to refrain from participating in sports[9]. Later, it was recommended that PWH participate in low-risk sports like hiking, golf, rowing[1,9]. Nowadays, young children with haemophilia are participating in high-risk sports like soccer and hockey[10]. Safe and healthy participation in sports among people with haemophilia is conditional on high adherence to prophylaxis to reduce the risk of bleeds and injuries.

An active, sportive lifestyle is a deliberate choice people make. Keeping in mind the inherent risks of injury and bleeding with sports, hypothesized that PWH who are active in sports are more adherent to prophylaxis than PWH who are not active in

sports, in order to prevent sports-induced bleeding. The aim of the present study was to assess the association between adherence to prophylaxis and participation in sports among people with haemophilia on prophylaxis.

METHODS

A nationwide cross-sectional questionnaire study was performed as part of the Haemophilia in The Netherlands 6 (HIN-6) study, a recurring study that is conducted every 6 to 9 years. The current questionnaire was administered in 2019[11]. The HIN study includes patient characteristics, treatment history, and numerous patient reported outcome measures. Medical ethical approval for the study was obtained from the Medical Ethical Committee Leiden (NL59114.058.17).

Population

All people with haemophilia registered at any haemophilia treatment centre in The Netherlands were invited to participate in HIN-6. Our study included people who used prophylaxis and had completed both the adherence and sports activity questionnaires.

Data collection

The data was collected completely anonymously. Participants completed online questionnaires stored in Castor EDC (Castor, Amsterdam, Netherlands). For the present study, patient characteristics and data from two questionnaires about prophylaxis adherence[12] and participation in sports[13] were extracted. Demographic characteristics included diagnosis details, age, body mass index (BMI), treatment details, and history of infections.

Prophylaxis adherence (VERITAS-Pro)

Prophylaxis adherence was evaluated using the Dutch version of the 'Validated Hemophilia Regimen Treatment Adherence Scale-Prophylaxis' (VERITAS-Pro)[12,14]. This instrument consists of a total score and six domain scores: Time, Dose, Plan, Remember, Skip, and Communicate. VERITAS-Pro scores were normalized into scores ranging from 0 to 100, with a high score indicating low adherence. The research team considered a 5-point increase in total VERITAS-Pro score was considered to be of clinical relevance. In addition, participants were compared

according to adherence level according to proposed cut-off scores (34 points) indicating non-adherence[12].

Sports participation (MAQ and HEP-Test-Q)

Sports and physical activity were evaluated using the Dutch 'Modifiable Activity Questionnaire' (MAQ) and 'Haemophilia & Exercise Project-Test-Questionnaire' (HEP-Test-Q)[15,16]. The MAQ assesses sports type, frequency of sports participation per month, and average duration of sports sessions (hours), resulting in an average of the total hours of activity per week over the past year (TOT-H week). The HEP-Test-Q assesses physical state, mobility, strength and coordination, endurance, and body perception. Participants who completed the HEP-Test-Q but skipped the MAQ questionnaire were classified as not playing sports[16]. Sports injury risk was identified using classifications from the National Hemophilia Foundation (NHF), based on joint impact and risk of falls and collisions[1]. Sports in the two highest risk categories – 2.5 (e.g., soccer) and 3 (e.g., field hockey) – were considered high-risk (HR) sports. Sports were categorized according to joint impact and risk of falls and collisions.

Analyses

Analyses were stratified into three age groups: children (0-11 years), adolescents and young adults (AYA; 12-30 years) and adults (>30 years). For children <12 years, parents completed the questionnaires. The age cut-off between AYAs and adults was based on the average age at which Dutch men have their first child, which impacts work-life balance[17]. VERITAS-Pro and MAQ results are presented as medians with 25th to 75th percentiles (i.e., interquartile range, IQR) or as proportions where appropriate and were analysed using descriptive statistics. Group differences were analysed using the Mann-Whitney U test because data were not normally distributed. Some participants skipped the MAQ questionnaire but completed the previous (VERITAS-Pro) and the next questionnaire (HEP-Test-Q)). To avoid selection bias, the HEP-Test-Q was used for patient selection only; data from this questionnaire were not analysed as HEP-Test-Q does not assess actual sports participation. P-values <0.05 were considered statistically significant. All statistical analyses was performed with SPSS statistical software, version 25 (IBM, Armonk, NY)

RESULTS

A total of 266 participants with haemophilia A or B who used prophylaxis were included in the analyses. This included N=221 participants who completed both MAQ and N=45 participants (all adults) who skipped the MAQ but completed the HEP-Test-Q and were categorized as not playing sports.

Participant characteristics

Table 1 summarizes the characteristics of the study participants. Median age was 34 years (IQR= 15-53), and most participants were diagnosed with haemophilia A (87%) and had severe haemophilia (91%). The median age was 51 in the adult subgroup, 20 in the adolescent subgroup, and 7 in the child subgroup.

Adherence

The median VERITAS-Pro total score of the total group was 18 (IQR= 10-25). All groups showed high treatment adherence, but median adherence was highest among young children (median 10, IQR= 9-14) compared to AYAs (21, IQR= 19-31) and adults (20, IQR= 11-26) ($p<0.01$). In adults, the three VERITAS-Pro domains with the highest percentage of non-adherence were Communicate (45%), Plan (34%), and Dose (27%). In AYAs, the top two domains remained the same, with Remember (25%) third. Non-adherence was rare in children.

Adherence and sports

A total of N=188 participants (71%) played regular sports, among whom 88 (40%) played high-risk sports. The five most popular sports overall among study participants were recreational cycling (28%), fitness (25%), walking (16%), soccer (14%), and recreational swimming (13%). Sports participation was associated with age: Children (93%) and AYAs (95%) were more involved in sports than adults (55%; $p<0.01$). Participation in HR sports decreased with age, falling from 67% in children to 35% in AYAs ($p<0.01$) and 27% in adults ($p<0.04$). Figure 1 illustrates participation in the five most popular sports according to age group.

Table 1 Participants, disease and treatment characteristics, adherence outcomes and sport

	All N= 266	Children (0-11year) N= 44	AYA (12-29year) N= 56	Adults (30+year) N= 167	p
	Median (IQR) or N(%)				
Age (years)	34 (15-53)	7 (5-10)	20 (15-23)	51 (41-61)	
Weight (kg)	70 (54-86)	28 (21-34)	70 (63-82)	85 (73-93)	
BMI	23 (19-26)	16 (15-17)	22 (20-24)	26 (23-28)	
Haemophilia A	194 (87)	39 (87)	49 (88)	106 (88)	
Severe	203 (91)	39 (87)	53 (95)	111 (92)	
Dose (IU/kg)	17 (12-26)	33 (22-44)	18 (13-22)	19 (12-24)	
Infusion frequency	3 (2-3)	3 (2-3)	3 (2-3)	3 (2-4)	
	Patient Reported Outcome Measures				p
	Median (IQR) or N(%)				
VERITAS-Pro total score[1]	17 (10-26)	10 (9-14)*	21 (19-31)	20 (11-26)	0.00
Participation in sports (N,%)	188 (71)	42 (93) †	54 (95) †	92 (55)	0.00
Participation in high-risk sports (N,%)*	88 (40)	30 (67) ‡	25 (45)	33 (27)	0.04
Sports (hrs/wk)	3.3 (1.6-5.9)	2.8 (0.9-5.5)	5.2 (2.4-7.1)	2.7 (1.4-5.6)	0.09
HR sports (hrs/wk)	2.6 (1.0-4.2)	2.3 (0.8-3.3)	3.8 (0.3-5.8)	2.1 (1.2-5.7)	0.33

Type of haemophilia, severity, dose, and infusion frequency were similar across all age groups. [1] A difference of 5 points was considered clinically relevant.
* Children reported better adherence than AYA and adults. † Sports participation was similar in children and AYA and higher than in adults (p=0.00).
‡ Children were more involved in HR sports than AYAs and adults.

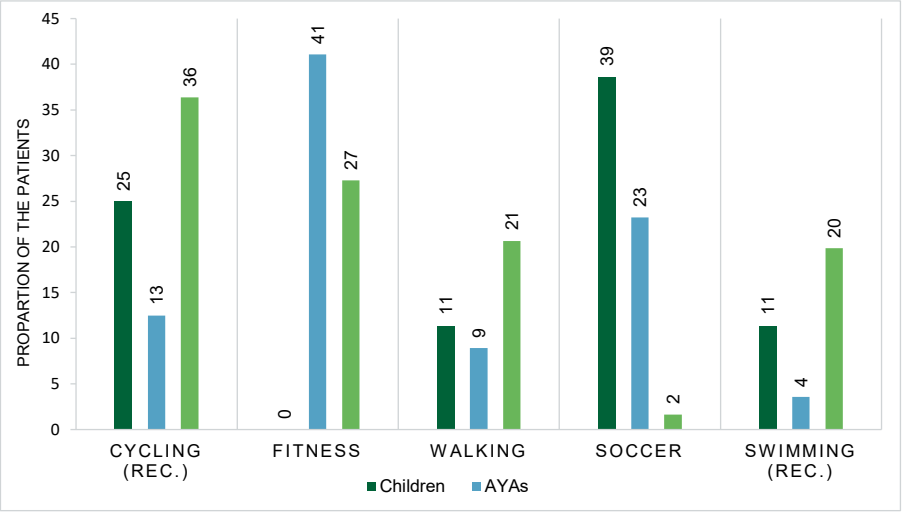

Figure 1 Participation in the five most popular sports among the total population according to age

Median prophylaxis adherence was similar between those who did and did not participate in sports in general (20, IQR= 11-28 vs. 17, IQR= 13-25; p=0.50) or in HR sports in particular (21, IQR= 12-28 vs. 20, IQR= 11-28; p=0.76). Adherence was also not associated with sports participation across the different age categories. Appendix 1 shows that adherence was independent of sports participation (children: p=0.16; AYA: p=0.96; adults: p=0.59) and HR sports participation (children: p=0.31; AYA: p=0.73; adults: p=0.50). figure 2 shows the median VERITAS-Pro domains subdivided for participating vs. not participating in high-risk sports. Finally, adherence was not associated with the weekly duration of sports participation (hours/week) in any age group (children: p=0,17; AYA: p=0,77; adults: p=0,41).

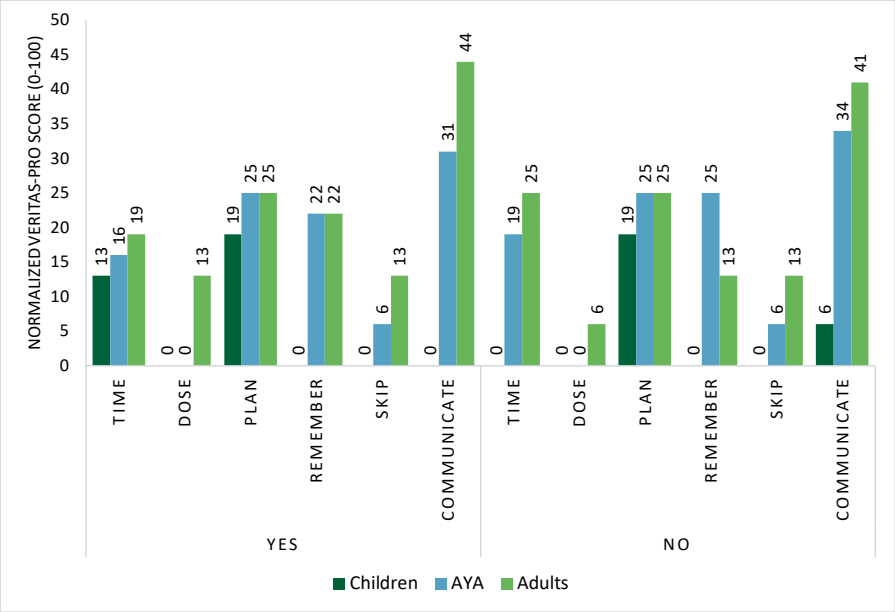

Figure 2 Median participation in high-risk sports according to age group

DISCUSSION

This study aimed to assess the association between adherence to prophylaxis and participation in sports among people with haemophilia on prophylaxis. Dutch men reported a high rate of adherence to prophylaxis, and more than 71% were active in sports. Children were especially engaged in high-risk sports. We did not detect an association between adherence to prophylaxis and participation in sports.

This study has both strengths and limitations. This study was a nationwide study, inviting all participants with haemophilia in The Netherlands. National commitment and collaboration resulted in a large and representative sample[18]. However, despite these efforts, patients with severe haemophilia were relatively underrepresented in the study population (34%) compared to the overall haemophilia population (±50%)[2,19]. Therefore there is a risk of selection bias[18], and the present sample potentially represents a selection of more adherent patients. However, it is unlikely that (non-)response was associated with sports participation. In addition, study participants may have overestimated both their prophylaxis adherence and their sports participation, potentially making it more difficult to detect an association.

A previous qualitative study reported that underlying reasons for non-adherence in AYAs (14-25 years) was based on a risk estimation per activity[20]. Based on this, it was expected that people participating in sports would be more motivated to be adherent to the prescribed prophylaxis treatment. Contrary to our expectations, this study demonstrates that treatment adherence is not associated with sports participation. The overall adherence rate in this study was relatively high (median 17, IQR= 10-26) but comparable with other studies that evaluated adherence using VERITAS-Pro. A previous Dutch paper (N= 41) reported a mean normalized VERITAS-Pro score of 21 in adolescents with haemophilia[14]. Miesbach et al.[22] (N= 397) reported normalized VERITAS-Pro score of 6 in young children (0-14 years), with a progressive decrease to 13 in adolescents (15-19 years) and further to 17 in adults (20-59 years)[22]. Participation in sports in the present study (71%) was comparable to that of the general Dutch population (53% ≥12 years)[21]. In the general male Dutch population, the five most popular sports are fitness (22%), football (14%), running (12%), tennis (6%) and swimming (4%)[21]. To our knowledge, only one other study has addressed the association between sports participation and treatment adherence. Zanon et al.[23] performed a prospective multicentre study including 42 patients with severe haemophilia A all participating in sports at baseline[23]. The majority (80%) showed adherent behaviour, which is comparable to this study. Adherence was evaluated using empty vials of clotting factor concentrate, while physical activity was assessed using the EPIC-Norfolk questionnaire. Given the different method of evaluating adherence and the fact that only patients participating in sports were included in this study, it is difficult to further compare these results with our own.

Although prophylaxis is very effective, non-adherence does not immediately result in increased risk of bleeding: Some people with severe haemophilia report low bleeding rates in the absence of prophylaxis, but they do show accelerated progression of arthropathy[24]. It can be challenging for clinicians to motivate

participant to develop and sustain strong adherence to prophylaxis if patients do not experience limitations as a result of non-adherence and remain able to participate in preferred activities[20]. This study anticipated that participants who wish to compete in HR sports would be more adherent to treatment in order to compensate for the inherent injury and bleeding risks of playing HR sports. However, this reasoning may be too simple; it is becoming increasingly clear that a patients' decision-making regarding haemophilia self-management is a complex and multifactorial process. Motivational interviewing to assess a patients' unique wishes and opinions may assist in promoting adherence behaviour. At the time of experiencing a bleed, a person with haemophilia is limited in their daily life, including and sports. This may be the best time for physicians to discuss the benefits of continuous regular prophylaxis. Frequent contact among participants and clinicians is needed to apply this intervention at the right time. In conclusion, our study suggests that being active in sports, even high-risk sports, does not necessarily promote adherence in this population of men with haemophilia and good overall adherence.

CONCLUSION

This study represents the first exploration of a potential association between participation in sports and adherence to prophylaxis in men with haemophilia. The overall adherence measured using the VERITAS-Pro rate was high – a mean score 18 with only 11% non-adherence. The majority (71%) of study Dutch participants were active in sports, ranging from 93% in children to 55% in adults. Young children especially participated in high-risk sports (67%). Contrary to our expectations, adherence was not associated with sports participation in Dutch PWH.

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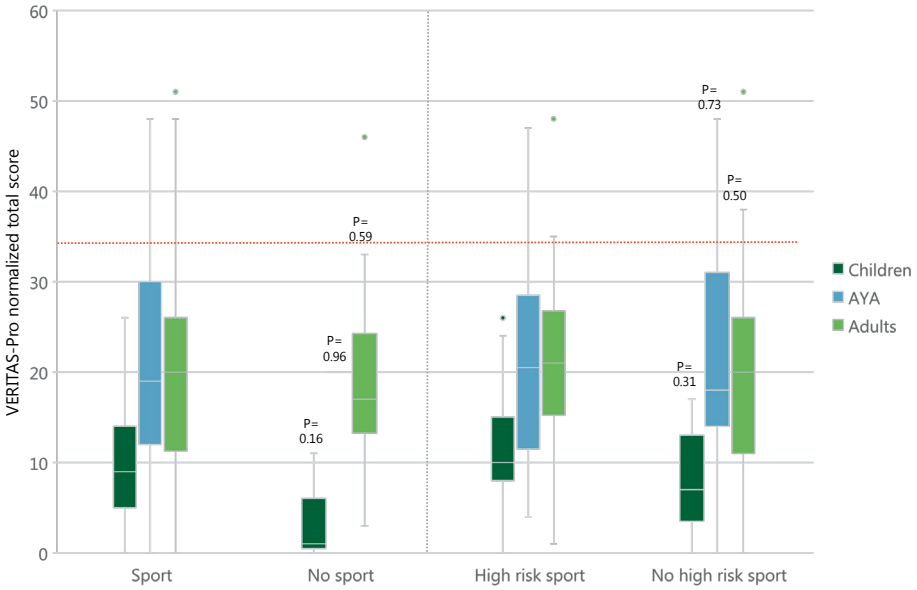
APPENDIX



Appendix 1 Treatment adherence for HR sports participation per age group *Above horizontal dotted line indicates non-adherence, P-values indicate a statistically significant difference between 'sport vs. no sport' and 'HR sport vs. no HR sport'

Flourishing

CHAPTER 5

A feasibility study on two tailored interventions to improve adherence in adults with haemophilia

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ABSTRACT

Introduction

Haemophilia is a congenital bleeding disorder mainly affecting males. To prevent bleeding, patients must perform regular intravenous injections (prophylaxis) throughout their entire lifetimes, and non-adherence is common. Problems with acceptance or self-management appear to be the main reasons for non-adherence in haemophilia. The aim of this study was to test the feasibility and effects of two interventions: a face-to-face intervention for acceptance (face-to-face) and an online intervention for self-management (online).

Methods

Patients with severe haemophilia and acceptance or self-management problems were eligible for the study. The face-to-face group intervention (ACT; 8 sessions/6 months, target N= 8) was based on Acceptance and Commitment Therapy. The online intervention (5–8 modules/2 months, target N= 8) was based on a successful online self-management program for rheumatoid arthritis. Both interventions were designed according to the Medical Research Council (MRC) framework, in collaboration with the patient society and experts. We measured adherence [Validated Haemophilia Regimen Treatment Adherence Scale–Prophylaxis (VERITAS-Pro), optimal score of 0], quality of life [36-Item Short-Form Health Survey (SF-36), optimal score of 100], and illness perception [Brief Illness Perception Questionnaire (BIPQ), optimal score of 0] before intervention start (T0) and after two months (T2). Feasibility criteria included: completion of training by > 50% of participants and the ability to collect at least 80% of outcome parameters.

Results

The face-to-face intervention was feasible (89% enrolment and recruitment, 100% retention), and 100% of the outcome parameters were collected. The results were promising. Adherence (VERITAS-Pro) remained stable (from median 64 to 62 points), but quality of life (SF-36) showed clinically relevant improvement (>5 points) in five of eight domains. Illness perception (BIPQ) showed a clinically relevant increase from 47 to 39 points. The patient evaluation was positive. However, the online intervention was infeasible, with only 20% (6/30) enrolment and only three patients signed informed consent (recruitment 10%). No patients completed

more than one module (retention 0%). Consequently, the online intervention was terminated.

Conclusion

The face-to-face acceptance intervention was considered feasible, with promising results. In contrast, the online intervention was infeasible and terminated. These findings suggested that the adaptation of effective interventions to other settings does not guarantee success, despite the use of an established methodology and patient participation. Population differences (only male participants, congenital disease) could explain the online intervention failure in haemophilia, despite success in rheumatoid arthritis.

BACKGROUND

The introduction of intravenous clotting factor replacement therapy has enabled the replacement of the missing clotting factors associated with haemophilia[1], which can be administered to treat bleeds (on-demand) or as regular replacement therapy (prophylaxis) to prevent bleeds[2]. Intravenous prophylactic treatments are self-administered by the patient, at home, approximately 3–3.5 times each week[1]. For the effective prevention of bleeding, a high level of adherence to prophylactic treatment is crucial. To maintain minimum clotting factor levels and preserve joint health, prophylaxis should be continued life-long, without interruption[1].

Non-adherence to prophylaxis (i.e. ≥25% missed infusions, ≥25% dose change, and/or 30% deviation in timing[3]) has been reported for approximately 50% of Dutch adults with severe haemophilia[4–7]. Non-adherence and the inadequate treatment of bleeds can cause irreversible damage, especially in the joints or the central nervous system[8]. Patients who stopped or interrupted treatment were found to have significantly worse joint status than patients who did not stop treatment [Hemophilia Joint Health Score (HJHS): 23 vs 14 points $p \leq 0.01$ and Pettersson score: 16 vs 5 points $p =\leq 0.01$][9]. This joint damage eventually results in a lower quality of life and reduced labour force participation[10,11], which stresses the importance of high adherence levels.

In a previous qualitative study, illness acceptance problems and the lack of self-management skills were identified as important reasons for non-adherence[12]. Patients with acceptance problems typically either stopped using prophylaxis or used prophylaxis only intermittently (e.g. only on demand or skipping doses). In cases of self-management problems, patients failed to administer prophylaxis due to inadequate routines, forgetfulness, and the complexity of the necessary self-management skills[12]. Our hypothesis was that both groups of patients would benefit from tailored interventions designed to improve adherence.

Therefore, two tailored interventions were developed. The first intervention was focussed on the improvement of illness acceptance, using a haemophilia-adapted version of Acceptance and Commitment Therapy (ACT). The second intervention was focused on the improvement of self-management through an online program that included peer-support. The aim of this study was to test the feasibility and

effectiveness of both interventions, 1) the acceptance program (Face-to-face) and 2) the self-management program (Online) in patients with severe haemophilia using prophylaxis.

METHODS

The study design for this feasibility study[13] is shown in figure 1. Patients who experienced difficulties with haemophilia acceptance were identified by the haemophilia treatment team and were invited to participate in the face-to-face group training, 'Living with haemophilia'. This group training program included seven training sessions and one follow-up session, which was guided by a trained haemophilia caregiver (social worker and nurse). Patients who experienced difficulties with self-management skills were invited to participate in an individual online training programme: 'Challenging your haemophilia'. This online programme included 5-8 modules, guided by a trained peer. We used the CONSORT 2010 guidelines for the transparent reporting of studies[14]. Trial registration NL55883.041.16

Face-to-face group training, focused on acceptance: 'Living with haemophilia'

The face-to-face group training, 'Living with haemophilia', was focused on improving illness acceptance, which could lead to increased adherence to prophylaxis.

This face-to-face group training was based on the ACT approach[15], which is an evidence-based intervention that uses cognitive behavioural strategies and mindfulness to create distance from negative thoughts, words, emotions, or physical sensations, based on relational frame theory[15,16]. This group training programme addressed topics like creating awareness of thoughts, discussing self-realisation, and exploring personal values in life (Table 1). Group dynamics and peer contact are important aspects of group training (17). ACT-based interventions have been successfully implemented in patients with chronic diseases, including diabetes, human immunodeficiency virus (HIV), and chronic pain[16–19]. The original ACT training protocol was adapted and modified for the haemophilia population in collaboration with the Department of Psychology (University Utrecht) and the support of The Netherlands Haemophilia Patient Society. Based on ACT principles and previous studies, the group training consisted of seven evening sessions, lasting two hours per session, and one follow-up session, performed after six

months[20,21]. The training was fully scripted in a handbook, including the use of specific exercises and metaphors. All sessions were supervised by two ACT-qualified haemophilia healthcare professionals. For logistical reasons, dinner was provided at the start of each session.

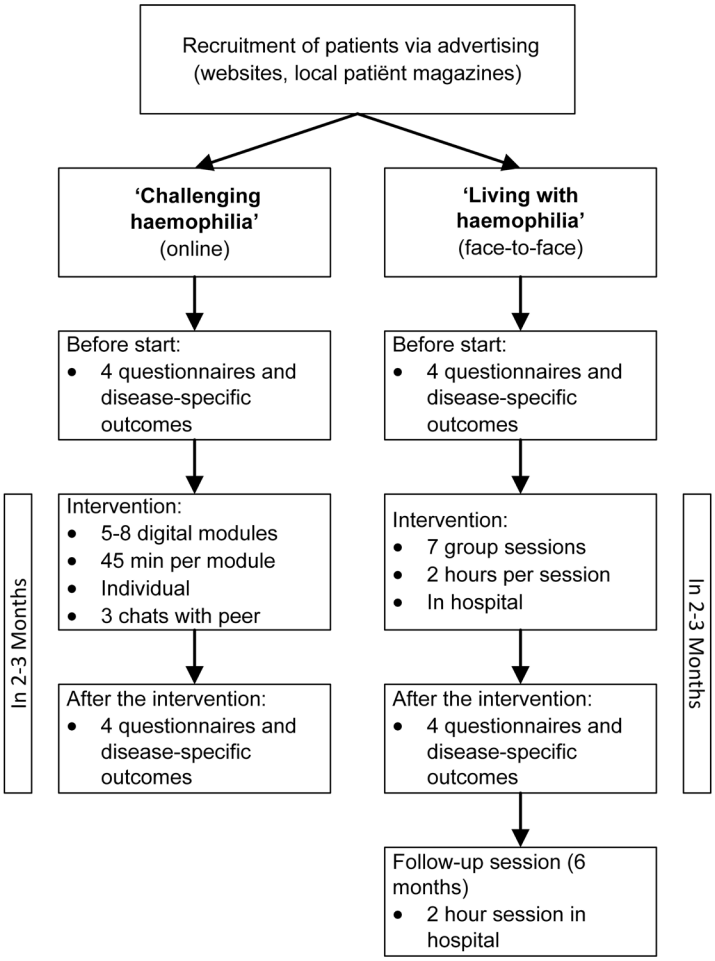

Figure 1 Study designs for both interventions

Online training focussed on self-management: 'Challenging your haemophilia'

The online training programme, 'Challenging your haemophilia', was aimed at improving self-management, which could lead to a higher adherence to prophylaxis. This online training programme was based on a comparable and successful online training programme that was developed to improve self-management in rheumatic arthritis[22] the Arthritis Self-Management intervention (ASMP), at Stanford University[23]. This training programme included 5 mandatory and 3 optional modules that were available on a secure website. These modules included exercises, short videos, written information, and the opportunity to chat with trained peer patients (N= 5 peer-trainers). The peer-trainers received formal peer-patient training from an external specialised agency. Each module took approximately 45 minutes, and training had to be completed within 2 months. Details regarding the modules are shown in box 1. These modules were adapted for haemophilia from the rheumatic arthritis format, following the six steps of the Medical Research Council (MRC) framework[24]. First, the evidence base was identified by performing a review of the literature[25]. Then, a problem analysis was performed (theory development)[4], and a modelling process was developed based on existing material[22].

Subsequently, a prototype of the online programme was developed, in collaboration with patients and a delegation of the patient organisation (three panel sessions). The prototype was then evaluated for look and feel during a patient panel meeting, followed by field usability testing [24].

Participants

For both interventions, male adults who were diagnosed with haemophilia and were prescribed prophylactic treatments were eligible for inclusion. The ability to understand both the written and spoken Dutch language was a prerequisite. Patients who were diagnosed with any serious psychiatric disorder that might interfere with training were not eligible. For the online training programme, access to the internet was a prerequisite. To allow the researchers to follow the conversations on the online platform and to perform oral evaluations of each participant, the maximum number of participants in each group was set at eight. At the beginning of each week, all patients who visited the clinic were discussed (multidisciplinary), and eligibility was considered. Patients who were eligible for

study inclusion were informed about this study (and both interventions) by their health care provider or through various digital platforms (different websites, newsletters of the patient society, social media). Patients received information about both interventions and were allowed to choose between both training programmes based on their personal preferences and their opinions regarding their reasons for non-adherence and whether they struggled with haemophilia acceptance or with self-management. Informed consent was obtained from each participant prior to the start of the study.

Data collection

For both interventions, data were collected before the start and directly after the intervention. The primary outcome for both interventions was adherence, whereas the secondary outcome was quality of life. Additionally, each intervention included an intervention-specific outcome measurement. Participants in the face-to-face intervention completed an illness perception questionnaire, whereas those in the online intervention completed a health education impact questionnaire.

Adherence was measured by the assessment of three domains (Dose changes, Time, Skip changes), based on a pre-specified definition of adherence[3] and the Validated Hemophilia Regimen Treatment Adherence Scale –Prophylaxis[26] (VERITAS-Pro) questionnaire, for which scores ranged from 100 to 0, with an optimal score of 0. Quality of life was measured using the Short Form-36 health survey questionnaire (SF-36), for which scores range from 0 to 100, with an optimal score of 100[27]. Intervention-specific secondary outcomes included illness-acceptance (face-to-face) and self-management (online).

Acceptance was assessed by the Brief Illness Perception Questionnaire (BIPQ), with scores ranging from 80 to 0, for which an optimal score was 0[28], whereas self-management was evaluated by the health education impact questionnaire (HEIQ), which featured scores ranging from 0 to 5, with an optimal score of 5[29]. In the study protocol, the minimally important difference (MID) level for each outcome was pre-defined. For the SF-36 the MID was established as a 5-point increase[30]. The study team decided to apply the same MID to all other questionnaires. All questionnaire details, including all examined domains, score ranges, and MID values, are provided in table 2, in the appendix. In addition, patient demographic variables (age, haemophilia severity, prescribed treatment, and employment) were collected

from the patients' medical records before the start of the intervention. During the final session (session 8) of the face-to-face group training programme, patient evaluations were performed using a short focus-group interview (10 minutes). The online training programme was evaluated using audio-taped individual phone interviews (10 minutes).

Data analyses

We considered an intervention to be feasible if more than 50% of the patients completed the training program, and if more than 80% of the data required to perform outcome parameters could be adequately collected. If these requirements were not met, the team considered the early determination of adaptation. Additionally, based on the definitions proposed by Craig et al.[14] feasibility was expressed as a comparison between the number of patients on prophylaxis who were identified as having difficulties with acceptance or self-management (eligible) and the number of patients who were willing to participate and signed informed consent (enrolment and recruitment), the number of patients that followed and completed the training (retention), and the time spent on the training in practice[24]. Patient characteristics were analysed using descriptive statistics. The collected data were analysed using descriptive statistics and, if possible, a Wilcoxon signed-rank test (SPSS version 21). Patient evaluations were transcribed, summarised, and thematically analysed. The themes were discussed by the research team.

RESULTS

This study was performed at the Van Creveldkliniek of the University Medical Center, Utrecht, The Netherlands. This clinic was established in 1964 and provides multidisciplinary treatment, including the designation of specialised physicians, nurses, physiotherapists, and a social worker. The Van Creveldkliniek treats 250 adults with severe haemophilia, including approximately 50% with adherence problems, resulting in approximately 125 eligible patients overall. For this feasibility study, our aim was to include N= 8 patients in each intervention.

Table 1 Overview of both training programmes

	Session/module:	Aim of the session:
'Living with haemophilia' (face-to-face)	1. Control	Creating the realisation that each patient controls their own thoughts, feelings, and physical sensations. Discussing whether this method of handling thoughts, feelings, and physical sensations is effective.
	2. Acceptance	Creating a space for tiresome thoughts, feelings, and physical sensations. Acceptance is part of tolerating challenging experiences patients can't get rid of.
	3. Letting go of thoughts	Creating the realisation how thoughts and how thoughts develop. Discussing whether thoughts always are effective and, if not, how to transform them to become effective.
	4. Self	Distancing ourselves from strict or rigid beliefs. Discussing individual identity. Discussing whether one's vision of oneself is real or based on thoughts, feelings, and physical sensations. Discuss who someone want to be.
	5. Values	Creating the realisation of what a patient must do, can do, and wants to do. Discussing which values are important to each patient and what he really wants in life.
	6. Handling	Discussing barriers, motivators, and strategies for achieving each patient's goals. Creating the realisation of each individual's sense of short- and long-time rewards. Developing concrete plans.
	7. Looking back and forward	Summarising the six concepts (control, acceptance, letting go of thoughts, self, values, and handling) and discussing the used metaphors and exercises.
	8. Follow-up session	Discussing progress and providing additional advice.

Table 1 Continued

'Challenging your haemophilia' (online)	1. Willing	Determining which values are important, learning about self-management, and setting personal goals.
	2. Knowledge	Defining haemophilia, exploring the advantage and disadvantages of haemophilia, and examining how to integrate prophylaxis regimens into daily life.
	3. Being able	Reviewing infusion tips, taking and maintaining control, making responsible choices, tackling problems, communicating, and giving and receiving feedback.
	4. Living together	Discussing haemophilia with others and examining how haemophilia impacts relationships and sexuality and the impacts of haemophilia on children.
	5. Exercise and sport	Examining how haemophilia affects goals and exertion levels during exercise, making active choices about exercise, exploring current exercise habits, and discussing the impacts of exercise on daily life and the importance of rest.
	6. Work	Examining the effects of haemophilia on work, including potential obstacles and how to tackle them.
	7. Looking ahead	Evaluating and setting personal goals.

Face-to-face group training focused on acceptance: 'Living with haemophilia'

Recruitment

Appendix 1 shows the CONSORT flow diagram, and the left side concerns the face-to-face group training. Over a period of two months, nine patients were informed of and invited to participate in the group training, and all nine patients were enthusiastic about participating in the group training. All patients were screened before the start of the intervention. One patient was excluded because he was receiving individual psychological treatment. All included patients (N= 8) completed all seven training sessions. Consequently, enrolment and recruitment was 88% (8/9), and retention was 100% (8/8).

Feasibility

On two occasions, a participant was unable to attend a session due to work or illness. In these cases, the continuity of the training was maintained by consulting with the participant individually before the start of the next session. The eventual participation retention for this intervention was 100%. All participants joined the free dinner at the start of each session. The trainers evaluated the training as being practical and achievable, and all necessary outcome parameters were collected. The trainers spent approximately 15-30 minutes to prepare before each session, which was considered achievable in a daily healthcare setting.

Participant characteristics

All patient and treatment characteristics are shown in table 2. All participants had severe haemophilia A, with a median age of 38 years (range= 27–51 years). The median prescribed frequency of intravenous clotting factor use was 3.2 infusions each week (range 0–7). One patient refused to take prophylactic treatment (although it was indicated), resulting in an infusion frequency of 0.

Baseline and follow-up assessments

The baseline and follow-up assessments are shown in appendix 2. After seven training sessions, adherence was measured with the VERITAS-Pro, which showed a minimal improvement to 62 points compared with the baseline score of 64 points (p=0.92). The quality of life (SF-36) measurement showed clinically relevant improvements for five of the nine domains. The tree mental domains showed large improvements: Role-emotional (83 points), role-physical (63 points), and social

functioning (13 points). Improvements were associated with emotional problems, social functioning related to work, and daily activities and social relations.

Surprisingly, the domains that are thought to be associated with 'physical' health, including general health (10 points) and pain (5.5 points), also showed improvement. Furthermore, illness perception (BIPQ) improved from a baseline score of 47 points to 39 points (p=0.46) indicating a clinically relevant improvement in illness acceptance, although this was not a significant change in this small sample.

Patient evaluation

All participants (N= 8) described that they were very satisfied and valued the training highly. All participants considered all sessions to have been valuable, and some indicated that they would have preferred additional sessions. Participants felt more accepting of haemophilia and felt less frustration regarding haemophilia-related limitations. They recognised themselves in the stories of the other participants. After the training, most participants reported experiencing more joy in daily life activities and felt more comfortable asking for help. They also mentioned that their partners experienced positive changes.

Online training focused on self-management: 'Challenging your haemophilia'

Recruitment

Appendix 1 shows the CONSORT flow diagram, for which the right side concerns the online training. Thirty patients were invited to participate in the training. Sixteen patients asked for more information about the training. Six were enthusiastic and willing to participate (enrolment 6/30). Only three patients returned the signed informed consent (including the baseline questionnaire; recruitment 3/30). None of the participants completed the online training (retention 0/3).

Feasibility

Eventually, two participants started the training. The third participant never started after signing informed consent and completing the questionnaires and provided no explanation for this lack of participation. The two participants who started the training only completed the first module and quit because of personal life-changing issues, instead of a lack of interest.

Table 2 Participant characteristics

	Adherence program (N= 8)		Self-management program (N= 3)	
	Number (%) or median (range)			
Participant characteristics				
Severe haemophilia A	8	(100%)	3	(100%)
Age (years)	38.8	(27–51)	24	(20-32)
Prescribed frequency of prophylaxis infusions per week	3.2	(0–7)	3	(2–3)
Employment - Full time paid	6	(75%)	1	(33%)
Adherence (VERITAS-Pro, 100–0, optimal score of 0)				
Adherence	64		56	
Quality of life (SF-36, 0–100, optimal score of 100)				
Physical function	60		95	
Role-Physical	13		100	
Bodily Pain	57		62	
General Health	57		82	
Vitality	63		65	
Social Functioning	63		75	
Role-Emotional	17		100	

Therefore, the retention rate for this intervention was 0%. Because of the early termination of participants, follow-up data collection was 50%. The study team evaluated the training as not feasible, and the training was discontinued.

Patient characteristics

These three participants (N= 3) had severe haemophilia A, with a median age of 24 years. Table 2 shows patient characteristics and baseline assessments.

Baseline assessments

Participants only completed the baseline questionnaire. One completed only 10/40 questions of the HEIQ. Before the start of the intervention, the adherence (normalised VERITAS-Pro score) median score was 56 points, indicating moderate

adherence. The quality of life (SF-36) domain scores varied between 62 and 100 points, indicating average quality of life. Self-management (HEIQ) varied between 3.0 and 3.8, indicating moderate self-management. No follow-up data are available because of early discontinuation.

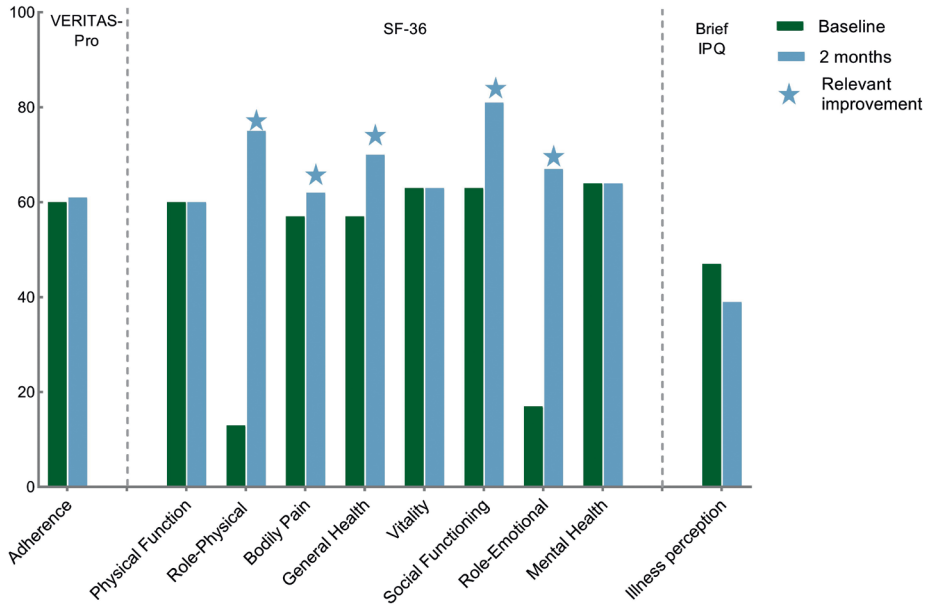

Figure 2 Baseline and follow-up assessments for the VERITAS-Pro, SF-36, and brief IPQ

Patient and peer-trainer evaluation

The two participants were willing to evaluate the training. Both were positive about the modules they completed. In their opinion, the format was easy to use, had a nice layout and design, and included relevant information. Both were surprised about the lack of interest expressed by other potential participants and the fact that the training was discontinued. One suggested the use of this training for a younger population due to the scholastic format. The peer-trainers (N= 3) were also contacted to evaluate the training. In retrospect, they suggested that the format was likely too scholastic for adult participants. All peer trainers wondered whether the participants would prefer face-to-face peer contact rather than online training. One trainer suggested that participants with haemophilia may not be aware of their own knowledge gaps because they have been living with this disease their entire life. All trainers were disappointed, yet understood the reasons for early intervention termination.

DISCUSSION

This study aimed to test the feasibility and primary effects of two interventions designed to improve adherence to prophylactic replacement therapy in haemophilia. The interventions consisted of either 1) a face-to-face group training focused on acceptance or 2) an online programme focused on self-management. The face-to-face training was evaluated as being feasible, and the preliminary results were promising, with improvements in adherence, quality of life, and illness perception. Both participants and the trainers evaluated the training positively. The online training programme was evaluated as not being feasible because of difficulties with enrolment, recruitment, and retention. One possible explanation for these difficulties could be a lack of perceived need to improve self-management among individuals with haemophilia or disease-specific aspects. This result was unexpected, as a similar online intervention was very successful for rheumatic arthritis.

Both interventions were based on systematic and extensive research, based on the van Meijel model[31] and the MRC framework[24], and required extensive patient participation. This project began with a literature review[25], followed by a problem analysis[4], and a need analysis[12]. Consequently, both interventions were designed according to evidence-based interventions with established effectiveness[16,23,32–34]. The Netherlands Haemophilia Patient Society (NVHP) was involved in the design of these interventions, including three sessions with patient panels during the development phase, the testing of the online training interface, and participation as trainers in the online intervention. The trainers for both interventions (face-to-face and online) received specific training during the development phase. Another strength of this study was the use of two different methods for adherence assessment. The literature recommends the use of different approaches for the evaluation of adherence in patients with chronic conditions[35]. The VERITAS-Pro[26] is the only disease-specific adherence questionnaire that is currently available. To provide more detailed information, we also assessed adherence according to the Delphi definition[36]. For the main study, the evaluation of pharmacy records will be added. The present study was limited by the small target population; severe haemophilia is a rare disease (1:5,000 males), but non-adherence is widely prevalent, at 57%[4,37]. An additional and important aspect is that the success of face-to-face training is conditional on the willingness of these men to work on their personal problems.

The face-to-face training group represents the first ACT-based training performed in haemophilia. However, ACT has been extensively applied to other chronic conditions. A systematic review showed that ACT could be effective for several chronic conditions (e.g. depression, obsessive-compulsive disorder, multiple sclerosis, and diabetes)[33,34], with a large effect sizes, even increasing up to 6 to 12 months after the intervention[33]. This current feasibility study only performed one follow-up measurement, 2 months after the last session (i.e. 6 months after the first session). In contrast, the main study will assess participants at 6 and 12 months after the beginning training. Graham et al. stated that ACT can have promising effects on self-management but reported that the effects of ACT on adherence have been insufficiently demonstrated[34]. Moreover, these authors recommended the use of a randomised controlled trial (RCT) to compare ACT against another behavioural change strategy, rather than the use of other study designs[34]. The preliminary results of this study showed almost no effect on adherence (mean difference of 2 points); however, the intervention had a major effect on quality of life. Although an RCT design was considered, in our opinion, allowing a participant struggling with acceptance to 'wait' in a control group was unethical. An RCT comparing two interventions was impossible because no other intervention for improving illness acceptance in haemophilia has been developed. A recent Cochrane review evaluated several psychological interventions for people with haemophilia[38], which included all published psychological interventions targeted at individuals, groups, or families[38]. This review only reported on self-administered interventions that were provided by technologies such as DVDs and computers.

Why did the online training fail? Several potential reasons for the failure of the online training programme were identified: age, gender, and disease-specific differences were considered likely contributing factors. The online training was based on a comparable training programme that was designed for rheumatic arthritis[22,32]. The training for rheumatic arthritis was evaluated in both a feasibility study and an RCT[32,39]. The feasibility study showed that the training was suitable for young adults, without recruitment problems (52% response rate). This result agreed with a recent Cochrane review reporting that online psychological interventions are effective among young people but are more difficult to accomplish in adults[38]. At the time that our intervention was designed, the RCT for rheumatic arthritis was ongoing, and we were unaware of its results. The eventual RCT turned out not

effective in terms of self-efficacy, but was evaluated appreciated and valuable for the participants. They participants in the rheumatic arthritis RCT were primary young females (88%, mean age of 19 years.). The Dutch RA population is nine times larger and has a larger incidence and prevalence than the Dutch haemophilia population[40]. Some studies have reported that men prefer to receive less information about their diseases compared with women and that men report lower disease specific health literacy[41–44]. Another aspect affecting recruitment may be the time since diagnosis: in diabetes newly diagnosed (< 1 year) patients were more willing to participate in self-management interventions than those diagnosed 2–3 year ago[45]. Based on our experiences, it is recommended to create more awareness of disease and gender differences related to selecting an intervention.

This study has clinical and research implications. In our opinion, the results of the present study provide sufficient reasons (preliminary results, feasibility, and evaluation) for the continuation of the face-to-face group training in a national pre-post-test study. To evaluate the long-term effects of this intervention, data collection will be extended to twelve months follow-up in the main study. If face-to-face group training is effective this intervention format could be applied to daily healthcare for both severe and non-severe haemophilia patients who are struggling with acceptance. For clinical practice, the positive feedback received from both patients and their relatives concerning the face-to-face group training has inspired us to continue the application of this intervention. We now believe that this type of acceptance intervention could improve daily healthcare. This acceptance and commitment therapy training is not country- or language-specific training[3,4]. In our opinion, this intervention can be applied to other (European) countries after proper translation. The online training was evaluated as being unfeasible in its current format. Based on participant evaluation, we have adapted it for use with young teenagers who are learning self-infusion. Instead of the printed information that was used in the past, children and their parents can access an online program containing four modules that feature educational videos, written information, and tests. Nurses are able to review patients' status and answer questions online.

CONCLUSION

This paper described the feasibility of two tailored interventions designed to address acceptance (face-to-face) and self-management (online) among individuals with severe haemophilia. Both interventions were adapted from previously existing and effective interventions. The face-to-face training was evaluated as being feasible, with promising preliminary results (especially on quality of life). The online training was evaluated as not being feasible because of recruitment problems and was stopped prior to the end of the study period. The failure of the online training may be due to age, gender, and disease-specific differences between previously described effective interventions and this tailored intervention designed for patients with severe haemophilia.

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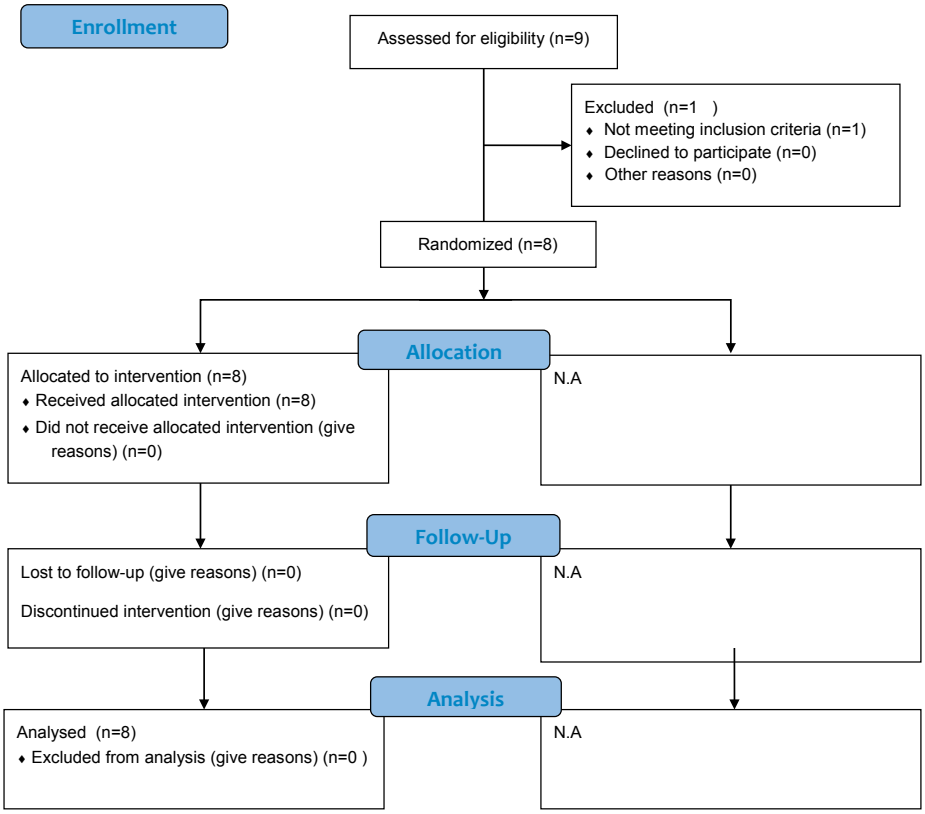
APPENDIX

Appendix 1 CONSORT flow diagram for both interventions

CONSORT 2010 Flow Diagram

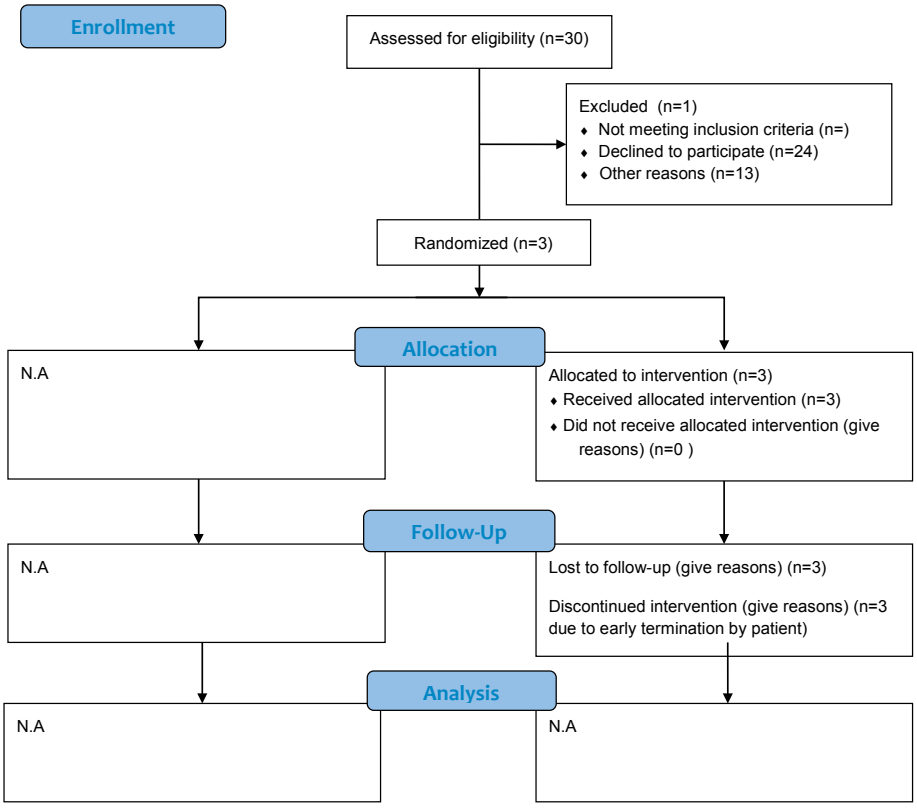
Face-to-face group training



CONSORT
TRANSPARENT REPORTING of TRIALS

CONSORT 2010 Flow Diagram

Online training



Appendix 2 Questionnaires used as outcome parameters

	Outcome	Questionnaire	Specifications	Minimal important difference
Used in both interventions	Adherence	Veritas-Pro [26]	- 6 domains (Time, Dose, Plan, Remember, Skip, and Communicate) - 24 multiple-choice questions - Cumulative normalised total score, range 0–100	Not officially defined. We considered an increase of 5 points to be clinically relevant.
	Quality of life	SF-36 [27]	- 8 domains [physical functioning (PH); role-physical (RH), bodily pain (BP), general health (GH), vitality (V), social functioning (SF), role-emotional (RE), and mental health (MH)]. - 36 multiple-choice questions	Increase by 5 points.[30]
Face-to-face training	Illness perception	BIPQ [28]	- Only a total score, no domains - 8 multiple-choice questions - Cumulative score, range 0–80	Not officially defined. We considered an increase of 5 points to be clinically relevant.

Flourishing

CHAPTER 6

A tailored intervention for illness acceptance improves adherence and quality of life in adults with haemophilia using prophylaxis

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ABSTRACT

Introduction

Adherence to prophylactic treatment (prophylaxis) in persons with haemophilia is challenging and has been reported at only ±50%. Acceptance problems are one of the main reasons for non-adherence in haemophilia. An evidence-based intervention was developed based on an Acceptance and commitment therapy (ACT) approach.

Aim

To evaluate a tailored intervention focused on illness acceptance in adults with haemophilia who were prescribed prophylaxis.

Methods

A pre-post study was executed in adults with haemophilia who were prescribed prophylaxis. A series of 8 2-hour group trainings were held, including 3-8 participantsa a series. Adherence (VERITAS-Pro, optimum 0), health-related quality of life (HRQoL, SF-36, optimum 100) and illness perception (BIPQ, optimum 0) were measured at start, after six and 12 months and analysed using Wilcoxon signed-rank test.

Results

Twenty four patients (median age 47 years, range 27-74) were included. After 12 months adherence improved in 68% of patients, quality of life in 48% and illness perception in 31%. Adherence (total score) improved from 35 to 25 ($p<0.01$). HRQoL showed clinically relevant improvement in domains of social-functioning ($p=0.04$), role-emotional, physical-functioning, role-physical and bodily-pain. Illness perception improved statistically significant on domains of affect ($p=0.01$), concern ($p=0.01$) and understanding($p=0.04$). Patients evaluated the training useful, an eye-opener, a personal enrichment and insightful.

Conclusion

The tailored group intervention resulted in significant improvement of adherence, quality of life and illness perception. Based on our current experience we have implemented it in clinical practice and collaborate with the patient association to make it available for all Dutch people with haemophilia.

INTRODUCTION

Haemophilia is a rare bleeding disorder, affecting approximately 1700 Dutch men, including ± 800 with severe haemophilia[1]. Patients with severe haemophilia have no measurable clotting factor FVIII or FIX and are at risk for spontaneous bleeds in joints, muscles or the central nervous system[2]. Treatment consists of lifelong prophylactic clotting factor replacement therapy (prophylaxis)[1,3]. Patients using prophylaxis perform intravenous injections at their homes approximately 2-3 times a week[2,3].

For effective prevention of bleeding, high adherence to the prescribed treatment is crucial. Similar to other chronic conditions, the non-adherence rate in haemophilia is estimated at 50%[4]. Non-adherence is very harmful, as even a single bleed can lead to irreversible damage with potential lifelong disabilities[5]. Previous research identified acceptance problems (present in ± 25% of patients) as one of the main reasons for non-adherence[6,7]. Patients with acceptance problems mostly administer concentrate inadequately (for example: only to treat bleeds, or dosing once weekly) and are thus at risk for serious bleeding[6].

Acceptance and commitment therapy (ACT) is a proven effective approach to support patients with illness related acceptance problems[8–11]. ACT is a psychological intervention combining acceptance, mindfulness, cognitive,- and behavioural therapy. This theory is focussed on changing a person's thoughts resulting in habit changes[12]. This method has been used in many diseases (e.g. HIV, cancer, epilepsy) with positive results like improving quality of life and symptom control and reducing distress[13].

Based on ACT, a tailored group invention for patients with haemophilia on prophylaxis was developed[14]. The intervention focused on illness acceptance showed promising results during feasibility testing[14]. This study aimed to evaluate the effect of the tailored invention for patients with haemophilia who were prescribed prophylactic treatment.

MATERIALS AND METHODS

A prospective pre-post-test study evaluated the effectiveness of a tailored intervention called "Living with haemophilia" (in Dutch: "Leven met hemofilie"). This training was based on the already existing and proven effective 'Acceptance and Commitment Therapy' (ACT)[9,11,13]. The study design is shown in figure 1. Patients completed a questionnaire prior to the intervention, followed the group training and subsequently completed questionnaires at six and twelve months after the first training session. The study was approved by the ethical committee of the University Medical Center Utrecht, The Netherlands.

Participants

Adult patients (>18 years) from all treatment centres of The Netherlands were eligible to participate if they were diagnosed with haemophilia and when prophylactic treatment was prescribed or indicated. Patients were excluded when they were diagnosed with a serious psychiatric disorder, which could in potentially interfere with the training.

Patients were informed about this study by their health care provider or through different digital platforms (websites, social media, newsletters and the patient society). When a patient was considering participation, a phone call with one of the trainers (RB, LH or JH) was scheduled to inform the patient and clarify his personal training goal. Patients signed informed consent prior start of the training. A formal power calculation was impossible due to lack of information and the small population. Prior to the study, the team considered 23-32 participants sufficient to evaluate outcome.

Data collection

Data was collected before start, after six months and after twelve months. The primary outcome was adherence[15,16], and secondary outcomes were Health Related Quality of Life[17], illness perception[18] and disease specific outcomes. Adherence was assessed according to two quantitative methods. Firstly based on the Delphi definition of non-adherence[15] evaluating missed infusions, dose changes and deviation in timing. Secondly using the Validated Hemophilia Regimen Treatment Adherence Scale –Prophylaxis (VERITAS-Pro).

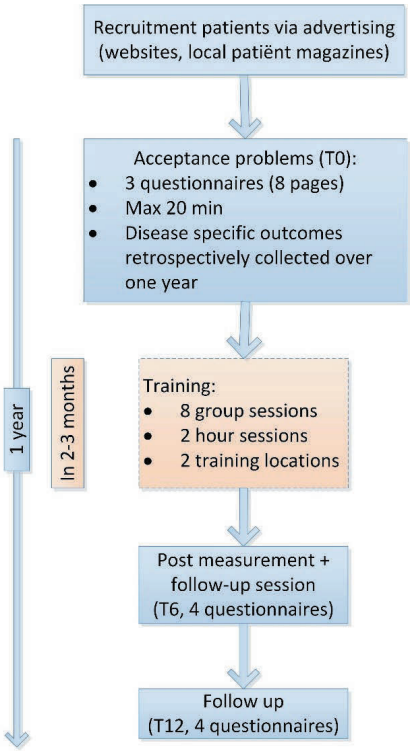


Figure 1 Study design

The VERITAS-Pro consists of 24 questions resulting in a total score and six domain scores (Time, Dose, Plan, Skip and Communicate). An increase of 5 points on the total score was considered of clinical relevance. VERITAS-Pro scores were normalized (0 indicates perfect adherence). Quality of life (QoL) was measured using the short form 36 health survey (SF-36), (100 indicates perfect QoL)[17]. The SF-36 consists of 36 questions in 8 domains, which can be subdivided into mental components including vitality (V), social functioning (SF), role-emotional (RE) and mental health (MH) and physical components including the domains physical functioning (PH), role-physical (RH), bodily pain (BP) and general health (GH). An increase of 5 points is considered clinically relevant[19]. Disease perception was measured using the Brief Illness Perception Questionnaire (BIPQ)[20]. The BIPQ consists of eight standalone questions, scoring from 0-10[21] (0 indicates perfect illness perception). A higher score represents a more threatening view of the illness. Because haemophilia is lifelong disease we decided to remove the second

question (Q2. How long do you think your illness will continue?). Clinical relevance was considered when a patient increased with 2-3 points (25th percentile). During the last session the training was evaluated using a qualitative group interview. This interview was executed by the trainers and was recorded.

Data analyses

Missing data by not completing a questionnaire was not replaced. In case of missing data by conscious skipping specific questions (on-demand regime instead of prophylactic regime), data were replaced (adherence cut-off value). Patient characteristics were analysed using descriptive statistics and reported as medians and interquartile ranges (IQR). Changes from start to 12 months follow-up at patient level were analysed using descriptive statistics. Data originating from questionnaires were presented as means and standard deviations (SD)[22]. The VERITAS-Pro was normalized into an 0-100 score (score-24/96*100, optimum 0 points). Differences over time were analysed using the Wilcoxon signed-rank test. Qualitative evaluation was summarized and analysed according to themes identified. The research team discussed the themes.

RESULTS

In total, 24 of 80 invited patients (response rate: 30%) signed informed consent and participated in the training. All patients completed the training and the majority of the patients completed the questionnaires (90%, 69/72 questionnaires) at the appropriate time.

Patient characteristics

Patient characteristics are shown in table 1. The majority of the patients was diagnosed with haemophilia A (N= 23, 96%) with a severe (N= 22, 92%) phenotype. The median age was 47 years (IQR= 39-56, range 27-74). The median prescribed frequency of prophylactic injections was three times a week (IQR= 3-4) with a prescribed dose of median 1000 units per infusion (IQR= 750-1625). The majority of patients completed vocational education (N= 8, 33%), and were full time employed (N= 14, 58%).

Adherence

Adherence increased (+ ≥5%) in 68% of the patients. Adherence over time is shown in table 2 and figure 2. Based to the Delphi definition of non-adherence

an improvement on all three domains was observed. Two improved significantly after six months: domain 'Administer prophylaxis' (increase by 14% p=0.04) and domain 'Correct time' (increase by 17%, p=0.01). One domain was still significantly improved after 12 months: 'Correct time' (increase by 19%, p=0.01). Based on the VERITAS-Pro an improvement (i.e. lower score) on the total score and all six domains was observed. Two domains improved significantly after six months: domain 'Time' (-14 points, p=0.03) and domain 'Remember' (-10 points, p<0.04). After 12 months the total score and four domains significantly improved: 'Total score' (-10 points, p=<0.01), domain 'Time' (-18 points, p=0.02), domain 'Remember' (-12 points, p=0.03), domain 'Skip' (-13 points, p=0.02) and 'Communicate' (-26 points, p=0.04).

Table 1 Patient characteristics

	Participants N= 24	
	N (IQR or %)	
Haemophilia A	23 (96%)	
*Severe**	22 (92%)	
*Moderate**	1 (4)	
Age (years)	47 (39-56)	
Prescribed frequency per week (med/IQR)*	3 (3-3)	
Prescribed FVIII dose/infusion (med/IQR)*	1000 (750-1625)	
Education level		
Primary education	1	(4%)
High school	4	(77%)
Vocational education	8	(33%)
Advanced vocational	7	(29%)
University	4	(17%)
Employment		
Full time paid	14 (58%)	
Part time	2 (8%)	
Unable to work	6 (25%)	
Other	2 (8%)	
Absence due to bleeds (med/IQR)	0 (0-2)	

* Haemophilia A only

Health-related quality of life

Health-related quality of life improved (+≥5 points) in 30-48% of the patients (depending on the different domains). HRQoL over time is shown in figure 3. HRQoL improved on all domains. After six months, 5/8 domains showed clinically relevant improvement: 'social functioning' (+8 points), 'role-emotional' (+10 points), 'physical functioning' (+5 points), 'role-physical' (+25 points, p=0.02) and 'general health' (+8 points, p=0.02). After 12 months, HRQOL scores were again compared to T0. 'Social functioning' improved further to eventually +12 points (p=0.04), while 'role-emotional' (+10 points, and 'physical functioning' (+5 points) remained stable since six months measurement moment. Compared to the measurement moment (+25 points) the improvement in the domain of 'role-physical' was partly reversed to end at +7 points. The domain of 'bodily pain' had increased by 5 points.

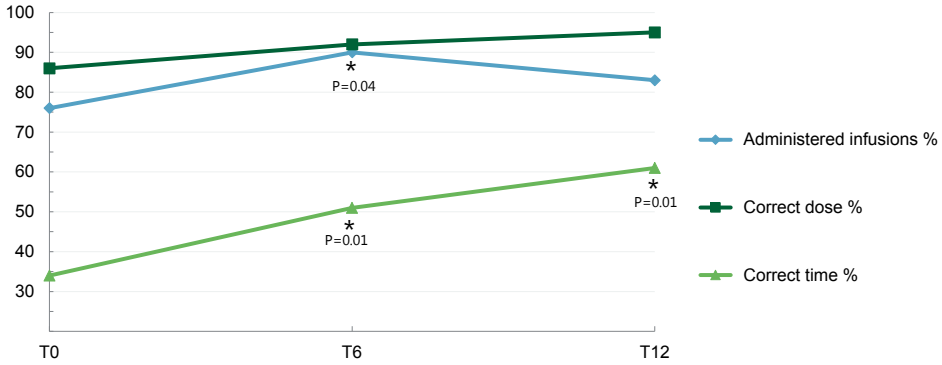
Table 2 Adherence measured with the VERITAS-Pro (Normalized values 0-100, optimum 0)

	T0 N=24	**T6** N=22	**T6-T0** N=22	**p value***	**T12** N=23	**T12-T0** N=23	**p value***
	Mean (SD)		Diff		Mean (SD)	Diff	
Total score	35 (13)	30 (13)	- 5	0.14	25 (12)	- 10	**<0.01**
Time	42 (27)	28 (23)	- 14	**0.03**	24 (18)	- 18	**0.02**
Dose	18 (15)	22 (18)	+ 4	0.46	13 (9)	- 5	0.10
Plan	34 (20)	32 (24)	- 2	0.76	32 (20)	- 2	0.34
Remember	42 (22)	32 (26)	- 10	**0.04**	30 (21)	- 12	**0.03**
Skip	37 (24)	28 (22)	- 9	0.09	25 (21)	- 12	**0.02**
Communicate	52 (17)	36 (17)	- 16	0.65	26 (16)	- 26	**0.04**

* Wilcoxon signed rank test

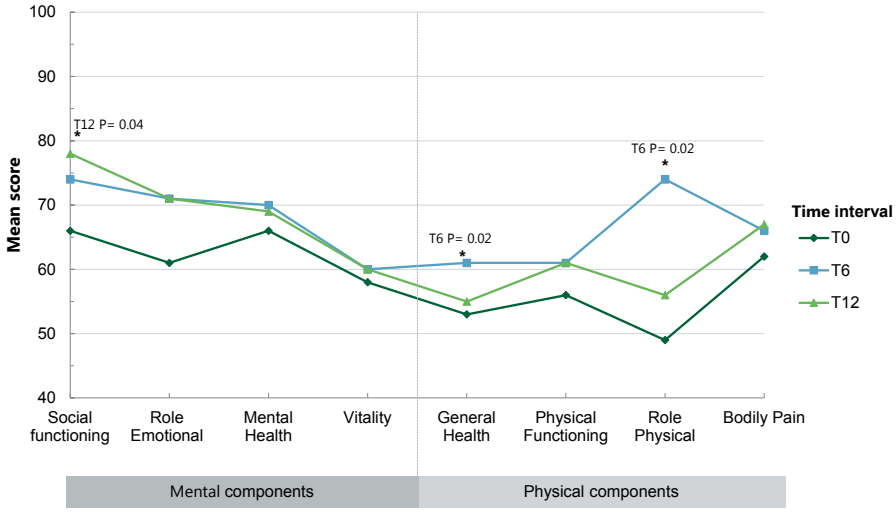
Illness perception

Illness perception increased in 31-68% of the patients (depending on the specific question). Illness perception (BIPQ) scores according to time are shown in table 3. Based on de BIPQ. At six months two questions showed statistically significant improvement: 'illness related concerns' (improved in 59% of the patients, p=0.04) and 'illness affected emotions' (improved in 59%, p=0.00).



* Indicates a significant (P=≤0.05) difference relative to baseline. Wilcoxon signed rank test was used.

Figure 2 Adherence over time



* Indicates a significant (P=≤0.05) difference relative to baseline. Wilcoxon signed rank test was used.

Figure 3 Health Related Quality of life using SF-36 (Range 0-100, optimum 100)

After twelve months statistically significant improvement remained in 'illness related concerns' (improved in 56%, p=0.01), while 'illness affected emotions' showed no improvement compared to start. In addition, statistically significant improvement was observed for 'illness affecting life'(improved in 65%, p=0.01), and understanding illness (improvement in 57%, p=0.04).

Table 3 Illness perception (Range 0-10, optimum 0)

	T0	T6	Improvement	T12	Improvement
	N=24	N=22		N=23	
	Mean (SD) or %				
Q1 How much does your illness **affect** your life?	7 (2)	6 (2)	68%	6 (2)	**65%***
Q3 How much **control** do you feel you have over your illness?	3 (2)	6 (2)	36%	3 (2)	39%
Q4 How much do you think your **treatment** can help your illness?	3 (2)	2 (1)	36%	1 (2)	48%
Q5 How much do you experience **symptoms** from your illness?	7 (2)	7 (2)	31%	7 (2)	43%
Q6 How **concerned** are you about your illness?	6 (2)	5 (2)	**59%***	5 (2)	**65%***
Q7 How well do you feel you **understand** your illness?	2 (2)	2 (2)	36%	2 (1)	**57%***
Q8 How much does your illness affect you **emotionally**?	6 (2)	5 (2)	**59%***	6 (2)	48%

* significant improvement (≤0.05), Wilcoxon signed rank test
Q2 is removed, explanation in methods section of this paper
A higher score represents a more threatening view of the illness (Løchting G.K., 2013)

Qualitative evaluation

Participants evaluated the training as useful, an eye-opener, a personal enrichment and insightful:

R11: 'This training met my expectations, exceptionally good'.
R14: 'It was more fun than I expected.'

Participants appreciated the peer-contact and stressed the importance of sharing experiences. In addition, they appreciated that this training was more than just 'talking'. The exercises were considered valuable:

R10: 'I experienced the combination of sharing experiences and exercises related to difficulties someone is facing as very powerful'.

One participant mentioned that he would have liked to have more sessions to create more time for reflection. None of the participants experienced eight sessions as too many. They appreciated the added value of peer contact compared to individual sessions with a psychologist. All participants recommend the training to others.

R21: 'The conversations and questions are challenging me. The training really changed my mind and thoughts. That is what I liked about this training and why I would like to recommend it to others'.

DISCUSSION

This study aimed to evaluate the effect of a tailored intervention focused on illness acceptance for patients with haemophilia on prophylaxis. The training was evaluated as effective, clinically relevant improvement in adherence was observed in 68% of patients, health-related quality of life improved in 48%, and illness perception improved in 31 of patients. Adherence improved significantly on the VERITAS-Pro domains of 'Time', 'Remember', 'Skip', and 'Communicate'. Quality of life improved on both mental components and physical components, with statistically significant improvement in the domain of 'social functioning'. In addition, Illness perception improved significantly on 'illness affecting life', 'related concerns' and 'illness understanding'. Patients evaluated the training positively, completion was 100%.

Strengths and weaknesses

Consistency and quality of the training was maintained by formally trained trainers, a fully scripted training and hands-on training for all trainers[14]. The training was executed by haemophilia health care professionals, rather than psychologists, who had a better understanding of practical aspects and challenges of intravenous home treatment. In our experience, the group format instead of an individual format promoted the understanding of metaphors. Discussing metaphors created more time to put these into perspective and relate these to their own life. Some limitations of the study need to be addressed.

Starting with the design: a randomized control trial (RCT) is the recommend design for intervention studies[23]. In this case, the RCT design was considered unethical and infeasible: at inclusion, eligible patients experienced disease burden affecting daily life and were motivated to accept help. Providing a scam treatment or doing a crossover study was considered unethical as it includes making patients in need wait for help, and could even increase problems. Therefore, a pre-post-test design was considered the most appropriate design in this population. Secondly, recruitment was challenging, resulting in extension of the recruitment period and a low response rate of 30%. Although acceptance related problems were frequently observed by the healthcare team, only patients who were burdened by acceptance problems were willing to participate. Furthermore, it was a difficult task to evaluate a qualitative intervention in a quantitative manner. Even in disease specific questionnaires some questions were perceived as confrontational. This was noted, but there is currently no solution to close the gap between patients' feelings or experiences and questionnaires.

These results were compared to other studies. Overall in chronic diseases, non-adherence is a big problem for which several adherence specific interventions are available. Conn et al.[24] performed a systematic review and in a meta-analysis evaluated 771 interventions improving adherence behaviour outcomes. They reported that the most effective interventions were delivered face-to-face (mainly by pharmacists) and the largest effect sizes were found in medication electric event monitoring and pill counts. The overall conclusion was that health care providers should focus on behavioural strategies (habit-based) instead of cognitive strategies designed to change knowledge and beliefs [24]. The current intervention is a face-to-face intervention and this has certain components which

could explain why this intervention turned out effective. There are two systematic reviews on ACT that have focused on the comparison with cognitive behaviour therapy rather than quantitative outcomes such as adherence[13,25]. Until now, there have been two adherence specific interventions studies in haemophilia. Lock et al. conducted an pre- and post-test study evaluating home visits (6 visits in 2 years) by a haemophilia nurse, who educated children and parents[26]. In this population, the overall baseline adherence score was relatively high (VERITAS-Pro total normalized: 30) and VERITAS-Pro showed a significant improvement on the communication domain only (mean difference -1 point, p=0.03). Cuesta-Barriuso et al. conducted an cross-sectional descriptive study evaluating 'Medtep': an online platform[27] (e.g. information about infusions, physical activities and an infusion log). This study reported significant improvement on adherence (VERITAS-Pro) after 12 months: total score (mean difference -11 points p<0.01 and domain 'Time', 'Plan', 'Remember', 'Skip' and 'Communicate' (mean difference ranging from -1.4 to -2.6 points, p<0.05). This effect may be underestimated as only 56% used Medtep after 12 months.

The use of point of care ultrasound as visual feedback to promote adherence in patients with haemophilia is mentioned by some researchers, but a formal evaluation of the effects of point of care ultrasound on adherence is lacking[28,29]. A recently published abstract reported a significant improvement in VERITAS-Pro scores following monitoring with ultrasound and diaries [30].

This study has clinical and research implications. Based on the positive results, we recommend to implement the ACT training on an annual basis. This time interval is recommended to create time to recruit patients. In our centre, we are currently expanding the training to all patients with clotting disorders with illness acceptance problems. Based on positive results of the ACT method in other chronic conditions (e.g. HIV, diabetes, parenting of children with chronic pain, brain injury and cancer[11,13]), we expect that these patients will benefit from this intervention too. Potential candidates should be aware of acceptance related problems and recruitment for the intervention is therefore most successful at the time the patient experiences problems. It is good to take into account that this training group not only reported improvement on mental domains of HRQoL but also in the physical domains (general health). The next research step will be to

implement this training in daily healthcare including patients with other diagnoses and perform a cost-effectiveness evaluation.

CONCLUSION

This study evaluated the effectiveness of and tailored acceptance intervention based on ACT. Clinically relevant and significant improvements in adherence, quality of life and illness perception were observed. Patients evaluated the training as positive and experienced the training as a personal enrichment and life-changing experience. The training will be implemented in haemophilia care in The Netherlands. Future research will focus on cost-effectiveness and exploring possibilities to implement this training in other clotting disorders.

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GENERAL DISCUSSION

GENERAL DISCUSSION

Adherence to prescribed medication is one of the primary determinant of treatment success and effectiveness[1,2]. Therefore, the aim of this thesis was to clarify and improve adherence to prophylaxis among patients with haemophilia. Non-adherence was defined as missing >15% of infusions, changing >10% of the doses without consultation of the treated, or taking <30% of infusions in the morning[3]. The first part of this thesis focused on exploring and clarifying (non) adherence in haemophilia. We reported that adherence progressively deteriorated from childhood to adolescence, to adulthood (Chapters 1 and 2[4]). Adherence was not associated with bleeding frequency (Chapter 2[4]) or with attitudes towards treatment or treatment satisfaction (Chapter 1). Based on an interview-based study performed with adolescent participants, two primary underlying components were identified as affecting adherence: 1) the level of treatment responsibility and 2) the estimated risk per activity and the planning of prophylaxis for a activity (Chapter 3[5]). A nationwide survey was performed and revealed that individuals with severe haemophilia on prophylaxis who participate in (high-risk sports (e.g. hockey, football) were not more adherent to prophylaxis than those who do not participate in sports (Chapter 4[6]). This finding suggested that sports participation does not affect patients' risk estimation, which contrasts the hypothesis developed based on the results of the qualitative study (Chapter 3[5]).

The second part of this thesis focused on improving adherence in haemophilia, this includes the development of an intervention to improve adherence to prophylaxis. The targets were illness acceptance and self-management because these aspects were identified as the primary reasons for non-adherence by Schrijvers et al.[7] Two separate interventions were developed, which each focused on one of these two aspects: a face-to-face group intervention was developed to enhance illness acceptance ('Living with haemophilia') and an online intervention was developed to improve self-management ('Haemophilia challenged'). The face-to-face group training was identified as being feasible and was evaluated as being effective during the follow-up research (Chapters 5[8] and 6). This program resulted in significantly improved adherence and quality of life. In contrast, the online intervention was unfeasible due to recruitment problems (Chapters 5[8]).

Measuring adherence

Among the general population, both patients and healthcare providers are known to overestimate medication adherence[9,10]. Therefore, an accurate evaluation of adherence is important for both research and clinical practice. Two methods can be used to assess adherence[11]. First, adherence can be measured directly, through the measurement of metabolite levels in blood or urine to observe the effects of the treatment protocol. Alternatively, adherence can be measured indirectly, using measures such as pill counting, self-reported questionnaires, or electronic databases or monitoring systems[11]. In haemophilia, the use of direct adherence monitoring methods based on blood-borne metabolite levels is not possible due to the short half-life of the clotting factor concentrate (CFC)[12], resulting in a reliance on indirect methods. Pill counting and medication electronic monitoring systems (MEMS) are often used in clinical trials and daily care[11,13,14]. These adherence measurement methods were not considered feasible for the research described this thesis because: 1) CFC dosing varies over time, each injection is packed individually 2) haemophilia medication can be used both prophylactically as in response to episodes of bleeding, traumas, or injuries, requiring very precise separate documentation and 3) in my opinion, this method includes a risk of bias if adherence is the primary outcome. Non-adherent patients may, consciously or subconsciously, fail to log their medication usage with the necessary precision, making this an unreliable method for tracking adherence. Therefore, the indirect methods are a reliable alternative in haemophilia. Currently, self-reported questionnaires are the most optimal method to evaluate adherence in haemophilia and therefore they remain the most commonly used method to measure adherence.

Some generic questionnaires have been applied to the evaluation of adherence in other conditions[15], including the Morisky Medication Adherence Scale (MMAS)[16] and Medication Adherence Report Scale (MARS)[17]. These questionnaires are short, evaluate adherence-related behaviour, and were often developed for disease-specific purposes before being applied more generically. However, due to the existence of a widely used, haemophilia-specific questionnaire, other measurement tools were not considered. In retrospect, some of these instruments should have been considered for use in this thesis. However, this would have hampered comparison of our results with other haemophilia studies since these mainly used the VERITAS-Pro to evaluate adherence.

Illness-specific adherence questionnaires, the VERITAS-Pro

The 'Validated Hemophilia Regimen Treatment Adherence Scale –Prophylaxis' (VERITAS-Pro) is a haemophilia-specific adherence questionnaire[18]. It consists of 24 questions, producing both a total score and six domain scores (Time, Dose, Plan, Remember, Skip, and Communicate)[18,19]. The VERITAS-Pro questionnaire was initially developed and validated in the United States of America[18]. The questionnaire evaluates various behavioural aspects, including background information (in the domains Plan and Communicate). In the American validation study, the internal consistency of VERITAS-Pro was found to be good-to-excellent (Cronbach's alpha 0.94), and the test–retest reliability correlations were very strong (Inter-item Pearson's correlation coefficient of r= 0.77)[18]. The VERITAS-Pro has been translated into at least 30 languages. The Dutch version was translated and validated in a paediatric population (1–18 years, N= 60 patients) by Lock et al.[18]. The internal consistency and test–retest reliability of the Dutch version was found to be lower than those for the original version (Cronbach's alpha total score 0.71, and inter-item Spearman's Correlation coefficient of 0.27)[19]. The cut-off value of the VERITAS-Pro (57 if using the 'raw' score calculation ranging from 24-120, and 34 if using the normalised score ranging from 0-100) is often described as being too absolute[18]. The addition of an intermediate value, to describe 'suboptimal adherence', has also been suggested[20]. Based on the original validation paper, the cut-off value appears to have been consciously and carefully determined; however, in my opinion, the addition of an intermediate level of adherence could be recommended, because the current cut-off is too arbitrary.

Other suggestions for improvement were explored in the German healthcare system[21]. Patients suggested the addition of questions regarding factors that influence adherence and use of an infusion log. Healthcare providers suggested the addition of questions regarding the use of an infusion log and the reasons for deviations from the treatment regime[21]. Despite the difficulties encountered when attempting to validate the Dutch version of the VERITAS-Pro and the suggestions for additional questions presented by Mackenson et al., we concluded that the VERITAS-Pro currently represents the best available tool for evaluating adherence to haemophilia treatment for the present study purposes.

In daily practice however, the use of a (long) questionnaire might be too time-consuming. Currently, a Dutch guideline for measuring adherence to medication

regimens for chronic conditions is currently being developed (LH. Schrijvers, personal communication). This guideline includes the recommendation that medication management and administration be observed, followed by an open and non-judgemental conversation regarding adherence and medication management. Finally, adherence should be measured using a short questionnaire (a maximum of 10 questions).

In my opinion, evaluating adherence represents a multidisciplinary task, for which haemophilia nurses can assume a great deal of responsibility. During out-patient visits, a patient can be asked to administer prophylaxis while being observed by nurses, which can be followed by a non-judgemental conversation regarding patients experience with adherent and bleeds. The haemophilia nurse can administering a adherence questionnaire. The VERITAS-Pro questionnaire is currently too long for clinical because it includes 24 questions. A shorter alternative for the VERITAS-Pro questionnaire is the Dutch Delphi definition of adherence, which consists of three questions focused on 1) missed infusions, 2) dose changes, 3) timing changes[3]. In Chapter 1, the three questions of the VERITAS-Pro that coincide with the Delphi definition were selected for analysis. The percentage of non-adherence, in terms of missed infusions, was comparable using the three-question estimation to the results of the VERITAS-Pro total score, suggesting that a short instrument consisting of 3 questions could be developed for use in clinical practice As described above, an exploratory analysis has been performed. Future research could focus on the validation of the set of 3 questions defined in the Delphi questionnaire. A research design that corresponds to how this instrument will be used in daily practice is recommended, including asking patients to fill out the VERITAS-Pro while they are in the waiting room, followed by having a nurse or healthcare provided ask the three Delphi questions during the appointment. The similarities and differences in the classification of adherent and non-adherent patients between VERITAS-Pro and the Delphi questions can then be compared and the risk for false negatives evaluated.

Interventions that improve adherence

Measuring and discussing adherence with patients represents an important component of treatment. However, after addressing non-adherence, offering an intervention is the next step that should be explored. Many attempts have been made to improve adherence, which is reflected in different studies[22–25]. A search on

PubMed using the terms 'interventions' and 'medication adherence' resulted in the identification of 2,791 publications (date search: 3 December 2020). A systematic review and meta-analysis was performed by Conn et al. (2017), which summarised the outcomes of 771 randomised controlled trials (RCTs) targeted at adherence[25]. Adherence interventions were identified as more effective if they met the following criteria: 1) were delivered by a pharmacist, 2) were delivered outside of the patients' home, 3) were delivered face-to-face rather than online, 4) were based on habits or behaviour rather than cognitive aspects, and 5) were individualized[25]. Point 4 and 5 are supported by studies reporting that psychological interventions are the most effective types of interventions[23,24,26]. Other studies, evaluated educational interventions and reminders. Educational interventions alone were insufficient, but were considered potentially effective when combined with behavioural strategies[23]. Although the short-term effectiveness of reminders is well-established, the long-term effectiveness of remainders remains unclear[24,26].

Chapters 5 and 6 describe the development of two interventions (one face-to-face and one online) and the evaluation of the face-to-face interventions for improving treatment adherence among haemophilia patients. As discussed in Chapter 5, the online intervention was evaluated as being infeasible, whereas the face-to-face intervention (Known as: 'Living with Haemophilia' was deemed feasible. Unfortunately, due to recruitment problems, we were unable to evaluate the effectiveness of the online intervention. The face-to-face intervention was evaluated as being feasible and its effectiveness was evaluated (Chapter 6). Based on the recommendations made by Conn et al., this intervention satisfied a most elements. The face-to-face intervention was standardised, was offered face-to-face, and was based on 'acceptance and commitment therapy[27] (ACT). ACT is focused on achieving behavioural changes using mindfulness-oriented cognitive and behavioural therapies[28]. The effectiveness study proved that this intervention improved adherence, quality of life, and disease acceptance (Chapter 6).

Haemophilia-specific adherence interventions

In the haemophilia-specific literature, we identified eighteen studies focused on improving adherence, yet only three had adherence as the primary outcome. One evaluated home visits by a haemophilia nurse (six visits in two years)[29]. During these home visits, children and their parents received haemophilia education. Adherence was measured using the VERITAS-Pro, resulting in a significant

improvement only for the communication domain (mean difference −1 point, p=0.03). Another study evaluated the 'Medtep' online platform, which features information regarding infusions, physical activities, and an infusion log[30]. This study reported significant improvements in VERITAS-Pro scores after 12 months (mean difference −11 points, p=< 0.01). Even though this study reported a significant difference, I have my concerns about this platform. Non-adherent patients may, consciously or subconsciously, fail to log their medication usage with the necessary precision, making this an unreliable method for tracking adherence. Finally, the study described in Chapter 5 and 6. This intervention and consisted of a face-to-face, ACT-based group training exercise (eight two-hour sessions). Adherence, as measured by the VERITAS-Pro total score, improved significantly (difference −10 points, p=< 0.01).

In daily practice, some healthcare providers use ultrasound to visualise joint status and emphasise the importance of adherence. Some studies have described this method as an intervention to promote adherence among patients with haemophilia[31,32]. However, formal evaluations exploring the effects of point of care ultrasound on adherence remain lacking. A recently published abstract reported a significant improvement in VERITAS-Pro scores following ultrasound-based monitoring and adherence diaries[33]. Future research should focus on evaluating the effects of this method on adherence.

Currently, this intervention ('Living with haemophilia') is implemented in daily healthcare practise and is available for all Dutch patients with haemophilia. We believe that this is an appropriate intervention that healthcare providers can recommend to their patients when difficulties regarding disease acceptance are observed. In the study, this face-to-face intervention encountered some recruitment challenges which delayed the study and patient involvement might thus be challenging when implementing this intervention in daily practice. Successful implementation of such interventions requires a multidisciplinary collaboration both within the treatment centre (nurses, doctors, physiotherapists, and social workers) and outside of the training centre (other treatment centres and patients). The target-group for this training has expanded from men with severe haemophilia to all men with haemophilia (all phenotypes). We believe that this training can also be offered to adults with other chronic conditions. Potential target groups include

women with a coagulation disorder, patients with other coagulation disorders, and individuals with chronic conditions that limit daily life.

Several parents have requested this training for their adolescents with haemophilia and have asked to be included in a similar training exercise for themselves. First, it must be explored whether, in addition to the parents' needs, adolescents need an age-adapted version. Thereafter, the training may be adapted, such as the use of other metaphors and exercises could be adapted for the new target group. When designing ACTs for parents, the challenge is to address ACT constructs that can impact not only their own lives but also the lives of their child must be carefully considered. Some studies have evaluated ACT in parents, most have focused on evaluating parent-related outcomes (Depression, Anxiety and Stress Scale-21)[34], rather than disease acceptance, attitudes towards treatment and the parent-child relationship. ACT for teenagers has been described in several books written by psychologists regarding ACT among young people[35–37]. Evaluating the intervention effectiveness is recommended in collaboration with an paediatrician and ACT-specialised psychologist[37]. Next, I would evaluate the intervention effectiveness using a pre–post-test study design using questionnaires. The actual effects of interventions on adherence (long-term) can be difficult to evaluate. Therefore, studies should focus on adherence-related outcome measures such as attitudes towards treatment and treatment satisfaction.

New treatments and the impacts on adherence

Currently, treatment of patients with haemophilia is changing rapidly. Some of these new treatments may influence adherence behaviours. For example, in the near future, a large number of Dutch patients with severe haemophilia are expected to switch from clotting factor concentrates to emicizumab[38,39], which is administered by a subcutaneous injection rather than an intravenous injection, and the infusion frequency will decrease to once every 1–4 weeks[38]. A first report stated that patients were more likely to adhere to emicizumab[40]. After a sufficiently large population of patients have switched and have become accustomed to the new medication routine, adherence levels should be re-examined in a larger cohort. In addition to change the mode of administration and the infusion frequency, emicizumab has a very long half-life. I expect this to affect adherence in two ways. In theory, there is a high chance that a patient with CFC will experience bleeding after repeatedly or for a long time skipping (non-adherence) treatment.

In some patients, a short feedback loop (non-adherence → bleed) motivates adherence. When the half-life of treatment increases, an extended feedback loop could result in increased rates of non-adherence. In contrast, an extended half-life-time might result in the opportunity to evaluate adherence using direct methods (metabolite levels). Monitoring the impacts of this medication switch on adherence is important, including the effects on haemophilia-related complications (minor bleeds). Therefore, I believe that in daily practice adherence, bleeding patterns and the recognition of bleeding events should be discussed during the switch from CFC to any new product. Nurses play an important role when a patient is switching between medications, providing both information and training, including discussions regarding adherence.

Finally, gene therapy is a second promising new treatment development for people with severe haemophilia[41,42]. Individuals are expected to be able to receive this therapy in the near future. With gene therapy, a patients' clotting factor levels are expected to increase significantly, shifting from severe phenotypes to mild phenotypes. Gene therapy is expected to eliminate the need for prophylactic treatment, and bleeds are likely to become increasingly rare. However, this situation immediately presents challenges regarding adherence for on-demand treatment. On-demand treatment consists of one or multiple clotting factor concentrate administrations after a bleed. In the absence of full correction of the FVIII/IX activity, these patients still suffer from mild haemophilia. The timely recognition of injury and the careful consideration of whether a bleed is occurring could be challenging. Most patients with mild phenotypes are unable to inject themselves, requiring a treatment centre visit. In these patients, adherence includes the timely contact of treatment centres. Future adherence-related research should determine the adherence rates to treatment recommendations of individuals who receive gene therapy. Qualitative research should also be performed to explore the underlying reasons and considerations that impact on how individuals decide to contact the treatment centre and adhere to treatment recommendations.

Summarising implications for daily practice

- **Measuring adherence:** Start evaluating adherence following the three principles: observing, having an open and non-judgemental conversation and measuring adherence using a short questionnaire. This is a multidisciplinary task in which the haemophilia nurse can play an important role.

- **Interventions improving adherence:** Multidisciplinary implementation of the face-to-face training group. Not only in patients with haemophilia but also in patients with other bleeding disorders or chronic conditions.

- **New treatments and the impact on adherence:** Alertness to the changing role of adherence from the moment a patient is switching from CFC to another product. Since the nurse informs and trains the patients, they can play an important role in patient awareness.

Summarising suggestions for future research

- **Measuring adherence:** Evaluating the Delphi definition questions usability in daily practice and validation in daily practice

- **Interventions improving adherence:** Adjust the face-to-face training for parents and children and evaluate its effectiveness. Secondly, evaluate the effect of ultrasound on adherence.

- **New treatments and the impact on adherence:** Determine the adherence (on-demand) rates and explore what the underlying reasons and considerations regarding adherence are. Summarise patients' needs and adjust the face-to-face training accordingly.

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SUMMARY

SUMMARY

Haemophilia is a rare congenital bleeding disorder that generally affects men. Due to a lack of clotting factor, people with haemophilia are at risk for spontaneous or traumatic bleeds, especially in the joints and muscles. To prevent bleeding, people with severe haemophilia are prescribed regular replacement therapy with intravenous clotting factor concentrates (prophylaxis), which can be administered at home through self-infusion. However, the effectiveness of prophylaxis is conditional on continuous adherence, which is estimated at 50%–80%. A patient is adherent to medication if the intravenous prophylaxis is administered on the right day, at the right time, and at the correct dose. The aim of this thesis was to clarify and improve adherence to prophylaxis among patients with haemophilia. The first part of this thesis focused on unravelling (non-)adherence in children and adolescents and young adults (AYAs). The second part of this thesis focused on flourishing adherence to life-long prophylaxis among adults.

Part 1: Unravelling

The first part of this thesis focused on unravelling the reasons for (non-)adherence among men with haemophilia who were prescribed prophylaxis. In **Chapter 1,** adherence to prophylaxis was quantified, and the associations between adherence and patients' attitudes towards prophylaxis and treatment satisfaction were assessed in children and adults. Data originating from a nationwide, cross-sectional, questionnaire-based cohort study (HIN-6) were analysed. A total of 321 participants were included in the analysis: 61 children (0–11 years), 29 adolescents (12–18 years), and 231 adults. Adherence was high (89% adherent) overall but worsened with age. Attitudes toward treatment and treatment satisfaction were similar between adherent and non-adherent patients (median 12 vs 10). A high score for attitude toward treatment in non-adherent patients is an indicator that patients are making the deliberate choice to be non-adherent.

In **Chapter 2,** the associations between adherence to prophylaxis and age and bleeding frequency were explored in children and adolescents. A single-centre, retrospective study using routine data collected during outpatient visits was executed. In total, 62 children with severe haemophilia were included. Overall, the adherence scores among these children were relatively high (95% adherent). The children also reported few bleeding events. However, younger children were

observed to be more adherent to prophylaxis than older children. Adherence did not increase or decrease with changes in the number of bleeds.

In **Chapter 3,** the underlying reasons for adherence and non-adherence were explored from the perspective of AYAs. A qualitative study was conducted, using both focus group interviews and individual interviews. In total, 24 AYAs aged 14–24 were interviewed. We found that parental support decreased when AYAs became more responsible for their own treatment, which coincided with a higher risk for non-adherence. AYAs weighed their potential bleeding risk per activity based on their desires to engage in daily activities while simultaneously wanting to feel safe. When they skipped or forgot a dose and experienced a bleed with little impact on their daily life or when no bleeding event occurred, AYAs felt safe, and the perceived need for prophylaxis decreased. We concluded that the two primary underlying reasons for (non-) adherence were the influences of 1) treatment responsibility 2) estimated risks per activity.

In **Chapter 4,** the association between adherence to prophylaxis and participation in sports was assessed. Data originating from a nationwide, cross-sectional, questionnaire-based cohort (HIN-6) study was analysed. Comparable to the findings from **Chapter 1,** the overall adherence was high (89%). Most participants (71%) were involved in sports (e.g. cycling, fitness, and soccer). Young children (<12 years) played significantly more sports (children: 93% vs. adults: 55%) and more high-risk sports (e.g. soccer) than adults (children: 67% vs. adults: 27%). Adherence scores were similar between those who did and did not play sports or high-risk.

Part 2: Flourishing

The second part focused on improving adherence in men with haemophilia who were prescribed prophylaxis. **Chapter 5** reports on a feasibility study that examined two tailored interventions, a face-to-face intervention for encouraging disease acceptance AYAs and an online intervention for encouraging disease self-management. The face-to-face group intervention was based on Acceptance and Commitment Therapy and consisted of eight 2-hour-long group sessions. The online intervention was based on a successful online self-management programme for rheumatoid arthritis and consisted of 5–8 modules. The face-to-face intervention was evaluated as being feasible. The preliminary results were promising, with adherence remaining stable and quality of life and illness

perception showing clinically relevant, significant improvements. However, the online intervention was infeasible due to inclusion and enrolment problems. Consequently, the online intervention was terminated.

In **Chapter 6,** the effectiveness of the face-to-face, tailored intervention was evaluated. A pre-post study with 12 months of follow-up was executed. The intervention consisted of eight 2-hour-long group sessions. A total of 24 patients (median age: 47 years, range: 27–74 years) participated. After 12 months, adherence improved in 68% of patients, quality of life improved in 48% of patients, and illness perception improved in 31% of patients. Based on our current experience, we have implemented the face-to-face intervention in clinical practice and have developed a collaboration with a patient association to make it available for all Dutch people with haemophilia.

The thesis ends with a **general discussion** that discusses the methods used to measure adherence in haemophilia and the interventions used to improve adherence. Based on the studies described in this thesis, in addition to other published literature, evidence-based recommendations for haemophilia professionals were formulated.

ADDENDUM

Nederlandse samenvatting

Dankwoord

Curriculum vitae

List of publications

NEDERLANDSE SAMENVATTING

Hemofilie is een zeldzame, aangeboren stollingsaandoening die voornamelijk voorkomt bij mannen. Door een tekort aan een stollingsfactor lopen mensen met hemofilie een verhoogd risico op bloedingen op. Dit kan zowel spontaan als na een trauma, zoals stoten of vallen, voorkomen in zowel gewrichten als spieren. Voor mensen met ernstige hemofilie (< 1% stollingsfactor) is een onderhoudsbehandeling met regelmatige intraveneuze behandeling met een stollingsfactor (profylaxe) nodig om bloedingen te voorkomen. Deze behandeling dienen patiënten zelf thuis toe door middel van intraveneuze (in het bloedvat) injecties. Een patiënt is therapietrouw zodra hij zijn medicatie toedient zoals afgesproken met de behandeld arts. In het geval van ernstige hemofilie betekent dit vaak drie keer per week, een hele ampul (1000IE=1ml) in de ochtend. We weten dat ongeveer 50-80% van de mensen met ernstige hemofilie het lukt de behandeling te nemen zoals afgesproken, ofwel therapietrouw zijn.

Dit proefschrift beoogt te ontrafelen waarom mannen met hemofilie met profylaxe niet therapieontrouw zijn en hoe wij dit kunnen verbeteren.

Deel 1: Ontrafelen

In het eerste gedeelte wordt ingegaan op het ontrafelen van beweegredenen om wel of niet therapietrouw te zijn bij mensen met hemofilie bij wie profylaxe is voorgeschreven. In **hoofdstuk 1** werd therapietrouw gekwantificeerd en werd de samenhang met de attitude (houding) ten aanzien van de behandeling of tevredenheid over de behandeling onderzocht bij kinderen, adolescenten en volwassenen. In dit hoofdstuk is gebruikgemaakt van data afkomstig uit een landelijke database (HIN-6) met vragenlijsten ingevuld door mensen met hemofilie. In totaal zijn data van 321 deelnemers geanalyseerd waarvan 61 kinderen (0-11 jaar), 29 adolescenten (12-18 jaar) en 231 volwassenen. Therapietrouw bleek hoog (89% therapietrouw), maar verslechterde over de leeftijdsgroepen heen. De attitude (houding) ten aanzien van de behandeling en tevredenheid over de behandeling was vergelijkbaar tussen mensen die therapietrouw dan wel therapieontrouw waren. Dit impliceerde dat patiënten die ontrouw zijn een actieve attitude hebben, dus potentieel een bewuste keus hierin maken.

In **hoofdstuk 2** werd het verband tussen therapietrouw, leeftijd en bloedingsfrequentie bij kinderen en adolescenten onderzocht. Dit onderzoek maakte gebruik van eerder verzamelde onderzoeksdata (retrospectief) aangevuld met data afkomstig uit elektronische dossiers van patiënten uit één behandelcentrum. In totaal werden data afkomstig van 62 kinderen en adolescenten gebruikt. Over het algemeen waren kinderen in deze studie zeer therapietrouw (95%). Uit de medische dossiers bleek dat er weinig bloedingen gerapporteerd waren. Jonge kinderen bleken therapietrouwer dan oudere kinderen. Er werd geen verband tussen therapietrouw en bloedingen gevonden.

In **hoofdstuk 3** is gekeken naar de onderliggende reden voor therapietrouw en therapieontrouw bij adolescenten en jongvolwassenen. Dit is onderzocht middels een kwalitatieve onderzoeksmethode ofwel groepsinterviews en individuele interviews. In totaal zijn 24 jongeren tussen de 14-24 jaar geïnterviewd. We zagen dat wanneer de ondersteuning van ouders afnam, en dus de eigen verantwoordelijkheid voor de behandeling toenam, therapietrouw afnam. Bij een toename van de eigen verantwoordelijkheid zagen wij dat jongeren potentiële risico's gingen afwegen. Hierbij keken ze naar het potentiële risico op een bloeding bij een bepaalde activiteit, hun wens om te doen wat ze graag wilden (deelname aan dagelijkse activiteiten) in combinatie met de wens om zichzelf veilig te voelen. Jongeren voelen zich veilig als ze geen bloeding doormaakten die hun dagelijkse leven beïnvloedde. Als er geen bloeding optrad na het vergeten of bewust overslaan van hun profylaxe, nam de behoefte aan het trouw nemen van de behandeling af en voelden de jongeren zich veilig zonder behandeling (therapieontrouw).

In **hoofdstuk 4** is gekeken naar het verband tussen therapietrouw en het beoefenen van sport bij kinderen, jongeren en volwassenen. In dit hoofdstuk is gebruikgemaakt van data afkomstig uit een landelijke database (HIN-6) met vragenlijsten ingevuld door mensen met hemofilie. Net zoals in hoofdstuk 1 (vergelijkbare database) was therapietrouw hoog (89%). De meeste deelnemers (71%) beoefenden een sport (bijv. fietsen, fitness, voetbal). Jonge kinderen (<12 jaar) beoefenden significant vaker een sport dan volwassenen (kinderen: 93% vs. volwassenen: 55%) en beoefenden vaker een risicosport zoals voetbal (kinderen: 67% vs. volwassenen: 27%). De therapietrouwscores waren vergelijkbaar tussen degenen die wel en niet (risicovolle) sporten beoefenden. Er bleek dus geen verband tussen therapietrouw en sport.

Deel 2: Laten opbloeien

In het tweede gedeelte wordt ingegaan op interventies ontwikkeld om therapietrouw te verbeteren bij mensen met hemofilie bij wie profylaxe is voorgeschreven.

In **hoofdstuk 5** werd een pilot- en haalbaarheidsstudie uitgevoerd naar twee op maat gemaakte interventies: 1) een fysieke groepstraining, en 2) een online interventie om therapietrouw te verbeteren. De fysieke groepstraining had als doel ziekteacceptatie en was gebaseerd op 'Acceptance and Commitment Therapy'. Deze training bestond uit acht groepsbijeenkomsten van elk twee uur. De online interventie had als doel om zelfmanagement te verbeteren en was gebaseerd op een succesvol online zelfmanagementprogramma voor reumatoïde artritis. Deze training bestond uit 5-8 modules. De groepstraining bleek haalbaar en toonde hoopvolle eerste resultaten: therapietrouw bleef onveranderd, maar de kwaliteit van leven en ziekteperceptie verbeterden (manier van omgaan met hemofilie). De online interventie bleek niet haalbaar in verband met onvoldoende animo. Om deze reden is de online interventie vroegtijdig beëindigd.

In **hoofdstuk 6** is de effectiviteit van de fysieke groepstraining geëvalueerd. Dit is gedaan door patiënten voorafgaand aan de trainingssessie, na afloop van de acht groepsbijeenkomsten en na twaalf maanden vragenlijsten in te laten vullen (pre-post test design). Deze training bestond uit acht groepsbijeenkomsten van elk twee uur. Vierentwintig patiënten tussen de 27 en 74 jaar volgden de training (mediane leeftijd van 47 jaar). Na twaalf maanden bleek therapietrouw bij 68% van de mensen, de kwaliteit van leven bij 48% en ziekteperceptie (manier van omgaan met hemofilie) bij 31% van de mensen verbeterd te zijn. Op basis van deze positieve resultaten is deze training ondertussen geïmplementeerd in de dagelijkse praktijk binnen de Van Creveldkliniek. Deze training is via de patiëntvereniging The Dutch Haemophilia Patient Society (NVHP) beschikbaar gesteld voor alle Nederlanders mannen met hemofilie.

Dit proefschrift eindigt met een algemene discussie. Hierin wordt, op basis van de ervaringen opgedaan in dit proefschrift, besproken hoe therapietrouw bij hemofilie kan worden gemeten en welke interventies om therapietrouw te verbeteren er nog meer beschikbaar zijn.

DANKWOORD

Een proefschrift schrijven lijkt een eenzaam proces, maar niets is minder waar. Dit proefschrift was niet mogelijk geweest met de hulp, steun en het vertrouwen van velen. Graag wil ik via dit dankwoord iedereen bedanken die een bijdrage heeft geleverd aan het tot stand komen van dit proefschrift.

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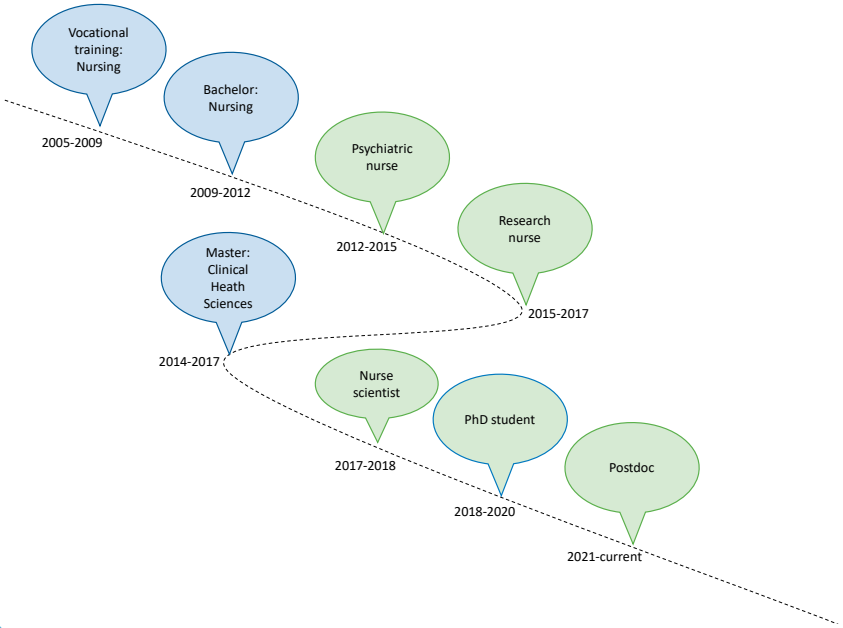
CURRICULUM VITAE

Johanna Wilhelmina (Anne) Hoefnagels was born on 14 December 1988 in Nijmegen. She was raised on a plant nursery. Anne graduated from high school (Montessori College Nijmegen) in 2005. She obtained her vocational nursing degree (ROC, Rijn IJssel, Arnhem) in 2009, and she completed her bachelor's nursing degree (University of Applied Science Utrecht) in 2012. After graduation, Anne volunteered as a nurse at the Kyotera Medical Centre, Uganda.

In 2012, she qualified for a traineeship at the psychiatric ward of the University Medical Centre Utrecht (UMCU), after which she continued to work in this ward as a general nurse (2013–2015). During her work as a nurse, she developed a growing interest in health innovations and research. In 2014, she entered the Master Clinical Health Sciences, Nursing Science program at the University of Utrecht. Anne began working as a research nurse at Medi-Flow Research (Harderwijk) in 2015. In 2016, she started an internship at the Van Creveldkliniek, UMCU. In 2017, she graduated and obtained her Master's degree in Clinical Health Sciences, Nursing Science and began work as a PhD student at the Van Creveldkliniek. In addition to this PhD position, she worked as a nurse and research nurse at the Van Creveldkliniek.

Starting January 2021, she began working as a postdoctoral researcher at the Wilhelmina Children's Hospital, Utrecht.



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