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Appendix

We scored the modifications of joints according to Melchiorre's US score (13) as follows:

1. Joint effusion: (absent = 0; small = 1; moderate = 2; large = 3).
2. Synovial hypertrophy with flags on PDUS (<3 flags = 1; >3 flags = 2).
3. Synovial hypertrophy without flags on PDUS: thickness measured in mm (score 1: <1.5 mm; score 2: 1.5–2.5 mm; score 3: >2.5 mm).
4. Fibrous septa: absent = 0; present = 1.
5. Haemosiderin deposition: it appears as a diffuse hyperechoic signal (absent = 0; small = 1; moderate = 2; large = 3).
6. Remodelling of bone: defined as joint surface irregularity and incongruence (absent = 0; present = 1).
7. Osteophytes: defined as marginal hypertrophic bone formation (absent = 0; present = 1).
8. Bone erosion: defined as a cortical 'break' with an irregular shape seen in the longitudinal or in the coronal plane (absent = 0; present = 1).
9. Cartilage damage: absent = 0; hyperechogenicity = 1; irregular profile = 2; calcification = 3.

Self-infusion of prophylaxis: evaluating the quality of its performance and time needed

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Prophylactic replacement therapy is the cornerstone of treatment in severe haemophilia. Regular infusions with clotting factor concentrate have been proven effective to prevent bleeding, subsequent (joint) damage, and positively affect the impact of haemophilia on daily life [1]. Patients or parents of younger patients learn to infuse clotting factor concentrate in a peripheral vein (i.v.) or a central venous access device (CVAD) [2].

As even a single bleed may cause irreversible damage, prophylaxis requires lifelong adherence and well-developed self-management skills [3]. The UKHCDO guidelines (United Kingdom Haemophilia Centre Doctors Organisation) described that competence in venous access technique as an important aspect of successful prophylaxis [4]. In the Netherlands, these skills are learned in an individualized training course with an average of eight sessions (IQR: 4–14 visits) [2]. After

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Table 1. Patient and treatment characteristics.*

	Total infusions (n = 161)
Number of assessments	
One	132
Two	13
Three or more	16
Age (median, IQR)	13.7 years (9.7–23.3)
Diagnosis	
Haemophilia A	135 (84%)
Haemophilia B	16 (10%)
von Willebrand disease	10 (6%)
Severity	
Severe haemophilia	146 (91%)
Moderate haemophilia	7 (4%)
Type III von Willebrand disease	8 (5%)
Route of administration	
i.v.	147 (91%)
CVAD	14 (9%)
Treatment	
Frequency prophylaxis (median, range)	3.0 (2–7)
Dose prophylaxis (median, range)	1000 (250–3000)

i.v., intravenous; CVAD, central venous access device.
Values are reported as frequencies or medians (interquartile range).
*26 patients were excluded from final analysis because they were engaged in learning self-infusion.

passing the exam, patients or parents are qualified to perform intravenous treatment independently [2,5]. There are no follow-up sessions and the quality of the procedure is never formally evaluated. In addition, many patients stated that they did not 'have enough time' to infuse in the morning [6], leading to non-adherence. However, the time needed for self-infusion has never been studied. The aim of this study was to quantify adherence to (self) infusion guidelines [5] as well as the time needed for prophylaxis in haemophilia.

This study comprised a cross-sectional observational study, which was embedded in the nursing consultation of three large Dutch Haemophilia Treatment Centres (Utrecht, Amsterdam and Rotterdam). Patients of all ages with a congenital clotting factor deficiency using prophylaxis with a minimum frequency of once weekly were eligible for inclusion. Convenience sampling was used: during outpatient clinic visits, patients were asked to administer their regular prophylaxis, while nurses observed the quality and duration of self-infusion procedure according to a checklist. The checklist was based on the Dutch guidelines for learning i.v. or CVAD infusion with a non-sterile (1 centre) and sterile approach (2 centres) [5]. Concomitantly, the time needed for self-infusion was recorded with a stopwatch and comprised the entire procedure from the start of preparation of the materials to completion of the infusion diary. Patient characteristics collected were: year and month of birth, the person performing the procedure (patient or parent), diagnosis (haemophilia A, B or von Willebrand type III), current treatment (prescribed frequency and dose), venous access route (i.v. or CVAD) and certification for (self-) infusion (present/ absent, including date).

Descriptive statistics were performed separately for i.v. and CVAD infusion. Due to the skewed distributions, the data was analysed using the Mann–Whitney U-test (significant at $P < 0.05$). All analyses were performed with SPSS® software, version 20 [IBM SPSS Statistics 20 (SPSS Inc., Chicago, IL, USA)].

Overall, 161 infusion procedures in 132 patients or parents were evaluated in the three centres (Utrecht n = 94, Amsterdam n = 57 and Rotterdam n = 10), comprising 48% of the total population on prophylaxis in these centres. Patient characteristics are presented in Table 1. Patients learning to self-infuse were excluded from analysis (n = 26), as infusion took significant longer (13:00 min, $P > 0.001$). For 31/ 161 procedures, only time assessment was performed. The patients had a median age of 13.7 years (Interquartile (IQR): 9.7-23.3). The majority of the patients were diagnosed with haemophilia A (84%), and the majority had severe haemophilia (91%). Most patients (47%) followed a prophylactic regimen of 3.0 times per week with 1000 IU per infusion.

Table 2. Evaluation of quality and timing of infusion procedures.

	i.v.		Central venous access device (CVAD)	
Activity	% Correct performance i.v. (n = 116*)	Median time i.v. (mm:ss/ n = 147)	% Correct performance CVAD (n = 14)	Median time CVAD (mm:ss/ n = 14)
Preparing materials	89	00:37	100	01:03
Washing hands	54†	00:40	69	00:42
Check product, date, dose	51	00:12	77	00:20
Dissolving product	100	02:15	100	03:05
i.v.: Correct injection of CFC	96	02:29	–	–
Failure of infusion	4			
CVAD: Non-sterile approach (n = 5)	–	–	100	02:00
Sterile approach (n = 8)			100	03:29
Safe disposal of needle	95	00:38	100	01:00
Complete infusion diary after infusion	40†	00:47	54	00:31
Total time (range)	–	06:40 (03:00–23:33)	–	11:07 (06:36–30:00)

i.v., intravenous; CVAD, central venous access device.
Values are proportions and medians (minutes: seconds).
*During 31 infusions, the checklist for self-infusion was not fully completed and excluded in this section.
†Parents performed this procedure significant more than the patients.

The mean experience with self-infusion was 4.9 years (range 0–25.6 years). The evaluation of the quality and timing of infusion procedures is shown in Table 2. Obtaining venous access and administrating CFC were performed correctly by all patients and parents with 96% succeeding at the first attempt. In contrast, only half the patients/ parents washed their hands before infusing and completed the infusion diary. For i.v. infusion, 147 procedures were performed by 85 patients and 49 parents in a median of 6.7 min (range 3–23.5 min). Most time was needed for the infusion procedure itself (min 2:29). Parents needed slightly longer for the procedure (median 8 min) than patients who performed self-infusion (median 6.5 min), yet, this difference did not reach statistical significance ($P = 0.23$). In total, 65% washed their hands according to procedure, including a higher proportion of parents (89%, $P = 0.001$) than patients (53%). Verifying the correct product, expiry date and correct dose before administration was not actively done by 47% of the patients and parents. In contrast, all performed the preparation of the clotting factor concentrate correctly. The majority of the patients and parents (95%) disposed the needle according to the protocol, yet, registration in the infusion diary after infusion was forgotten by majority of patients (60%). Parents completed the infusion diary significantly more often than patients (67% vs. 35%, $P = 0.001$). Patients who perform for a longer period self-infusion (≥40 years of age) were not more adherent to the infusion procedures than patients who recently started with self-infusion (13–25 years old).

For CVAD infusion, 14 infusions performed by 10 parents were evaluated. The median total time needed for CVAD infusion was 11.1 min (range 6.5–30 min). Before preparation of the materials, 69% of parents washed their hands and 77% checked the product name, date and dose. All parents dissolved the CFC correctly (3 min); this took slightly longer than for i.v. infusion, due to preparation of extra solvents (heparin, water). CVAD infusion according to the non-sterile approach ($n = 5$) took a median of 2 min and 3.5 min ($n = 8$), according to the sterile approach. All parents removed the needle and disposed it according to protocol. Registration of the infusion in a diary direct after the infusion was performed by 54%.

Some limitations of this study should be discussed. Convenience sampling led to selection of relatively younger patients (median 13.7 years), as young children visited the outpatient clinic more often than adult patients. In addition, the number of CVAD procedures assessed was limited ($n = 14$) due to practical reasons; CVAD infusion procedures usually required the assistance of two nurses (one observer and one holding the child), which was difficult to combine with the study assessment. All assessments were performed in the outpatient clinic and not in the home setting: blood sampling was sometimes required. Nurses tried to emphasize to perform the procedure just the same as at home and stopped the stopwatch during blood withdrawal.

These findings were compared to a Dutch study assessing the effect of an e-learning program on self-infusion by Mulders *et al.* [7]. This study reported equal proportions of diary keeping (40% in both studies), but higher rates of hand washing (75% vs. 45% in this study). After following the e-learning programme, performance significantly improved to 75% (increase of 27%). We hypothesize that regular check-ups of the quality of the infusion procedure, including reminders for washing hands and completing the infusion diary, could help to maintain the quality of the procedure. Patients did not actively check the product name, dose and date of expiry, before administration. Most patients check the whole batch after receiving this at the pharmacy. The time needed for the procedures was not studied before.

In conclusion, self-infusion of prophylaxis takes only a little time: a median of 6.7 min for i.v. infusion or 11.1 min for CVAD infusion. Adherence to the essential infusion activities (preparing and injection of CFC) were generally performed correctly. Washing hands was forgotten by 46% of the patients/parents and completion of the infusion diary was skipped by 60%. Therefore, standard follow-up every other year to check correct performance of self-infusion may improve these aspects of home treatment.

Disclosures

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PBAC score: an easy-to-use tool to predict coagulation disorders in women with idiopathic heavy menstrual bleeding

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Women with inherited bleeding disorders suffer significant morbidity and impaired quality-of-life associated with heavy menstrual-related bleeding [1]. Heavy menstrual bleeding (HMB), also referred to as menorrhagia, is defined as uterine bleeding that lasts for >7 days or blood loss >80 mL per menstrual cycle [2]. The wide variation in what constitutes 'normal' bleeding makes identifying patients with HMB difficult for both clinicians and patients [1]. Indeed some women, especially those from families with hereditary bleeding disorders, do not realize they have HMB so do not seek medical advice for their condition.

HMB is often a presenting symptom of coagulation disorders, and may be the only bleeding symptom [3]. An increased prevalence of von Willebrand disease (VWD) has been observed in women with HMB (13% [95% CI 11–16%] compared with 0.8–1.3% in the general population) [4] and it has been proposed that mild platelet function defects are even more common, with ~50% diagnosed with platelet aggregation defects compared with a control frequency of 17.3% [5].

A semi-objective method to quantify menstrual blood loss is the alkaline haematin technique, which requires the collection of all tampons or sanitary towels for laboratory analysis [6]. Although the most accurate method, it is too time-consuming and expensive for routine clinical practice. Alternatives include collecting and weighing all products used or the use of vaginal cups for menstrual collection; however, these methods can encounter problems with fluid evaporation and/or leakage. Another method is the pictorial blood assessment chart (PBAC) Score [7]. This method records the number of tampons or towels used and the degree to which they are stained with blood. A validation study found that the PBAC Score was superior to a woman's subjective assessment of menstrual blood loss, with a positive predictive value of 85.9% [8]. Additionally, a comparison of PBAC Score with the alkaline haematin method found a significant correlation between the two [9]. PBAC Scores >100 have been confirmed in the majority of women diagnosed with coagulopathic disorders [10].

We performed a retrospective analysis to assess whether the amount of menstrual blood loss, determined using the PBAC Score, can be used as a predictor for the presence of coagulation disorders in women with idiopathic HMB. All patients with a history of HMB referred to our coagulation centre between September 2011 and October 2013 were included. Known causes of gynaecological and endocrinological HMB had been ruled out by the patients' gynaecologists, and patients were not receiving any treatment that may have affected the PBAC Score, such as tranexamic acid, desmopressin or factor concentrate. Women without a history of HMB were recruited from among the patients' family, friends and associates as a control group; patients were not age-matched, but were similar in age. None of the participants were on oral contraceptives. Informed consent

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