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ORIGINAL ARTICLE

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Peri-operative desmopressin combined with pharmacokinetic-guided factor VIII concentrate in non-severe haemophilia A patients

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Abstract

Introduction: Non-severe haemophilia A patient can be treated with desmopressin or factor VIII (FVIII) concentrate. Combining both may reduce factor consumption, but its feasibility and safety has never been investigated.

Aim: We assessed the feasibility and safety of combination treatment in nonsevere haemophilia A patients.

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Methods: Non-severe, desmopressin responsive, haemophilia A patients were included in one of two studies investigating peri-operative combination treatment. In the single-arm DAVID study intravenous desmopressin (0.3 μg/kg) once-a-day was, after sampling, immediately followed by PK-guided FVIII concentrate, for maximally three consecutive days. The Little DAVID study was a randomized trial in patients undergoing a minor medical procedure, whom received either PK-guided combination treatment (intervention arm) or PK-guided FVIII concentrate only (standard arm) up to 2 days. Dose predictions were considered accurate if the absolute difference between predicted and measured FVIII:C was ≤0.2 IU/mL.

Results: In total 32 patients (33 procedures) were included. In the DAVID study (n = 21), of the FVIII:C trough levels 73.7% (14/19) were predicted accurately on day 1 (D1), 76.5% (13/17) on D2. On D0, 61.9% (13/21) of peak FVIII:C levels predictions were accurate. In the Little DAVID study (n = 12), on D0 83.3% (5/6) FVIII:C peak levels for both study arms were predicted accurately. Combination treatment reduced preoperative FVIII concentrate use by 47% versus FVIII monotherapy. Desmopressin side effects were mild and transient. Two bleeds occurred, both despite FVIII:C > 1.00 IU/mL.

Conclusion: Peri-operative combination treatment with desmopressin and PK-guided FVIII concentrate dosing in nonsevere haemophilia A is feasible, safe and reduces FVIII consumption.

KEYWORDS
combination treatment, desmopressin, FVIII concentrate, haemophilia, pharmacokinetic, treatment

1 | INTRODUCTION

Haemophilia A is an inherited X-linked bleeding disorder characterized by a deficiency of factor VIII (FVIII).[1] Nonsevere haemophilia A patients (FVIII:C ≥ .01–.40 IU/mL) mainly suffer from bleeding complications after trauma or surgery. In order to prevent bleeding peri-operatively, anonsevere haemophilia A patient can be treated with desmopressin or factor VIII (FVIII) concentrate. Desmopressin increases FVIII:C plasma levels by releasing von Willebrand factor (VWF) and FVIII from extrahepatic endothelial cells.[2–5] If FVIII:C response is sufficient, minor medical procedures can be performed with desmopressin only. However, the FVIII:C response to desmopressin varies strongly from patient to patient, and is often considered insufficient. In such cases, patients are treated with FVIII concentrate. Additionally, desmopressin's use is suboptimal in many patients who have an adequate FVIII:C response.[6]

Both desmopressin and FVIII concentrates have certain drawbacks. In haemophilia A patients exposure to FVIII concentrate is associated with the risk of developing FVIII inhibitors, thereby increasing the risk of morbidity and mortality.[7–9] On the other hand, desmopressin is associated with vasoactive side effects. These are generally mild and transient, such as flushing. Rarely, severe side effects occur, such as hyponatremia, which is usually preventable by restriction of fluid intake.[10] Importantly, repeated administration of desmopressin over short periods of time (12–24 hours) leads to a reduced response (tachyphylaxis).[11]

Both desmopressin and FVIII concentrate are treatments with high interpatient variability in FVIII:C response.[11,12] Recent studies have shown that FVIII concentrate dosing based on body weight leads to postoperative FVIII:C trough levels above and below target ranges in a large proportion of patients.[13,14] This is clinically relevant as levels below targeted peak or trough level increase bleeding risk and levels above targeted peak levels might increase the risk of thrombosis.[15–17] Consequently, population pharmacokinetic (PK) models of both FVIII concentrate and desmopressin treatment have been developed to optimize dosing.[12,18–20] These models can be applied to personalize haemostatic treatment peri-operatively.[20]

The 2020 World Federation of Haemophilia (WFH) guideline stated that the downsides associated with exclusive use of only desmopressin or FVIII concentrate can be overcome by combination treatment using both desmopressin and FVIII concentrate.[21] Since desmopressin is less expensive than FVIII concentrate, is available in many parts of the world, and is on the WHO Essential Medicines List, combination treatment may lead to considerable FVIII concentrate savings and is useful when FVIII concentrate resources are limited. However, no studies on personalized combination treatment have been performed. Therefore,

we initiated two studies in nonsevere haemophilia patients applying peri-operative desmopressin followed by PK-guided FVIII concentrate dosing to evaluate the feasibility, predictive performance and safety of this combination treatment.

2 | MATERIALS AND METHODS

2.1 | Study description and primary study endpoints

2.1.1 | DAVID study

The DAVID study was designed as an observational multicentre single-arm study to assess the feasibility, safety and predictive performance of combination treatment peri-operatively in nonsevere haemophilia A patients, focusing on major surgical procedures. The DAVID study protocol has been published before.[22] In short, combination treatment consisted of intravenous desmopressin (0.3 μg/kg body weight with no capped dose), immediately after full desmopressin administration and blood sampling followed by a PK-guided dose of FVIII concentrate preoperatively (D0) and possibly postoperatively, with a maximum of three consecutive days combination treatment. If needed, patients were treated with FVIII monotherapy from day 3 onwards, with a possibility of combination treatment between days 6–8 as well. The use of peri-operative antifibrinolytics such as tranexamic acid was allowed. A general fluid restriction of 1.5 L for 24 hours was applied after desmopressin administration. The primary study endpoint was the proportion of patients with measured FVIII:C levels within the physician's target FVIII:C trough range in the 72 hours of combination treatment, without the need for additional FVIII concentrate. To assess the effect of combination treatment on the FVIII concentrate consumption a hypothetical preoperative dose of FVIII concentrate was calculated for each individual, assuming an increase of 0.02 IU/mL per IU of FVIII concentrate per kilogram body weight, as is used in standard care. An example of how combination treatment would be performed in the DAVID study is illustrated in Figure 1.

2.1.2 | Little DAVID study

The Little DAVID study was designed as a randomized clinical trial to compare feasibility, predictive performance and safety of combination treatment with standard treatment in peri-operative nonsevere haemophilia A patient undergoing minor medical procedures. Standard treatment with PK-guided FVIII concentrate (standard arm) was compared to combination treatment of intravenous desmopressin (0.3 ug/kg body weight with no capped dose), immediately after full desmopressin administration and blood sampling followed by a PK-guided FVIII concentrate (intervention arm). The Trans European Network for Clinical Trials Services (TENALEA), a web-based randomization system, was used to randomize patients (1:1), stratified according to centre, severity of disease (mild or moderate), age (<18 years or ≥18 years)

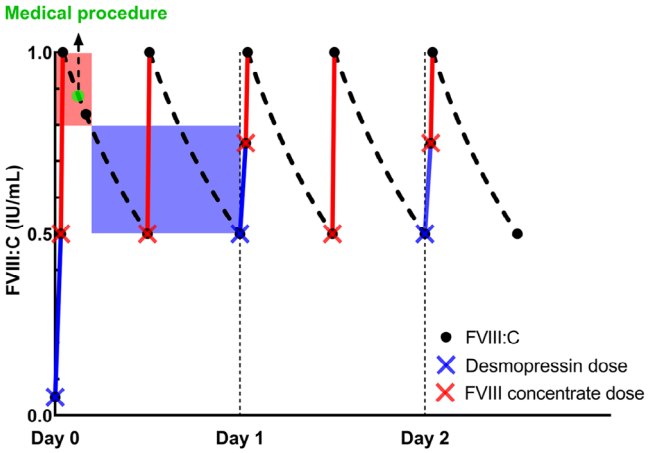

FIGURE 1 Example of combination treatment in a DAVID study patient.

and bleeding risk of the procedure (low or medium bleeding risk, see Supplementary appendix 1). The use of peri-operative antifibrinolytics such as tranexamic acid was allowed. A general fluid restriction of 1.5 L for 24 h was applied after desmopressin administration. The primary endpoints were the accuracy of predicted FVIII:C (see Supplementary appendix 2) and FVIII concentrate consumption in U/kg.

2.2 | Secondary endpoints

Secondary endpoints for both studies were predictive performance of the PK-model by the Bayesian approach for measured FVIII:C (see below for definition), bleeding during D0-13, other adverse events during D0-13, the need for off-protocol FVIII concentrate, patient reported experienced quality of care (haemophilia care and peri-operative care in general on a scale of 0–10), and inhibitor development.

2.3 | Patient inclusion

Patients of 12 years and older with nonsevere haemophilia A (FVIII:C 0.01–.40 IU/mL) who were planned to undergo a (minor) medical procedure were included in either the DAVID or Little DAVID study, depending on the expected duration of treatment. All patients needing a procedure requiring ≥48 hours of FVIII concentrate administration were included in the DAVID study (major medical procedure). Patients who were expected to require <48 h of FVIII concentrate administration were included in the Little DAVID study (minor medical procedure).

Patients were recruited from a Dutch haemophilia treatment centre (Rotterdam, Groningen, Eindhoven, Nijmegen, Utrecht, Leiden, Amsterdam and Maastricht) for the DAVID study and five haemophilia treatment centres (Rotterdam, Nijmegen, Groningen, Maastricht) for the Little DAVID study.

Exclusion criteria were: not responsive to desmopressin (<0.2 IU/mL absolute FVIII:C increase one hour after desmopressin administration in the past), clinically significant FVIII inhibitors (>0.5 Bethesda units), contra-indications for desmopressin or interacting co-medication (see Supplementary appendix 3 for the applied list of both), or intolerance to desmopressin (Figure 2). Both the DAVID and Little DAVID studies were approved by the local Medical Ethics Committee of the Erasmus University Medical Centre Rotterdam (MEC-2015-751 and MEC-2016-726) and by the boards of all participating hospitals and were registered at the Netherlands Trial Register (NTR5383 and NTR6036). Patients were included from 27th February 2017 to 31st December 2020 for the DAVID study and from 27th January 2018 to 31st December 2020 for the Little DAVID study.

2.4 | Study procedures and definitions

In the patients receiving combination treatment first desmopressin was administered in a dose of 0.3 μg/kg body weight intravenously followed by PK-guided FVIII concentrate administration. FVIII:C was measured before and after desmopressin and FVIII concentrate administrations, see 'Sampling and assays' for more details. For predictive performance, a predicted FVIII:C was considered accurate if difference between measured and predicted FVIII:C was ≤0.2 IU/mL.

As combination treatment may be more demanding for patients, patient experiences with regard to perceived quality of care were studied using a questionnaire, rating experienced haemophilia care on a scale ranging from 0−10 (worst to best) (Supplementary Appendix 4).

Side effects were studied using a previously developed questionnaire before and after combination treatment.[10] All patients were followed up for 90 days to assess the occurrence of inhibitors, bleeding or thromboembolic events according to protocol.[22] Procedures were classified in bleeding risk categories, that is, low, intermediate and high, based on the ACCP guideline for antithrombotic therapy.[23]

2.5 | Pharmacokinetic-guided dosing of FVIII concentrate by Bayesian forecasting, targeting physician set FVIII:C range

Bayesian forecasting of FVIII:C after dosing desmopressin and FVIII concentrate was performed in NONMEM software (version 7.3, (ICON Development Solutions, Ellicott City, MD, United States). Population PK models were previously developed by our group and available for both desmopressin and FVIII concentrate.[12,22] For the used PK model, the PK profiles of FVIII:C after intravenous administration of desmopressin and FVIII concentrate were used in both studies. The PK model of desmopressin was used to calculate the clearance of the desmopressin induced FVIII:C response, which was taken into account for the PK-guided dose of FVIII concentrate. If the FVIII:C response after previous FVIII concentrate administration(s) was available, these responses were used to calculate individual PK parameters to obtain the preoperative dose of FVIII concentrate. The individual PK parameters were iteratively updated based on measured FVIII:C and doses were adjusted accordingly. If FVIII:C response was unavailable, mean population PK parameters were used.

For each included study participant, the treating physician was asked to specify the physician's desired preoperative peak FVIII:C range or level on the day of surgery (day 0; D0), and the physician's desired postoperative target trough FVIII:C ranges or levels one day (day 1; D1), 2 days (day 2; D2) and 3 days (day 3; D3) after surgery, if applicable. These targets were based on the national haemophilia treatment guideline, which is based on literature and the international (WFH) guideline.[24] The dose of FVIII concentrate (in IU) for D1 and D2 was calculated based on the PK model and the measured peri-operative FVIII:C on D0. With respect to anticipated desmopressin tachyphylaxis, the first five patients were modelled with 30% decrease in FVIII:C response, based on earlier studies.[11] Since the observed tachyphylaxis of these five patients was approximately 50%, an anticipated 50% decrease of FVIII:C response was used for the following patients for the second and (if applicable) third desmopressin administration.

2.6 | Sampling and assays

To measure FVIII:C, blood was drawn before and fifteen minutes after every desmopressin infusion, after FVIII concentrate administration following desmopressin, and immediately after surgery. FVIII:C trough levels were also measured prior to desmopressin administration on D1 and D2 in the DAVID study. Sodium was measured before each desmopressin administration. FVIII:C were measured using a one-stage assay. FVIII inhibitor testing was performed levels according to the Nijmegen modification of the Bethesda assays.

2.7 | Statistical analysis

Categorical and ordinal data are presented as frequencies and proportions. Categorical and ordinal data between multiple groups were compared using a Chi-squared (cell count >5) or Fisher exact test (cell count ≤5). Paired ordinal data (e.g. side effects before and after combination treatment) were compared using Wilcoxon signed rank test. Continuous data are presented as median and interquartile range. Continuous variables between 2 groups were compared by using Wilcoxon signed rank test with $\alpha = 0.05$ for statistical significance and Bonferroni correction for multiple testing. Continuous variables between three or more groups were compared by using a Friedman test. In order to assess the efficacy for the DAVID study of combination treatment in comparison to historical data[13] (proportion of 0.31 based on post-operative FVIII:C levels) with a power of 90% and alpha of 0.05, 25 procedures were needed. Noninferiority of the accuracy of the predicted peak range between both Little DAVID study arms was assessed by studying the difference of the deviation per arm as defined and explained in Supplementary 2. In order to assess noninferiority with a power of 80% and alpha of 0.05, 68 procedures were needed. All statistical analyses were performed in IBM Statistics SPSS v25.

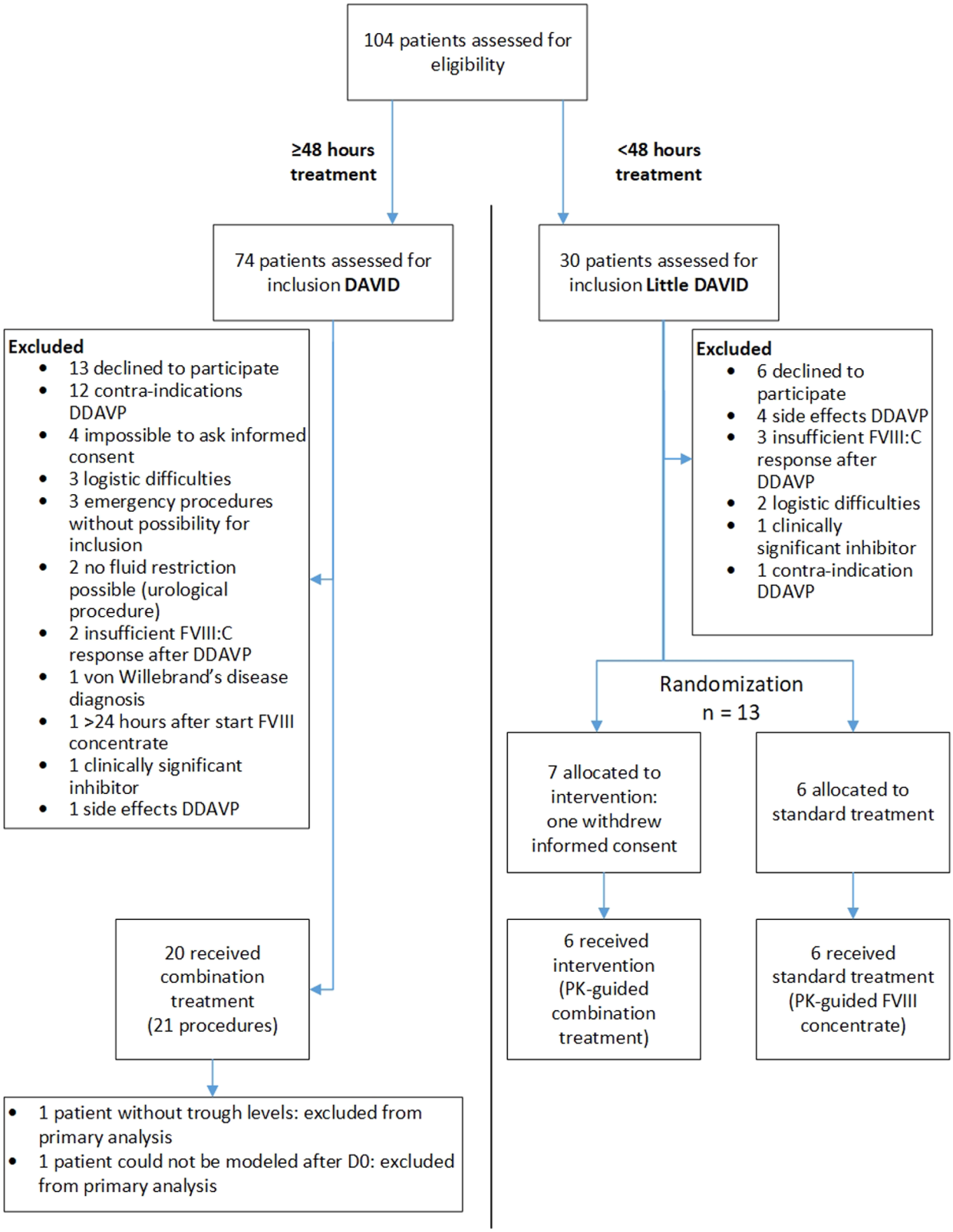

FIGURE 2 Inclusions in DAVID and Little DAVID study.

3 | RESULTS

3.1 | Patients and medical procedures

In total 32 patients underwent 33 medical procedures in the DAVID studies. Unfortunately, both studies were stopped before inclusion was complete. The main reasons for a lower inclusion rate than anticipated were that the COVID-19 pandemic resulted in a reduced number of procedures and that some patients preferred standard treatment over study participation.

3.1.1 | DAVID study

Twenty-one procedures were performed in 20 haemophilia A patients, of whom 19 had mild and one moderate haemophilia A. Two patients had received desmopressin 36–48 hours before the procedure, which was taken into consideration with PK modelling. One patient was excluded at D1 because of logistic issues. For the analysis of the primary endpoint, two procedures were excluded due to the cessation of the study participation and additional factors concentrate treatment because of bleeding postoperatively. Four patients had received continuous factor VIII concentrate administration, of whom three also received a bolus loading dose of FVIII concentrate at D0.

3.1.2 | Little DAVID study

Thirteen patients were included, six in the standard arm (FVIII concentrate only) and seven in the intervention arm (combination treatment). One patient (intervention arm) withdrew consent after randomization, did not receive study treatment and was not included in study analysis. One patient in the standard arm used off-protocol intranasal desmopressin the evening after the procedure and after peak FVIII:C levels were measured (D0). Inclusion for both studies is shown in Figure 2. Patient and procedure characteristics of both studies are described in Table 1.

3.2 | Measured FVIII:C compared to physician's FVIII:C target range

3.2.1 | DAVID study

Of the 19 procedures included in the primary endpoint analysis (FVIII:C levels within target in the first 72 h), 31.5% (6/19) of all measured trough levels (D1, D2 and D3) per procedure were within or equal to the physician's target trough level. Of all measured trough levels after combination treatment, 42% (8/19), 47% (8/17) and 63% (5/8) were in target on D1, D2 and D3, respectively. Of the trough FVIII:C not in target on D1, 27% (3/11) were lower than physician's target with absolute deviations of 0.03 IU/mL, 0.05 IU/mL, 0.09 IU/mL. The other 73% (8/11) trough FVIII:C not in target on D1 were above the physician's target level but with a FVIII:C lower than 1.3 IU/mL and a maximum absolute deviation of 0.26 IU/mL. On D2 and D3 all trough FVIII:C not in target were above the physician's target level but with a FVIII:C lower than 1.15 IU/mL and a maximum absolute deviation of 0.34 IU/mL. On D0 all measured peak levels were within (12/21, 57%) or above (9/21, 43%) the physician's target FVIII:C.

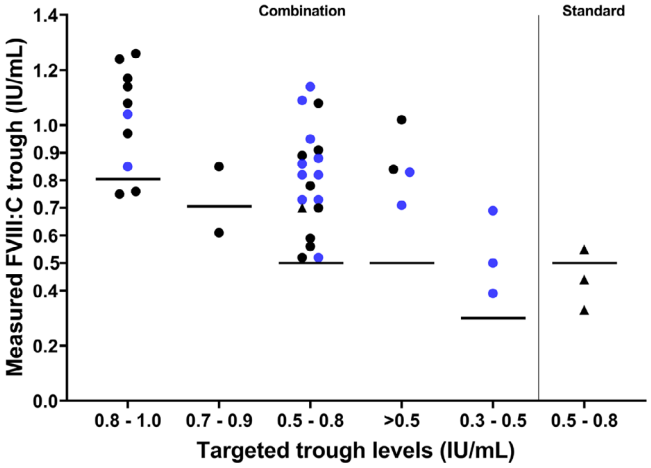

FIGURE 3 Measured trough FVIII:C (IU/mL) in relation to physician's FVIII trough target range (IU/mL) after combination treatment (DAVID study, circles; Little DAVID study, triangles) and standard treatment (Little DAVID, triangles) on D1 (black) and D2 (blue). The lower limit of FVIII target ranges is marked by a black line. For patients who received combination treatment, eight patients on D1 and two on D2 had a FVIII:C target trough range of .8–1.0 IU/mL, two patients on D1 a FVIII:C target trough range .7–.9 IU/mL, eight patients on D1 and ten on D2 a FVIII:C target trough range of .5–.8 IU/mL, two patients on D1 and two on D2 a FVIII:C target trough level > .5 IU/mL and three patients on D2 a FVIII:C target trough range of .3–.5 IU/mL. For patients who received standard treatment, three patients on D1 had a FVIII:C target trough level between .5–.8 IU/mL.

3.2.2 | Little DAVID study

In the standard arm all (6/6) of the measured D0 peak levels were above the physician's target range. In the intervention arm using combination treatment, all measured D0 peak levels were within (2/6, 33%) or above (4/6, 66%) physician's target range.

The comparison between measured and physician's target FVIII:C is visualized in Figures 3 and 4.

3.3 | Predictive performance of the Bayesian approach of the PK-model

In addition to the aforementioned physician's target levels, we also assessed the accuracy of the PK model predictions, comparing predicted FVIII:C to measured FVIII:C.

TABLE 1 Patient and medical procedure characteristics of DAVID and Little DAVID study.

DAVID		Little DAVID	
		Number (%)/median [IQR]	
Characteristic ($n = 20$)	Number (%)/median [IQR]	Standard ($n = 6$)	Intervention ($n = 6$)
Hemophilia severity			
Mild	19 (95%)	5 (83.3%)	6 (100%)
Moderate	1 (5%)	1 (16.7%)	0
Lowest FVIII:C measured (IU/mL)	0.16 [0.08–.21]	.11 [0.08–0.14]	.12 [0.06–.19]
Age at procedure (years)	47 [38–59][a]	32 [23.3–54.8]	59.5 [46.3–63.5]
Weight at procedure (kg)	80 [76.35–93.1][a]	83 [72.5–95.1]	80 [70.9–95.0]
Time between desmopressin test and inclusion (years)	3 [0–11][a]	1 [0–10]	4.5 [1.5–13.3]
Consecutive days of combination treatment			
One	2 (9.5%)	–	5 (83.3%)
Two	6 (28.6%)[a]	–	1 (16.7%)
Three	13 (61.9%)	–	–
Mode of FVIII concentrate administration			
Bolus	17 (81%)	6 (100%)	6 (100%)
Continuous	4 (19%)[a]	–	–
Type of medical procedure			
Orthopedic	6[a] (28.6%)	–	–
Oromaxillary/dental	6[a] (28.6%)	5 (83.3%)	2 (33.3%)
Urological	4 (19%)	–	–
Biopsy/excision	3 (14.3%)	1 (16.7%)	2 (33.3%)
Endoscopy	1 (4.8%)	–	1 (16.7%)
Lumbar puncture	–	–	1 (16.7%)
Laparoscopic colectomy	1 (4.8%)	–	–
Bleeding risk of procedure			
High	14 (66.7%)[a]	–	–
Intermediate	6 (28.6%)	2 (33.3%)	3 (50%)
Low	1 (4.8%)[a]	4 (66.7%)	3 (50%)

[a]One patient had undergone two procedures.

3.3.1 | DAVID study

The Bayesian predictions were accurate for preoperative peak levels at D0 in 61.9% (13/21), accurate for trough levels at D1 in 73.7% (14/19) and at D2 in 76.5% (13/17). For ten procedures, FVIII:C levels after previous FVIII concentrate administration were available for calculation of the PK-guided FVIII concentrate dose. For these patients with previous FVIII:C pharmacokinetic data, 59.3% (16/27) levels were on target versus 76.7% (23/30) in patients without these data (n.s.).

3.3.2 | Little DAVID study

The Bayesian predictions were accurate for preoperative peak levels at D0 in 83.3% (5/6) in the standard arm and in 83.3% (5/6) in the intervention arm. The two inaccurate predictions gave higher measured FVIII:C levels. Due to the low number of included patients, it was not possible to test for noninferiority (Supplementary appendix 2). Figures 5 and 6 show model accuracy for both studies concerning preoperative peak and postoperative trough levels after combination treatment or standard treatment with FVIII concentrate.

3.4 | Factor VIII concentrate consumption

3.4.1 | DAVID study

After administration of desmopressin a median dose of 2000 IU FVIII concentrate (IQR 1500–3125 IU) was infused to reach the target FVIII:C on D0. This is significantly less (39%; $p < .001$) than the calculated median FVIII concentrate dose of 3250 IU (IQR 3250–4000)

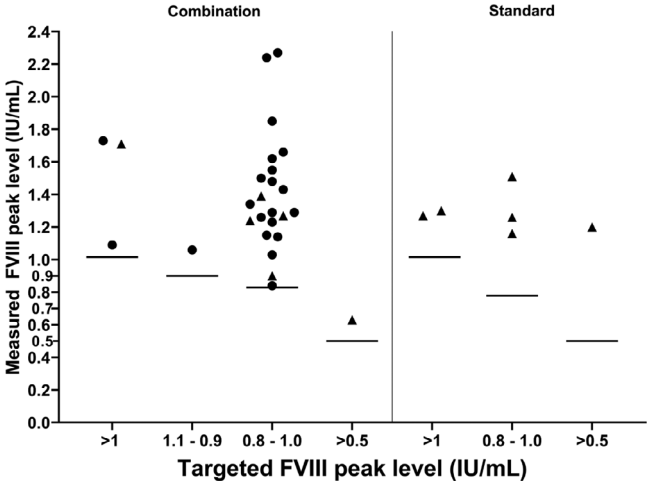

FIGURE 4 Measured peak FVIII:C (IU/mL) in relation to the physician's target peak FVIII:C (IU/mL) at D0 of patients who received combination treatment (DAVID study (circles) and Little DAVID study (triangles)) and standard treatment (Little DAVID only, triangles). The black line signifies the lower limit of the physician's target range.

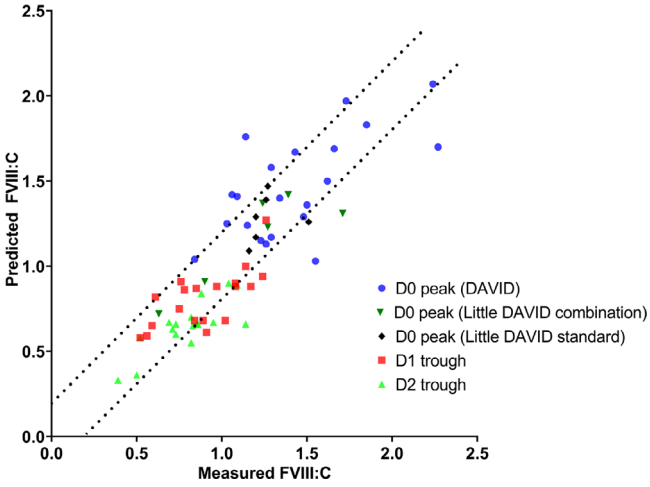

FIGURE 5 Comparison of measured FVIII:C (IU/mL) and predicted peak and trough FVIII:C (IU/mL) in all patients (DAVID and Little DAVID study) with combination treatment or standard treatment. Dotted lines signify ±.2 IU/mL. One patient received only desmopressin before the procedure.

which would have been given as bolus infusion with FVIII concentrate based on body weight. Because of the achieved high desmopressin response, one patient only received desmopressin preoperatively without the need of additional FVIII concentrate.

3.4.2 | Little DAVID study

In the standard arm median PK-guided preoperative dose of FVIII concentrate on D0 was 3750 IU (IQR 3500–4000 IU; 44.23 IU/kg; IQR 37.2–53.3 IU/kg) versus 1750 IU (IQR 1500–2500 IU; 21.46 IU/kg; IQR 18.75–27.3 IU/kg) following desmopressin administration in the intervention arm resulting in a significant reduction of FVIII concentrate consumption (47%; $p = 0.009$).

3.5 | (Serious) adverse events

In total, three bleeding events occurred in both studies. In the DAVID study, two patients suffered a bleeding event. Both patients had a high (>1.00 IU/mL) FVIII:C at the time of bleeding. In the Little DAVID study, one patient in the standard arm suffered a bleeding event 6 days after dental procedure. Details of these patients are given in Supplementary appendix 5.

In total, testing for inhibitor formation was performed within 3 months after treatment in 26/32 (81%) of the procedures. One patient included in the DAVID study developed an inhibitor against FVIII (6.8 Bethesda units). This changed his phenotype from mild to severe (<0.01 IU/mL FVIII:C). The *F8* mutation of this patient was c.6956C > T p. Pro2319Leu on exon 26 (C2 domain), is known to be associated with an increased risk for inhibitor formation.[25] The procedure performed was the resection of a neck cyst without any postoperative complications. In addition, in three patients inhibitor testing occurred later than three months and no inhibitor was found. No thromboembolic events were reported.

3.6 | Side effects

For patients with combination treatment, the median sodium level was 141 mmol/L (IQR 140–142) on D0 (n = 25), 139 mmol/L (IQR 137–141) on D1 (n = 19) and 140 mmol/L (IQR 136–141) on D2 (n = 16; p = 0.037). Three patients had mild asymptomatic hyponatremia on day 2, of whom two a sodium level of 133 mmol/L and one 131 mmol/L, none had symptomatic hyponatremia. Flushing was reported by 76% of patients (n = 21) after desmopressin and by none (n = 6) after treatment with FVIII concentrate only. All reported symptoms were mild and transient. No significant difference in side effects was found in the Little DAVID between the standard and intervention arm.

3.7 | Experienced quality of care of combination treatment

3.7.1 | DAVID study

Fourteen patients rated the experienced combination treatment with a median score of 10 [IQR 8.9–10]. Six of these patients previously underwent a surgical procedure with standard FVIII concentrate treatment, of whom four preferred combination treatment above standard treatment. One patient preferred standard treatment above combination treatment because of the side effects of desmopressin and one patient had no preference.

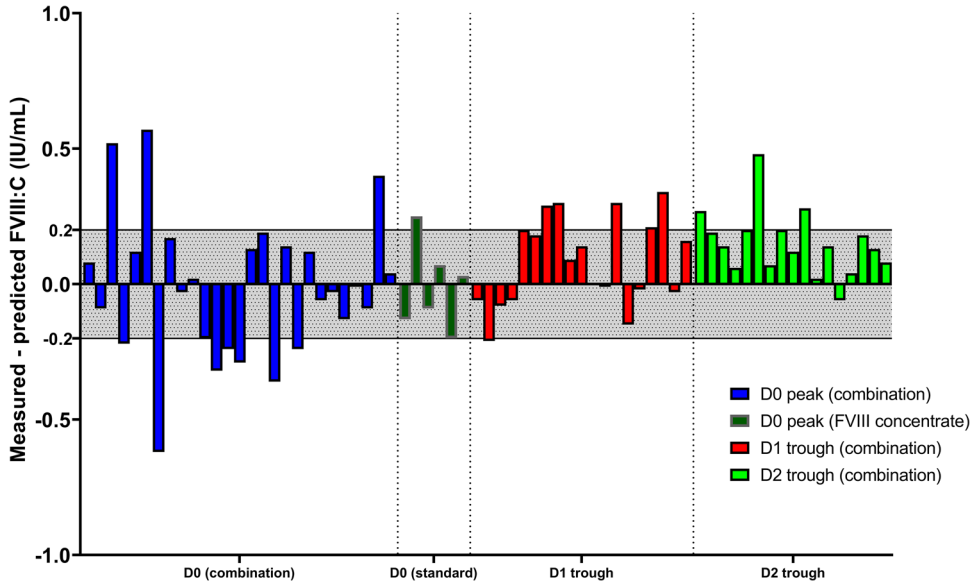

FIGURE 6 Comparison of the absolute difference (delta) of measured FVIII:C (IU/mL) and predicted peak and trough FVIII:C (IU/mL) in patients who received combination treatment (DAVID study and Little DAVID study, $n = 27$) or standard treatment (Little DAVID study, $n = 6$). Each box represents one patient. The grey-arced background signifies ±.2 IU/mL. One patient only received desmopressin at D0.

3.7.2 | Little DAVID study

Six patients in the standard arm and five in the combination treatment arm rated the procedure with a median score of 9.5 [IQR 8–10] in the standard arm and median score of 9 [IQR 8.3–10] in the combination treatment arm (n.s.). For the experienced care in general, six in the standard arm scored 9.4 [IQR 8–10] and five in the combination arm 9 [IQR 8.5–10] (n.s.).

4 | DISCUSSION

The DAVID and Little DAVID studies are the first studies on the peri-operative use of combination treatment of desmopressin immediately followed by FVIII concentrate in nonsevere haemophilia A patients. Combination treatment turned out to be feasible and safe, with mild and transient side effects of desmopressin and resulted in a reduction of FVIII concentrate in comparison with PK-guided FVIII concentrate monotherapy. By using a PK-guided approach for both desmopressin administration and FVIII concentrate we were able to personalize treatment with a high predictive performance of the model.

In a previous retrospective study in nonsevere haemophilia A patients treated with FVIII concentrate we have shown that only 12% of peri-operative measurements of FVIII:C levels were within the physician's target range.[13] In the DAVID study, combination treatment resulted in a higher proportion of FVIII:C levels (31.5%) in the targeted range. In both DAVID studies, almost half of the peak (D0) and trough (D1, D2, D3) FVIII:C measurements were above the targeted level (48%) and only 10% of all trough FVIII:C measurements were below the targeted level with a limited absolute deviation (<0.10 IU/mL).

In our two studies FVIII concentrate savings were evident using combination treatment due to the achieved increase in FVIII:C after desmopressin, thereby reducing the required dose of FVIII concentrate compared to monotherapy FVIII to reach target FVIII levels. Another possible FVIII concentrate saving strategy may be PK-guided dosing instead of body weight dosing. This was studied by our group in a recent randomized study (OPTI-CLOT trial) on peri-operative management of patients with moderate and severe haemophilia A. The study showed that FVIII concentrate consumption was comparable between both arms.[20] This suggests that the savings in FVIII concentrate using combination treatment with desmopressin followed by PK-guided FVIII concentrate in our studies is mainly due to the use of desmopressin, rather than PK-guidance.

Implementation of combination treatment can be facilitated for patients and clinicians by administering desmopressin subcutaneously instead of intravenously and by limiting the number of measurements to only a peak FVIII:C after the administration of combination treatment. In practice, the most savings are expected for the preoperative FVIII dose, as illustrated by the Little DAVID study.

The Bayesian predictions for FVIII:C by the population PK model after combination treatment were accurate in the majority of cases (75%) for D1 and D2 trough levels in the DAVID study and in 83.3% of the peak levels in the Little DAVID study. We hypothesized that available PK data of previous FVIII concentrate administration in an individual patient could influence the accuracy of the predicted FVIII:C levels. As only 50% of included patients had prior measurements of FVIII:C levels after administrations of FVIII concentrate, statistical power was lacking to ascertain the effects of PK data on FVIII concentrate administrations on model predictions. Also, concerning PK model predictions for D0 peak levels, multiple factors influence prediction accuracy. The majority of patients was dosed using bolus

administration. As a result, in the case of treatment with bolus twice daily a higher than the physician's requested target peak FVIII:C level was necessary in order to achieve an adequate trough FVIII:C. This explains the difference in the accuracy of the predictive performance of this treatment strategy compared to the proportion of patients with FVIII levels within the physician's target range. Therefore, in the case of body weight dosing, a more on target peak level could have been more difficult to achieve. Moreover, previous studies on peri-operative PK-guided FVIII concentrate treatment showed that surgery and increased von Willebrand factor (VWF) levels were associated with a decreased postoperative FVIII clearance.[19] In contrast, a trend towards a small increase of FVIII clearance ($p = 0.07$) was found in four severe haemophilia A patients who received desmopressin followed by a bolus of FVIII concentrate.[26] In nonsevere haemophilia patients, as in the present DAVID studies, the release of endogenous FVIII and VWF by surgery—a major physical stress factor—may influence levels postsurgery the most.

Side effects of combination treatment, associated with the use of desmopressin, were mild and transient. Stoof et al. reported earlier on side effects after desmopressin, where flushing was also observed after desmopressin administration.[10] Additionally, 5% (4/108) of the patients had a mild hyponatremia 24 hours after one dose, whereas in our study mild hyponatremia only occurred after multiple doses and was asymptomatic.

The experienced quality of care of combination treatment was very rated high, even up to the maximum score, despite the additional time and blood draws in our study in comparison to standard treatment. In comparison, other studies have reported a moderate to high treatment satisfaction in haemophilia A patients with FVIII concentrate prophylaxis and/or treatment.[27,28]

Our studies had some limitations. The most important limitation is that we did not reach our desired number of included patients, since inclusion was hampered by patients preferring standard treatment and the COVID-19 pandemic, as less elective procedures were performed. As a result, the assessment of noninferiority of PK-guided combination treatment versus PK-guided standard FVIII concentrate treatment in the Little DAVID study was inconclusive. In addition, as the DAVID trial was not a randomized clinical trial, we could not assess whether PK-guided dosing or combination treatment lead to more accurate physician's target FVIII:C levels than standard treatment. Strengths of our study were the safety assessment and the savings achieved for the preoperative FVIII dose, regardless of the procedure or base FVIII:C. Furthermore, the feasibility of our study was also shown by the accuracy of combination treatment, despite the heterogeneity of our study population, reflecting the daily practice of haemophilia care.

5 | CONCLUSION

Peri-operative PK guided combination treatment of desmopressin and FVIII concentrate in nonsevere haemophilia A is feasible and safe. The majority of the predicted FVIII:C trough levels for combination treatment were accurate. This novel approach may result in considerable FVIII concentrate savings in nonsevere haemophilia patients undergoing medical procedures.

AUTHOR CONTRIBUTIONS

Lorenzo G.R. Romano wrote the manuscript and was involved in analysing data. Lisette M. Schütte designed the studies and critically reviewed the manuscript. Marieke J.H.A. Kruip, Frank W.G. Leebeek were involved in designing the studies, analysing data and critically reviewed the manuscript. Ron A.A. Mathôt and Michiel Coppens were involved in designing the studies and critically reviewed the manuscript. Lisette M. Schütte, Reinier M. van Hest, Karina Meijer, Britta A.P. Laros-van Gorkom, Laurens Nieuwenhuizen, Jeroen Eikenboom, Floor C.J.I. Heubel-Moenen, Nanda Uitslager, Michiel Coppens, Karin Fijnvandraat, Mariëtte H.E. Driessens, Suzanne Polinder critically reviewed the manuscript. All authors approved the manuscript.

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CONFLICT OF INTEREST STATEMENT

L.R. received a travel grant (in 2019) as well as the Young Investigators Award 2020, both from Sobi. L.S. has no disclosures. R.M.V.H. has no disclosures. K.M. reports speaker fees from Alexion, Bayer and C.S.L. Behring, participation in trial steering committee for Bayer, consulting fees from Uniqure, participation in data monitoring and endpoint adjudication committee for Octapharma (all fees go to her institution). B.L.v.G. reported no conflicts of interest. L.N. reported no conflicts of interest. J.E. received research support from CSL Behring. F.C.J.I. reported no conflicts of interest. N.U. reported no conflicts of interest. M.C. reported no conflicts of interest. The institution of K.F. has received unrestricted research grants from CSL Behring, SOBI and NovoNordisk and her institution received consultancy fees from SOBI, Grifols, Takeda, Novo Nordisk and Roche. M.H.E.D. reported no conflicts of interest. S.P. reported no conflicts of interest.

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DATA AVAILABILITY STATEMENT

For original data, please send a reasonable request to m.kruip@erasmusmc.nl.

ETHICS STATEMENT

Both the DAVID and Little DAVID studies were approved by the local Medical Ethics Committee of the Erasmus University Medical Center Rotterdam (MEC-2015-751 and MEC-2016-726) and by the boards of all participating hospitals. Both studies were registered at the Netherlands Trial Register (NTR5383 and NTR6036) before patient enrolment.

TRIAL REGISTRATION

Both the DAVID and Little DAVID study were registered before the onset of patient enrolment at the Netherlands Trial Register (NTR5383 and NTR6036).

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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