Received: 22 August 2023 | Revised: 25 January 2024 | Accepted: 11 February 2024

https://doi.org/10.1016/j.rpth.2024.102367

BRIEF REPORT

Tachyphylaxis and reproducibility of desmopressin response in perioperative persons with nonsevere hemophilia A: implications for clinical practice

L. G. R. Romano[1] | L. M. Schütte[1] | R. M. van Hest[2] | K. Meijer[3] | B. A. P. Laros-van Gorkom[4] | L. Nieuwenhuizen[5] | J. Eikenboom[6] | F. C. J. I. Heubel-Moenen[7] | N. Uitslager[8] | M. Coppens[9,10] | K. Fijnvandraat[11,12] | M. H. E. Driessens[13] | S. Polinder[14] | M. H. Cnossen[15] | F. W. G. Leebeek[1] | R. A. A. Mathôt[2] | M. J. H. A. Kruip[1] | on behalf of the DAVID and SYMPHONY Consortium

[1]Department of Hematology, Erasmus MC, Erasmus University Medical Center, Rotterdam, The Netherlands

[2]Department of Hospital Pharmacy and Clinical Pharmacology, Amsterdam University Medical Centers - University of Amsterdam, Amsterdam, The Netherlands

[3]Department of Hematology, University Medical Center Groningen, Groningen, The Netherlands

[4]Department of Hematology, Radboud University Medical Center, Nijmegen, The Netherlands

[5]Department of Hematology, Máxima Medical Center, Veldhoven, The Netherlands

[6]Department of Internal Medicine, Division of Thrombosis and Hemostasis, Leiden University Medical Center, Leiden, The Netherlands

[7]Department of Hematology, Maastricht University Medical Center+, Maastricht, The Netherlands

[8]Van Creveldkliniek, University Medical Center Utrecht, Utrecht, The Netherlands

[9]Department of Hematology, Amsterdam University Medical Centers - University of Amsterdam, Amsterdam, The Netherlands

[10]Pulmonary Hypertension & Thrombosis, Amsterdam Cardiovascular Sciences, Amsterdam, The Netherlands

[11]Department of Paediatric Hematology, Amsterdam University Medical Centers - University of Amsterdam, Emma Children's Hospital, Amsterdam, The Netherlands

[12]Department of Plasma Proteins, Sanquin Research, Amsterdam, The Netherlands

[13]Netherlands Hemophilia Patient Society, Nijkerk, The Netherlands

[14]Department of Public Health, Erasmus MC, Erasmus University Medical Center, Rotterdam, The Netherlands

[15]Department of Pediatric Hematology, Erasmus MC - Sophia Children's Hospital, Erasmus University Medical Center, Rotterdam, The Netherlands

Correspondence
M. J. H. A. Kruip, Erasmus University Medical Center, Wytemaweg 80, 3015 CN Rotterdam, The Netherlands.
Email: m.kruip@erasmusmc.nl

Handling Editor: Dr Suely Rezende

Abstract

Background: Desmopressin is frequently used perioperatively in persons with nonsevere hemophilia A. However, increase in factor (F)VIII:C after desmopressin use is interindividually highly variable. Tachyphylaxis has only been reported in test setting for persons with hemophilia A, with a remaining response of approximately 70% after a second dose compared with that after a first dose.

Objectives: To study tachyphylaxis of FVIII:C response after multiple administration(s) of desmopressin in perioperative persons with nonsevere hemophilia A.

Methods: We studied FVIII:C levels after desmopressin before (day 0 [D0]) and on days 1 (D1) and 2 (D2) after surgery in 26 patients of the DAVID and Little DAVID studies.

We studied tachyphylaxis by comparing the responses at D1 and D2 with that at D0. We also assessed the reproducibility of the D0 response in comparison to an earlier performed desmopressin test.

Results: The median absolute FVIII:C increase was 0.50 IU/mL (0.35-0.74; *n* = 23) at D0, 0.21 IU/mL (0.14-0.28; *n* = 17) at D1, and 0.23 IU/mL (0.16-0.30; *n* = 11) at D2. The median percentage of FVIII increase after the second administration (D1) compared with the first (D0) was 42.9% (29.2%-52.5%; *n* = 17) and that of the third (D2) compared with the first (D0) was 36.4% (23.7%-46.9%; *n* = 11). The FVIII:C desmopressin response at D0 was comparable with the desmopressin test response in 74% of the patients.

Conclusion: Tachyphylaxis in the surgical setting was considerably more pronounced than previously reported, with FVIII:C at D1 and D2 of 36% to 43% of the initial response. Our results may have important implications for monitoring repeated desmopressin treatment when used perioperatively.

KEYWORDS
desmopressin, FVIII concentrate, hemophilia, perioperative period, tachyphylaxis

Essentials

- The factor (F)VIII:C increase after desmopressin in nonsevere hemophilia A is highly variable.
- We studied 26 patients who received multiple desmopressin doses perioperatively.
- Tachyphylaxis was higher than reported earlier: FVIII:C increase was ~40% of the first response.
- It is advised to monitor FVIII:C after repeated dosing of desmopressin perioperatively.

1 | INTRODUCTION

Hemophilia A is an inherited X-linked bleeding disorder characterized by a deficiency of factor VIII (FVIII) [1]. In order to prevent bleeding during and after surgery or trauma, most persons with nonsevere hemophilia A can be treated with desmopressin. Desmopressin increases FVIII:C plasma levels by releasing endogenous von Willebrand factor (VWF) and FVIII from extrahepatic endothelial cells [2–5]. The desmopressin response is highly variable interindividually and is partially determined by baseline FVIII:C and *F8* mutations [6,7].

Repeated administration of desmopressin over a short period of time is characterized by tachyphylaxis: a decrease of released FVIII after repeated administration. The interindividual variation and the occurrence of tachyphylaxis have led the World Federation of Hemophilia to recommend performing a desmopressin test before clinical use of desmopressin and a treatment schedule for desmopressin up to 2 daily doses for a maximum of 3 consecutive days [8].

Tachyphylaxis was previously studied in 22 persons with mild hemophilia A receiving once-a-day intravenous desmopressin (0.3 μg/kg) for 4 consecutive days. Compared with the response on day 1, the FVIII increase after the second administration (day 2) was 70%, with a similar response for days 3 and 4 [9]. In 2 previous studies, in 10 and 14 persons with mild hemophilia A, respectively, the reproducibility of desmopressin FVIII:C response (intraindividual variation) was assessed [10,11]. A desmopressin response was defined as reproducible in these studies if the absolute deviation between this desmopressin response and an earlier desmopressin response was less than 20% in the first or less than 25% in the second study. The reproducibility between 2 desmopressin administrations for these patients was 42% in the first and 70% in the second study [10,11].

Because of the widespread use of desmopressin, more data on the intrapatient reproducibility of the desmopressin response are needed. Furthermore, data on tachyphylaxis in persons with nonsevere hemophilia A undergoing a medical procedure and subsequent clinical implications have not yet been reported.

Therefore, we assessed tachyphylaxis and reproducibility of FVIII:C response after desmopressin in perioperative persons with nonsevere hemophilia A who underwent a medical or surgical procedure requiring repeated daily desmopressin administrations in combination with additional pharmacokinetic-guided FVIII concentrate (combination treatment).

2 METHODS

This study is a substudy of the D**DAV**P treatment comb**I**ne**D** with FVIII clotting factor concentrates in patients with non-severe hemophilia A (DAVID) and Little DAVID studies, which included adult

persons with nonsevere hemophilia A of Dutch hemophilia treatment centers who received a maximum of 3 consecutive days perioperative combination treatment of both intravenous desmopressin once-a-day (0.3 μg/kg) followed by pharmacokinetic-guided FVIII concentrate to reach the target FVIII level (combination treatment) [12]. Patients were only included if their peak FVIII:C response was ≥0.20 IU/mL. The DAVID study was designed as an observational, multicenter single-arm study to assess feasibility, safety, and predictive performance of combination treatment perioperatively in persons with nonsevere hemophilia A. The Little DAVID study was a randomized clinical trial to compare feasibility, predictive performance, and safety of combination treatment (intervention arm) with standard treatment of only pharmacokinetic-guided FVIII concentrate (standard arm). Data on hemophilia severity, consecutive days of desmopressin administration, lowest historical FVIII:C, most recent FVIII:C baseline before participation, and most recent VWF antigen (VWF:Ag) baseline were collected from patients' electronic medical records. FVIII:C was measured before (trough) and 15 minutes after (peak) each desmopressin administration on day 0 (D0, day of surgery) up to day 2 (D2). Medical ethical approval was obtained from the Medical Ethics Committee (MEC-2015-751 and MEC-2016-726), and performance of the studies was approved by the boards of all participating hospitals. Categorical and ordinal data are presented as frequencies and proportions or percentages. Continuous data are presented as median and IQR. Differences between 2 groups with continuous data were analyzed using a Wilcoxon signed-rank test. All FVIII:C levels were measured using a one-stage assay.

2.1 | Definitions

Tachyphylaxis was calculated as a percentage, calculating the ratio of the absolute FVIII:C increases of 2 treatment days (ie, day 1 [FVIII:C_{after} - FVIII:C_{before}]) / day 0 ([FVIII:C_{after} - FVIII:C_{before}] * 100%).

The D0 desmopressin FVIII:C response was considered reproducible if the absolute D0 FVIII:C response deviated less than 25% from the previously performed desmopressin test absolute peak response (ie, if 75% < day 0 [FVIII:C_{after} - FVIII:C_{before}]) / desmopressin test ([FVIII:C_{after} - FVIII:C_{before}] * 100% < 125%, day 0 response is reproducible). If this aforementioned deviation was more than or equal to 25%, the D0 desmopressin FVIII:C response was not considered reproducible.

The similarity of the desmopressin test response related to D0 was calculated as a relative percentage by dividing the absolute desmopressin test response by the absolute D0 FVIII:C response (ie, desmopressin test [FVIII:$C_{t = 45\ min}$ - FVIII:$C_{t = 0\ min}$] / day 0 [FVIII:$C_{t = 45\ min}$ - FVIII:$C_{t = 0\ min}$] * 100%).

3 | RESULTS AND DISCUSSION

In total, 26 patients participated in this substudy. Twenty-one procedures in 20 patients with combination treatment were performed in the DAVID study and 6 procedures with combination treatment in 6 patients in the Little DAVID study. In the patients included for tachyphylaxis analyses, no bleeding complications had occurred. Two patients were excluded from all analyses (tachyphylaxis, reproducibility, and similarity) because they had received a desmopressin dose <48 hours before the first preoperative dose. Only the treatment data of the first procedure of the patient who had undergone 2 procedures in the DAVID study were included. Of the remaining 24 patients, 7 patients had received 1 dose of desmopressin. Therefore, 17 persons with hemophilia A were included for the assessment of tachyphylaxis (1 moderate and 16 mild). Of the aforementioned remaining 24 patients, 1 had no available post-desmopressin FVIII:C measurement.

TABLE Patient characteristics of included patients

Characteristics of patients in whom tachyphylaxis was analyzed (*n* = 17)	
Characteristic	***n* (%) or median [IQR]**
Hemophilia severity	
Moderate	1 (6)
Mild	16 (94)
Age (y)	47 [35-59]
Historically lowest FVIII:C (IU/mL)	0.15 [0.08-0.19]
Most recent FVIII:C at inclusion (IU/mL)	0.18 [0.11-0.31]
Most recent VWF:Ag (IU/mL) (n = 15)	1.24 [1.02-1.60]
Consecutive days desmopressin	
At least 2 d	17 (100)
At least 3 d	11 (65)
Type of medical procedure, n	
Orthopedic	4[a]
Oromaxillary/dental	6[a]
Urological	5
Biopsy/excision	1
Endoscopy	1
Laparoscopic colectomy	1
Characteristics of patients in whom reproducibility and similarity were analyzed (*n* = 23)	
Characteristic	***n* (%) or median [IQR]**
Hemophilia severity	
Moderate	2 (9)
Mild	21 (91)
Age (y)	49 [36-59]
Historically lowest FVIII:C (IU/mL)	0.15 [0.08-0.19]
Most recent FVIII:C at inclusion (IU/mL)	0.18 [0.11-0.29]
Most recent VWF:Ag (IU/mL) (n = 20)	1.28 [1.04-1.69]

VWF:Ag, von Willebrand factor antigen.
[a]One patient had an orthopedic and dental procedure combined.

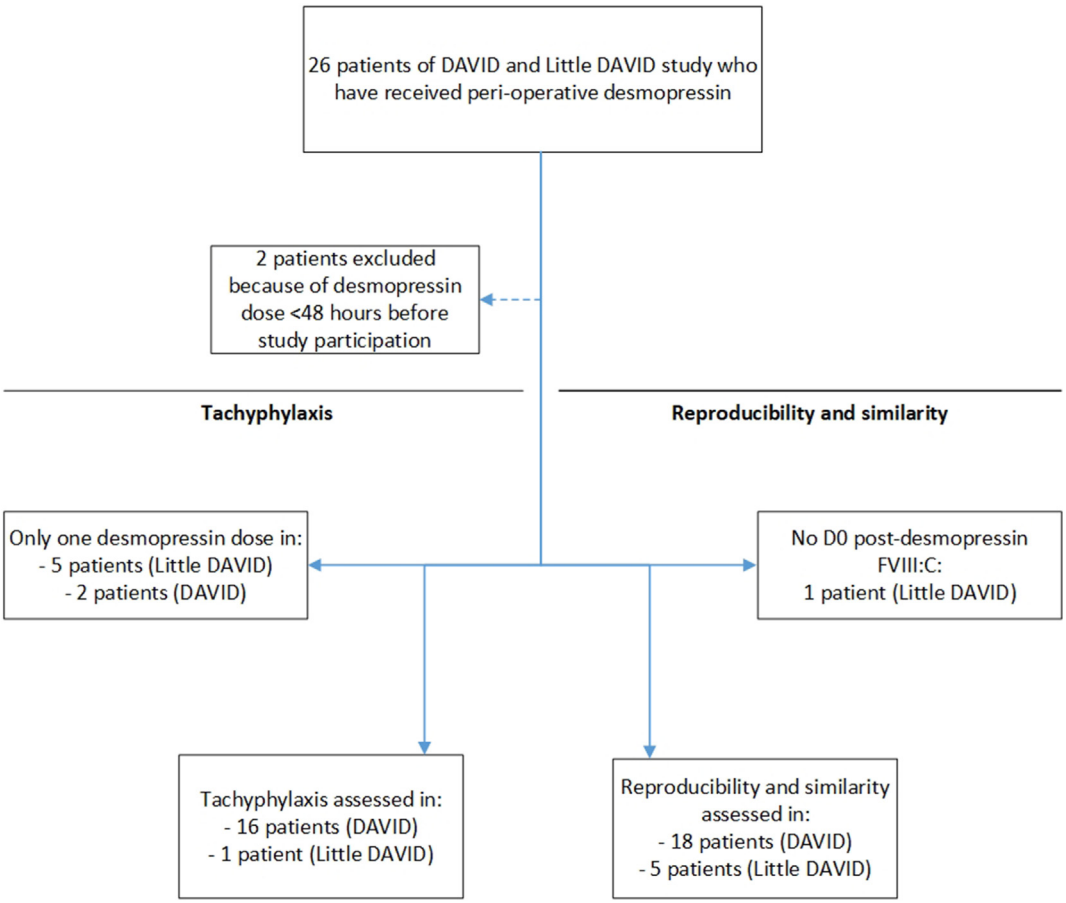

FIGURE 1 **Flowchart of the substudy inclusion for the analyses of tachyphylaxis, reproducibility, and similarity in the DAVID and Little DAVID studies.**

Therefore, 23 persons with hemophilia A were included for the assessment of desmopressin response reproducibility and similarity (2 moderate and 21 mild). In 2 of these 23 patients, a bleeding event occurred on the first day of combination treatment with a high FVIII:C >1.00 IU/mL at the time of the bleed; these 2 persons with mild hemophilia A were withdrawn from further study participation. Of these 2 patients, 1 had an absolute FVIII:C increase of 0.39 IU/mL after desmopressin and the other 0.79 IU/mL, comparable with the other included persons with hemophilia A. Patient characteristics for both groups are shown in the Table. A flowchart of the substudy inclusion is shown in Figure 1.

The FVIII:C increased from a median of 0.20 IU/mL (IQR, 0.12-0.32) to 0.72 IU/mL (0.45-1.00; *n* = 23) after desmopressin administration, on D1 from 0.89 IU/mL (0.73-1.11) to 1.12 IU/mL (0.86-1.31; *n* = 17), and on D2 from 0.85 IU/mL (0.77-1.00) to 1.12 IU/mL (0.89-1.26; *n* = 11). As FVIII concentrate had been administered before baseline measurements on D1 and D2, the baseline FVIII:C levels are higher than possibly expected. The median absolute FVIII:C increase was 0.50 IU/mL (0.35-0.74; *n* = 23) on D0, 0.21 IU/mL (0.14-0.28; *n* = 17) on D1, and 0.23 IU/mL (0.16-0.30; *n* = 11) on D2 (Figure 2). The median percentage of FVIII increase after the second administration (D1) compared with the first (D0) was 42.9% (29.2%-52.5%; *n* = 17), and of the third (D2) compared with the first (D0) was 36.4% (23.7%-46.9%; *n* = 11). The median percentage FVIII increase after desmopressin on the third day (D2) compared with the second day (D1) was 95.7% (71.4%-111.1%; *n* = 11).

The FVIII:C desmopressin response at D0 was reproducible to the desmopressin test FVIII:C response in 74% of the patients (Figure 3). The median similarity of the desmopressin test compared with FVIII:C response preoperative on D0 (*n* = 23) was 95.5% (82.1%-117.2%). In the 1 person with moderate hemophilia A included in the analysis of tachyphylaxis, the absolute FVIII:C increase after desmopressin on D0 was 0.35 IU/mL, on D1 was 0.15 IU/mL, and on D2 was 0.16 IU/mL, comparable to those for the persons with mild hemophilia A.

Our study is the first to report on tachyphylaxis of multiple consecutive administrations of desmopressin in the perioperative setting in persons with nonsevere hemophilia A. We showed that the FVIII:C increase after a second administration of desmopressin is only 43% of that obtained by the first administration and even lower (36%) after the third administration. In this substudy, patients also had received FVIII concentrate before the trough measurements on D1 and D2. As a consequence, these measured trough levels are higher than possibly expected.

The reduction in FVIII:C response after the second administration of desmopressin compared with the initial dose in our study was 57%. In a previous study, Mannucci et al. [9] demonstrated in a test setting

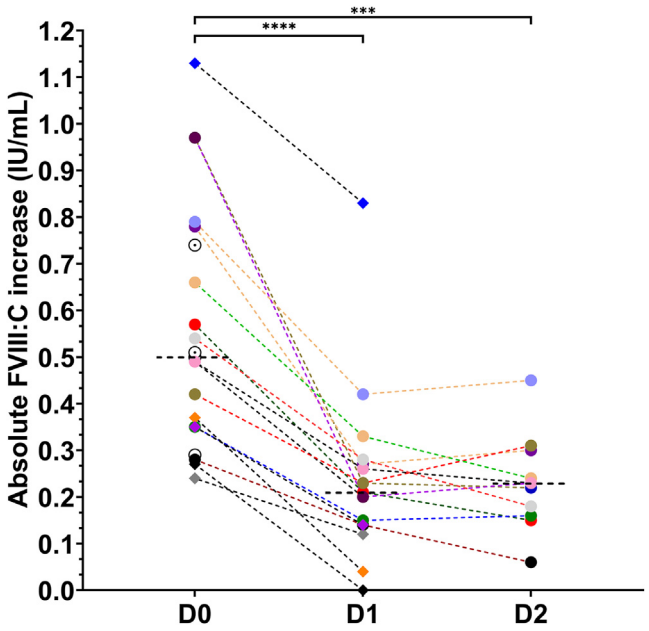

FIGURE 2 **Absolute FVIII:C increase 45 minutes after starting desmopressin in persons with nonsevere hemophilia A on day 0 (D0; *n* = 23), day 1 (D1; *n* = 17), and day 2 (D2; *n* = 11) of a medical procedure.** The median absolute FVIII:C increase of the respective day is depicted by a dotted line. Patients with only a D0 response are shown as a circle with a center dot. Patients with a response on D0 and D1 are shown as rhomboids with matching colors. Patients with a response on D0, D1, and D2 are shown as a full circle with matching colors with a connecting line.

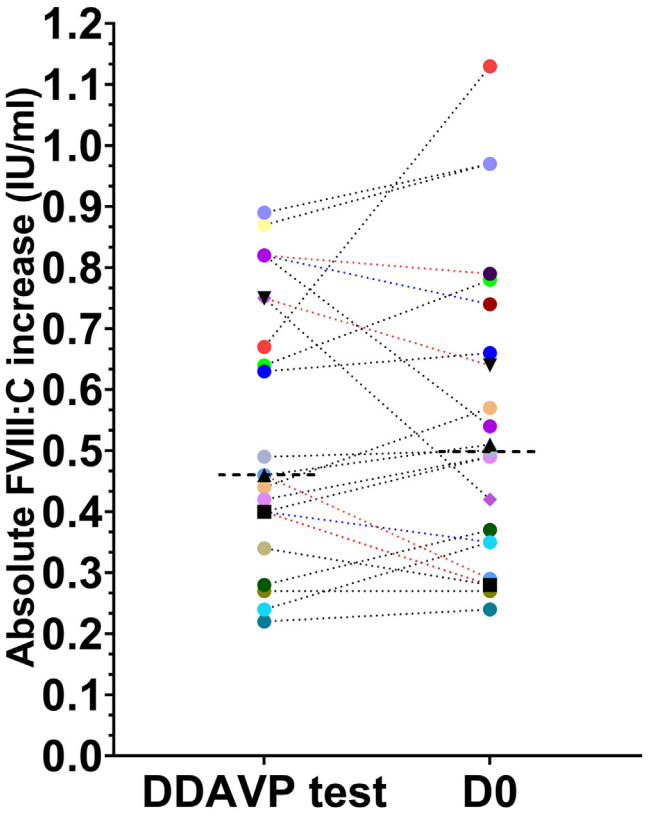

FIGURE 3 **Reproducibility and similarity of desmopressin response, comparing an earlier desmopressin test with the first preoperative absolute desmopressin response on day 0 (D0; *n* = 23).** The median absolute desmopressin (DDAVP) test FVIII:C increase (IU/mL) compared with the first preoperative (D0) absolute desmopressin increase after administration of desmopressin (IU/mL). Matching patient data are visualized with the same shape and color with a connecting line.

with daily (every 24 hours) dosing that this reduction in FVIII:C response was only 30%. A possible explanation for this difference is that our study was performed perioperatively in contrast to the previous study, which was performed in a test setting. In the same study, patients with von Willebrand disease were included, and they also showed a reduction of FVIII:C response of approximately 30% [9]. Another study in 6 healthy volunteers showed a mean reduction of FVIII:C response of approximately 50% for each consecutive dose up to 3 doses at 12-hour dosing intervals with a high interindividual variation [13]. We hypothesize that this difference between previous studies and our study may be caused by the additional release of stored FVIII and VWF in endothelial cells due to stress caused by the medical procedure. Also, the difference in interval between dosing desmopressin (12-hour dosing vs 24-hour dosing) may contribute to the observed findings. A significant postoperative increase of FVIII:C and high–molecular-weight VWF multimers has been reported in healthy individuals undergoing a surgical procedure [14]. Similarly, this stress response may have led to a perioperative release of stored FVIII and VWF in our patients, eventually leading to less FVIII and VWF being available from stored endothelial pools to be mobilized by the second administration of desmopressin. The observation of our study has clinical consequences, as repeated perioperative use of desmopressin apparently leads to a lower than previously reported response after repeated desmopressin administrations.

The preoperative desmopressin response had a good reproducibility of 74% compared with the previously performed desmopressin test, somewhat higher than in earlier studies (42%-70%) [10,11]. This underscores, as reported earlier, that a desmopressin test is an important and reliable tool to predict the preoperative desmopressin response [8,10,11]. These results underline the potential of repeated desmopressin administration in perioperative persons with nonsevere hemophilia A, especially in case of limited FVIII concentrate resources.

A limitation of our study is that we did not assess the effect of certain determinants of FVIII:C levels, such as VWF levels or the use of FVIII concentrate on tachyphylaxis. Other studies in test setting have reported certain determinants such as *F8* mutation, age, pre-desmopressin administration FVIII:C, and difference in VWF:Ag before and after desmopressin administration (at t = 1 hour). These factors could also have influenced the tachyphylaxis response in our patients [7,15,16]. FVIII concentrate has shown a minimal to no effect on FVIII and VWF clearance in perioperative persons with hemophilia A [17]. Therefore, we expect a minimal effect of FVIII concentrate on tachyphylaxis as well. Furthermore, the sample size of our cohort

treated with desmopressin for 3 days was limited. Additionally, the comparison made with other earlier studies in test setting and our studies is indirect, with other possible factors of influence such as other formulations of desmopressin. Earlier studies were performed in a test setting and were executed many years ago.

To conclude, tachyphylaxis in perioperative nonsevere hemophilia A resulted in a FVIII:C response of only 43% after the second desmopressin administration compared with the initial response. This remaining response is lower than that reported previously, which may lead to lower FVIII:C levels than expected. The reproducibility of the desmopressin test response was high, which emphasizes the role of desmopressin as a low-cost treatment modality with high convenience (ie, intranasal spray) in persons with nonsevere hemophilia A with an adequate response. Repeated desmopressin administration should be considered as a treatment modality in the perioperative setting in persons with nonsevere hemophilia A, but more pronounced tachyphylaxis should be anticipated. Our results may have important implications for monitoring repeated desmopressin treatment when used perioperatively.

FUNDING

The DAVID study received funding from Netherlands Organization for Health Research and Development (ZonMw) and Ferring. The Little DAVID study received funding from the Dutch Innovatiefonds Zorgverzekeraars. The DAVID study was funded by the Netherlands Organization for Scientific Research in the framework of the National Science Agenda Program Research Along Routes by Consortia Call Grant agreement NWA.1160.18.038 (principal investigator, M. H. Cnossen).

ETHICS STATEMENT

Medical ethical approval was obtained from the Medical Ethics Committee (MEC-2015-751 and MEC-2016-726), and performance of the studies was approved by the boards of all participating hospitals. Informed consent was provided by all included patients.

AUTHOR CONTRIBUTIONS

L.R. wrote the manuscript and was involved in analyzing data. L.S. designed the studies and critically reviewed the manuscript. M.K. and F.L. were involved in designing the studies, analyzing data, and critically reviewing the manuscript. R.A.A.M. and M.C. were involved in designing the studies and critically reviewed the manuscript. L.M.S., R.M.v.H., K.M., B.A.P.L.-v.G., L.N., J.E., F.C.J.I.-H.M., N.U., M.C., K.F., M.H.E.D., and S.P. critically reviewed the manuscript. All authors approved the manuscript.

RELATIONSHIP DISCLOSURE

L.R. received a travel grant (in 2019) as well as the Young Investigators Award 2020, both from Sobi. L.S. and R.M.V.H. have no disclosures. K.M. reports speaker fees from Alexion, Bayer, and CSL Behring; participation in trial steering committee for Bayer; consulting fees from uniQure; and participation in data monitoring and endpoint adjudication committee for Octapharma (all fees go to her institution). B.L.v.G. and L.N. reported no conflicts of interest. J.E. received research support from CSL Behring. F.C.J.I. and N.U. reported no conflicts of interest. M.C. has received financial support for research from Bayer, CSL Behring, Novo Nordisk, Roche, and uniQure, as well as honoraria for lecturing or consultancy from Bayer, CSL Behring, and Sobi. The institution of K.F. has received unrestricted research grants from CSL Behring, Sobi, and Novo Nordisk, and her institution received consultancy fees from Sobi, Grifols, Takeda, Novo Nordisk, and Roche. M.H.E.D. and S.P. reported no conflicts of interest. M.H.C.'s institution has received investigator-initiated research and travel grants as well as speaker fees over the years from the Netherlands Organization for Scientific Research (NWO) and Netherlands National Science Agenda (NWA), the Netherlands Organization for Health Research and Development (ZonMw), the Dutch Innovatiefonds Zorgverzekeraars, Baxter/Baxalta/Shire/Takeda, Pfizer, Bayer Schering Pharma, CSL Behring, Sobi Biogen, Novo Nordisk, Novartis, and Nordic Pharma, and for serving as a steering board member for Roche, Bayer, and Novartis for which fees go to Erasmus MC as an institution. F.W.G.L. has received grants/research funding from CSL Behring, uniQure, Sobi, and Takeda for research unrelated to the current study; consultancy fees from BioMarin, CSL Behring, Takeda, and uniQure (all fees to the institution); and served as DSMB member for a study sponsored by Roche. M.K. received grants from governmental research institutes, such as the Dutch Research Institute (ZonMW/NWO), Dutch Thrombosis Foundation, and Innovation Fund; an unrestricted grant from Sobi and speaker's fee from Sobi, Roche, and BMS (fees directly to the institution). R.A.A.M. has received grants from governmental and societal research institutes such as NWO, ZonMW, Dutch Kidney Foundation, and Innovation Fund and unrestricted investigator research grants from Baxter/Baxalta/Shire/Takeda, Bayer, CSL Behring, Sobi, and CelltrionHC; has served as an advisor for Bayer, CSL Behring, Merck Sharp & Dohme, and Baxter/Baxalta/Shire/Takeda. All grants and fees were paid to the institution.

ORCID

L. G.R. Romano https://orcid.org/0000-0003-0348-658X
K. Meijer https://orcid.org/0000-0001-9447-0465
J. Eikenboom https://orcid.org/0000-0002-3268-5759
K. Fijnvandraat https://orcid.org/0000-0003-0904-4360
M. H.E. Driessens https://orcid.org/0000-0001-7423-8538
F. W.G. Leebeek https://orcid.org/0000-0001-5677-1371
R. A.A. Mathôt https://orcid.org/0000-0001-8401-0879
M. J.H. A. Kruip https://orcid.org/0000-0002-0265-4871

X, FORMERLY KNOWN AS TWITTER

L.G.R. Romano @lgrromano

REFERENCES

[1] Fijnvandraat K, Cnossen MH, Leebeek FWG, Peters M. Diagnosis and management of haemophilia. *BMJ*. 2012;344:e2707. https://doi.org/10.1136/bmj.e2707

[2] Pan J, Dinh TT, Rajaraman A, Lee M, Scholz A, Czupalla CJ, et al. Patterns of expression of factor VIII and von Willebrand factor by endothelial cell subsets in vivo. *Blood*. 2016;128:104–9.

[3] Kaufmann JE, Vischer UM. Cellular mechanisms of the hemostatic effects of desmopressin (DDAVP). *J Thromb Haemost*. 2003;1:682–9.

[4] Shahani T, Covens K, Lavend'homme R, Jazouli N, Sokal E, Peerlinck K, et al. Human liver sinusoidal endothelial cells but not hepatocytes contain factor VIII. *J Thromb Haemost*. 2014;12:36–42.

[5] Everett LA, Cleuren AC, Khoriaty RN, Ginsburg D. Murine coagulation factor VIII is synthesized in endothelial cells. *Blood*. 2014;123:3697–705.

[6] Castaman G, Fijnvandraat K. Molecular and clinical predictors of inhibitor risk and its prevention and treatment in mild hemophilia A. *Blood*. 2014;124:2333–6.

[7] Stoof SC, Sanders YV, Petrij F, Cnossen MH, de Maat MP, Leebeek FW, et al. Response to desmopressin is strongly dependent on F8 gene mutation type in mild and moderate haemophilia A. *Thromb Haemost*. 2013;109:440–9.

[8] Srivastava A, Santagostino E, Dougall A, Kitchen S, Sutherland M, Pipe SW, et al. WFH guidelines for the management of hemophilia, 3rd edition. *Haemophilia*. 2020;26:1–158.

[9] Mannucci PM, Bettega D, Cattaneo M. Patterns of development of tachyphylaxis in patients with haemophilia and von Willebrand disease after repeated doses of desmopressin (DDAVP). *Br J Haematol*. 1992;82:87–93.

[10] Rodeghiero F, Castaman G, Di Bona E, Ruggeri M. Consistency of responses to repeated DDAVP infusions in patients with von Willebrand's disease and hemophilia A. *Blood*. 1989;74:1997–2000.

[11] Schutte LM, van Hest RM, Stoof SCM, Leebeek FWG, Cnossen MH, Kruip MJHA, et al. Pharmacokinetic modelling to predict FVIII:C response to desmopressin and its reproducibility in nonsevere haemophilia A patients. *Thromb Haemost*. 2018;118:621–9.

[12] Schutte LM, Cnossen MH, van Hest RM, Driessens MHE, Fijnvandraat K, Polinder S, et al. Desmopressin treatment combined with clotting factor VIII concentrates in patients with non-severe haemophilia A: protocol for a multicentre single-armed trial, the DAVID study. *BMJ Open*. 2019;9:e022719. https://doi.org/10.1136/bmjopen-2018-022719

[13] Vicente V, Estellés A, Laso J, Moraleda JM, Rivera J, Aznar J. Repeated infusions of DDAVP induce low response of FVIII and vWF but not of plasminogen activators. *Thromb Res*. 1993;70:117–22.

[14] Kahlon A, Grabell J, Tuttle A, Engen D, Hopman W, Lillicrap D, et al. Quantification of perioperative changes in von Willebrand factor and factor VIII during elective orthopaedic surgery in normal individuals. *Haemophilia*. 2013;19:758–64.

[15] Loomans JI, Kruip M, Carcao M, Jackson S, van Velzen AS, Peters M, et al. Desmopressin in moderate hemophilia A patients: a treatment worth considering. *Haematologica*. 2018;103:550–7.

[16] Jacquemin M, Lavend'homme R, Benhida A, Vanzieleghem B, d'Oiron R, Lavergne JM, et al. A novel cause of mild/moderate hemophilia A: mutations scattered in the factor VIII C1 domain reduce factor VIII binding to von Willebrand factor. *Blood*. 2000;96:958–65.

[17] van Moort I, Bukkems LH, Heijdra JM, Schutgens REG, Laros-van Gorkom BAP, Nieuwenhuizen L, et al. von Willebrand factor and factor VIII clearance in perioperative hemophilia A patients. *Thromb Haemost*. 2020;120:1056–65.