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ORIGINAL ARTICLE

Desmopressin in nonsevere hemophilia A: patient perspectives on use and efficacy

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Abstract

Background: Desmopressin increases plasma factor VIII and von Willebrand factor levels in persons with nonsevere hemophilia A. Patients' perspectives on desmopressin are relevant to increase and optimize its suboptimal use. However, patients' views on desmopressin are not reported.

Objectives: To evaluate the perspectives of persons with nonsevere hemophilia A on desmopressin use, barriers for its use, side effects, and their knowledge about desmopressin's efficacy and side effects.

Methods: Persons with nonsevere hemophilia A were included in a cross-sectional, national, multicenter study. Questionnaires were filled out by adult patients and children aged ≥12 years themselves. Caretakers filled out questionnaires for children aged <12 years.

Results: In total, 706 persons with nonsevere hemophilia A were included (544 mild, 162 moderate, [age range, 0–88 years]). Of 508 patients, 234 (50%) patients reported previous desmopressin use. Desmopressin was considered as at least moderately effective in 171 of 187 (90%) patients. Intranasal administration was the modality of choice for 138 of 182 (76%) patients. Flushing was the most reported side effect in 54 of 206 (26%) adults and 7 of 22 (32%) children. The most frequently reported advantage and disadvantage were the convenience of intranasal, out-of-hospital administration by 56% (126/227) and side effects in 18% (41/227), respectively. Patients' self-perceived knowledge was unsatisfactory or unknown in 28% (63/225).

Conclusion: Overall, desmopressin was most often used intranasally and considered effective, with flushing as the most common side effect. The most mentioned advantage was the convenience of intranasal administration and disadvantage was side effects. More information and education on desmopressin could answer unmet needs in patients with current or future desmopressin treatment.

KEYWORDS
advantages, desmopressin, hemophilia A, patient perspective, side effects, survey

Essentials

- In nonsevere hemophilia A, desmopressin is an established but underused treatment option.
- We assessed patients' perspectives on desmopressin use in a multicenter study.
- Desmopressin was most often used intranasally and considered at least moderately effective by 90% of patients.
- Flushing was the most common side effect in 26% of the adults and 31% of the children.

1 | INTRODUCTION

Hemophilia A is an X-linked disorder characterized by a deficiency in functional coagulation factor (F) VIII (FVIII). In nonsevere hemophilia A (FVIII:C, 0.01-0.40 IU/mL), patients mainly experience bleeding provoked by trauma or surgery. Available treatments for hemophilia A range from FVIII concentrate or desmopressin to novel therapeutics such as emizicumab and adeno-associated virus vector gene therapy [1]. Of these treatments, desmopressin is widely available and included in the World Health Organization's List of Essential Medicines [2]. Desmopressin administration increases plasma FVIII and von Willebrand factor (VWF) levels by stimulating endogenous VWF and FVIII release from endothelial cells [3–7]. VWF acts as a chaperone protein that protects exogenous and endogenous FVIII from degradation, thereby increasing its half-life [8]. Because of high interindividual variation in FVIII response, a desmopressin test is advised to assess FVIII response [1]. If adequate, desmopressin can be used as bleeding prophylaxis before invasive procedures or treatment for minor bleeds. Advantages of desmopressin include its potential for intranasal self-administration, which enables out-of-hospital management, and lower costs compared to FVIII concentrate. Furthermore, induction of VWF and FVIII release by administration of desmopressin and not clotting factor concentrate may reduce the incidence of inhibitors in persons with hemophilia A by reducing exposure to exogenous FVIII concentrate. The development of FVIII inhibitors in persons with nonsevere hemophilia A can cause significant mortality and morbidity, with a notoriously unpredictable bleeding tendency [9]. Side effects of desmopressin, such as flushing, headache, and fatigue, are limited and transient [10]. Contraindications for treatment are age <2 years, comorbidities that put patients at an increased risk of developing hyponatremia, and (a high risk of) cardiovascular disease or thrombosis [1]. Recent literature has shown that its current use in persons with nonsevere hemophilia A with an adequate test response is suboptimal: in 54% of bleeds treated with 1 dose of FVIII concentrate, the desmopressin FVIII:C response exceeded the level targeted with concentrate [11]. In other words, desmopressin could have been used for these bleeds instead of FVIII concentrate. Knowledge on patients' perspectives on desmopressin is relevant for increasing and optimizing the usage of desmopressin in these patients. Despite the worldwide use of desmopressin in patients with hemophilia and its merits, patients' views on the use of desmopressin have, to our knowledge, not been reported in the literature. Therefore, we initiated the present study to evaluate the views on treatment and use of desmopressin in persons with nonsevere hemophilia A. Furthermore, we evaluated to what degree persons with nonsevere hemophilia A have been sufficiently informed about desmopressin.

2 | METHODS

2.1 | Patient inclusion

Men with hemophilia A (FVIII:C < 0.40 IU/mL) were included in the cross-sectional, national, multicenter Hemophilia in the Netherlands 6 (HiN6) study [12]. For the present analysis, we included all persons with nonsevere hemophilia A who also participated in the survey from May 2018 to August 2019. This survey contained questions on multiple aspects of hemophilia care, such as desmopressin use, quality of care, treatment, and employment. In children aged between 12 and 18 years and adults, the survey was filled out by patients themselves. For children aged <12 years, parents or caregivers filled out the survey. This study was approved by the Committee of Medical Ethics of Leiden University Medical Center (NL59114.058.17).

2.2 | Survey

The survey included multiple topics with respect to desmopressin, namely whether a desmopressin test was ever performed, year of desmopressin testing (if performed), and if there had been at least 1 treatment with desmopressin, which, if answered positively, was followed by the following questions: efficacy of desmopressin for certain bleeds (multiple answers possible, including an open text box), frequency of use in the last 3 years, its efficacy in general (only 1 answer possible), reported side effects after use of desmopressin, perceived advantages and disadvantages of desmopressin, patients' opinion on their knowledge on the effectiveness and side effects of desmopressin, and patients' advice to increase the use of desmopressin. All patients were asked whether desmopressin was the first choice in the management plan in case of a bleed (for children, this question in the survey was only asked to adolescents between 12 and 18 years old) and what treatment was used in case of a bleed or as prophylaxis for a bleed (in general). Only answers relevant to the question were included in case of free text boxes. Side effects asked in the survey were as follows: dizziness, nausea, fatigue, flushing, headache, unknown, stuffed nose and/or inflammation of nasal mucosa, other (free text). The severity of symptoms was asked on a scale from 1 to 5, "not that severe" to "very severe," respectively. Possible advantages asked in the survey were as follows: none, easy to use, no need for FVIII concentrate or no need for an infusion (intranasal administration), home treatment (intranasal administration), treatment is fast, treatment is safe, treatment is cheap, unknown, other (free text). Possible disadvantages asked in the survey were as follows: none, expensive, side effects, unknown, other (free text).

The management plan options were limited to only 1 choice, specifically FVIII concentrate, active prothrombin complex concentrate, recombinant FVII, intranasal desmopressin, or intravenous desmopressin.

The options for treatment in case of a bleed or for prophylaxis were as follows: FVIII concentrate, activated prothrombin complex concentrate, recombinant FVIIa, intranasal desmopressin, or i.v. desmopressin (multiple answer options possible). For this specific question, we only reported patients who filled out the use of intranasal and/or i.v. desmopressin.

TABLE Patient characteristics of all included patients.

Characteristic	Adults (≥18 y) Median (IQR) / *n* (%) (*N* = 589)	Children (<18 y) Median (IQR) / *n* (%) (*N* = 117)
Lowest historical measured factor (F) VIII:C (1-stage, IU/mL)	0.10 (0.05-0.19) (*n* = 457)	0.09 (0.03-0.15) (*n* = 77)
Age (y) at inclusion	51 (34-63) (*n* = 586)	9 (5-13) (*n* = 116)
Desmopressin test		
Performed	210 (48%)	40 (43%)
Not performed/did not know	216 (52%)	53 (57%)
Age at desmopressin test (y)[a]	40 (26-52) (*n* = 138)	7 (4-9) (*n* = 20)
Hemophilia severity		
Mild	461 (78.3%)	83 (70.9%)
Moderate	128 (21.7%)	34 (29.1%)
Previous desmopressin treatment (*n* = 426 / *n* = 82)		
Yes	211 (49.5%)	23 (28%)
No	105 (24.7%)	49 (60%)
Do not know	110 (25.8%)	10 (12%)
Treatment frequency		
>10 times	11 (5%)	4 (17%)
1-10 times	135 (65%)	16 (70%)
Do not know	60 (30%)	3 (13%)
FVIII inhibitor in history	45 (9.9%) (*n* = 457)	1 (1%) (*n* = 77)
Negative inhibitor assay after an earlier measurable inhibitor	33 (83%) (*n* = 40)	1 (100%) (*n* = 1)

[a]Calculated by the difference between the reported year of desmopressin testing and birth date.

2.3 | Statistical analysis

Categorical data are reported as frequencies and proportions. Continuous data are reported as median (interquartile range). All statistical analyses were performed in IBM Statistics SPSS, version 28.

3 | RESULTS

3.1 | Patient inclusion and reported desmopressin use

In total, 706 men with nonsevere hemophilia A were included in the HiN6 study and responded to the survey; 589 of 706 (83%) were adults with an age range of 18 to 88 years, and 117 of 706 (17%) were children with an age range of 0 to 17 years. About 50% (211/426) of the adults and 28% (23/82) of the children reported being treated

with desmopressin at least once. Patient characteristics, including data on historical desmopressin treatment and desmopressin testing, are described in the Table. In total, 208 of 389 (54%) and 26 of 119 (22%) persons with mild and moderate hemophilia A, respectively, who answered the question on historical desmopressin use reported previous desmopressin treatment. The age in children as well as the baseline FVIII:C in adults and children seemed higher in patients who had been treated with desmopressin at least once in comparison to those who did not (Supplementary Table S1).

In 172 adults who reported desmopressin as current treatment option for bleeds or prophylaxis (multiple answer options per patient possible), desmopressin was used intravenously in 72 (42%) and intranasally in 128 (74%). Among 10 children aged between 12 and 18 years, 1 used desmopressin intravenously (10%) and all 10 (100%) used it intranasally. Among 21 children aged <12 years, 2 (10%) used desmopressin intravenously and 20 (95%) used it intranasally.

In total, 164 adults and 23 children answered general questions on the perceived effectivity of desmopressin, of whom 131 (80%) adults and 19 (83%) children stated that it was effective, 19 (11.5%) adults and 2 (9%) children stated that it was moderately effective, and 14 (8.5%) adults and 2 (9%) children stated that desmopressin was not effective.

Furthermore, 206 adults and 23 children answered specific questions on whether desmopressin was sufficiently effective to treat their bleeds, of whom 38 (19%) adults and 3 (13%) children stated that they did not know how effective desmopressin is. Ten (5%) adults and 1 (5%) child stated that desmopressin was not effective at all for their bleedings; for 60 (29%) adults and 14 (61%) children, it was effective to treat mucosal bleedings (ie, epistaxis); and for 96 (47%) adults and 12 (52%) children, it was effective to treat larger bleedings. In addition, among the aforementioned 206 adults, other uses of desmopressin, such as after small trauma, were reported by 28 (13%) adults (Supplementary Table S2).

In 236 adults and 9 children, desmopressin was primarily mentioned as part of the patients' management plan for a mild bleed by 85 (36%) adults and 6 (69%) children, moderate bleed by 28 (13%) adults and 5 (56%) children, and life-threatening bleed by 5 (3%) adults and 2 (29%) children.

3.2 | Reported side effects

Patients were asked whether they had experienced side effects while using desmopressin and, if so, what they were. Two hundred six adults and 22 children answered the questions on potential side effects after desmopressin: 86 (42%) adults and 7 (32%) children reported no side effects, and side effects were unknown in 28 (14%) adults and 3 (14%) children. Ninety-two (45%) adults and 12 (55%) children had experienced at least 1 side effect. The most frequently reported side effects in adults were flushing in 54 (26%), headache in 36 (17%), and fatigue in 24 (12%). The most frequently reported side effects in children were flushing in 7 (31%), headache in 7 (31%), and fatigue in 5 (23%). The frequency and severity of the reported side effects are shown in Figure 1.

3.3 | (Dis)advantages of desmopressin

Patients were asked what they perceived as advantages or disadvantages of desmopressin use. Of 205 adults and 23 children, 143 (70%) adults and 19 (83%) children reported at least 1 advantage of desmopressin, 22 (10%) adults and 2 (9%) children reported no advantage, and 40 (20%) adults and 2 (9%) children filled out unknown. The most reported advantages in both adults and children were convenience of intranasal desmopressin in 108 (53%) and 18 (78%), respectively, followed by the possibility of home treatment in 80 (39%) and 12 (52%), respectively. Furthermore, 206 adults and 21 children reported the potential disadvantages of desmopressin. Ninety (44%) adults and 8 (38%) children reported no disadvantage; in 44 (21%) adults and 3 (14%) children, the question on possible disadvantages was answered as unknown. At least 1 disadvantage was reported by 72 adults (35%) and 10 children (48%). The most common disadvantages in both adults and children were its side effects in 38 (18%) and 6 (28%), respectively, followed by its expensive cost in 26 (12%) and 3 (14%), respectively. These advantages and disadvantages are depicted in Figures 2 and 3. In addition, the differences between persons with mild and moderate hemophilia A are reported in Supplementary Tables S3 and S4, with comparable responses for both groups of patients.

3.4 | Information on desmopressin

Patients were asked if their knowledge of the efficacy and side effects of desmopressin was sufficient. In total, 310 adults and 31 children replied.

Of 204 adults and 21 children who also reported to have been treated with desmopressin, 101 (50%) adults and 9 (43%) children classified their knowledge as enough, 46 (23%) adults and 6 (28.5%) children classified their knowledge as moderately satisfactory, 24 (12%) adults and 4 (19%) children classified their knowledge as not enough, and 33 (16%) adults and 2 (9.5%) children did not know. Seven adults and 2 children who had been treated with desmopressin in the past did not answer the aforementioned question.

Of the 106 adults and 10 children who did not know if they had received desmopressin, 3 (3%) adults and 3 (30%) children classified their knowledge as enough, 7 (7%) adults and 4 (40%) children classified their knowledge as moderately satisfactory, 31 (29%) adults and none of the children classified their knowledge as not enough, and 65 (61%) adults and 3 (30%) children did not know. The difference between persons with mild and moderate hemophilia A is depicted in Supplementary Table S5, with comparable responses between both groups.

3.5 | Barriers to and facilitators of desmopressin use

Adult patients and children were asked in the open question how the use of desmopressin could be improved and stimulated. In total, 48 adults answered. The reported answers were as follows: presence of a relative contraindication (ie, chronic heart failure; n = 9), fewer side

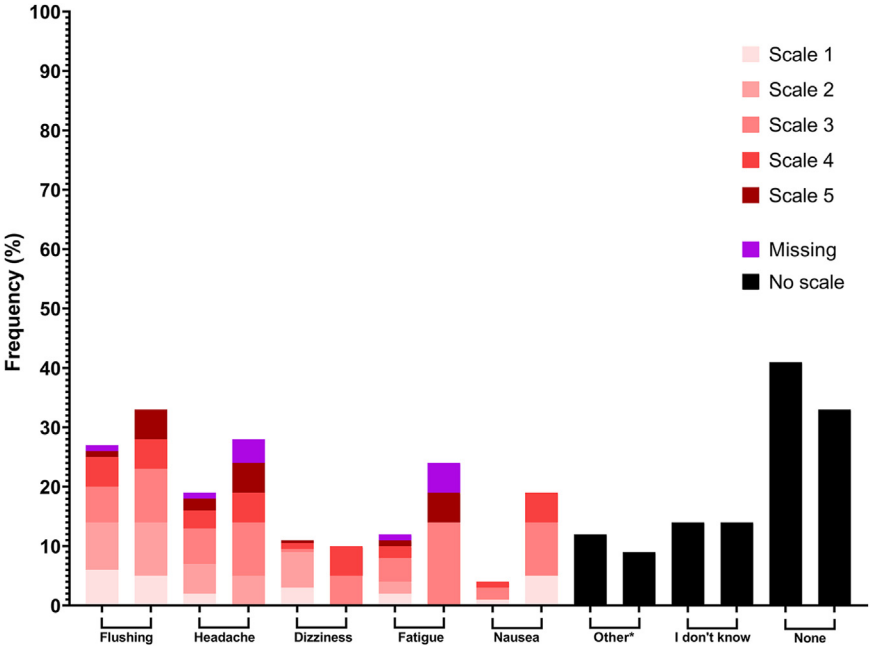

FIGURE 1 Reported side effects of desmopressin treatment in adults (first bar; *n* = 206) and children with nonsevere hemophilia A (second bar; *n* = 22). Severity was reported on a scale from 1 (not that severe) to 5 (very severe), or missing (no severity reported). *The other reported side effects and severity (scale [s], 1-5) in adults were as follows: stuffed nose and/or mucosal inflammation (*n* = 1,s = 2), ureter clotting (*n* = 1, s = 5); thirst (*n* = 1, s = 3), flu-like symptoms (*n* = 1, s = 5), fluid retention (*n* = 2; s = 2 and 2), muscle cramp (*n* = 1, s = 4), shakiness (*n* = 1, s = 5), malaise (*n* = 1, s = 5), limited decrease in blood pressure (*n* = 1, s = 2), (sub)febrile temperature (*n* = 2, s = 1 and 5), difficult urination (*n* = 6, s = 2, 3, 1, 3, 1, and 3), chest pain (*n* = 1, s = 5), fluid restriction is not pleasant (*n* = 2, s = 5 and 3), sleepiness (*n* = 1, s = 1), polyuria (*n* = 1, s = 1), and feeling inebriated (*n* = 1,s = 4). The other reported side effects in children were as follows: (sub)febrile temperature (*n* = 1) and limiting fluid restriction (*n* = 1).

effects (*n* = 7), less costs (*n* = 6), more information on desmopressin (*n* = 7), more efficacy (*n* = 8), more availability of desmopressin (*n* = 4) (ie, more easily obtainable nose spray), longer shelf-life (of intranasal administration; *n* = 4), availability as a home treatment option, reassuring the patient, (*n* = 1), good efficacy (*n* = 1), and its use for participation in sports (as facilitator). Interestingly, 1 patient reported that because of his work in a country with low FVIII concentrate resources, he was dependent on the use of intranasal desmopressin for emergencies. Among children, 1 child wanted more efficacy and fewer side effects. Two caretakers reported that they did not know what desmopressin was, 1 of them emphasizing that they would want more information. The findings are summarized in Supplementary Table S6, with quotes of interest depicted in Supplementary Table S7.

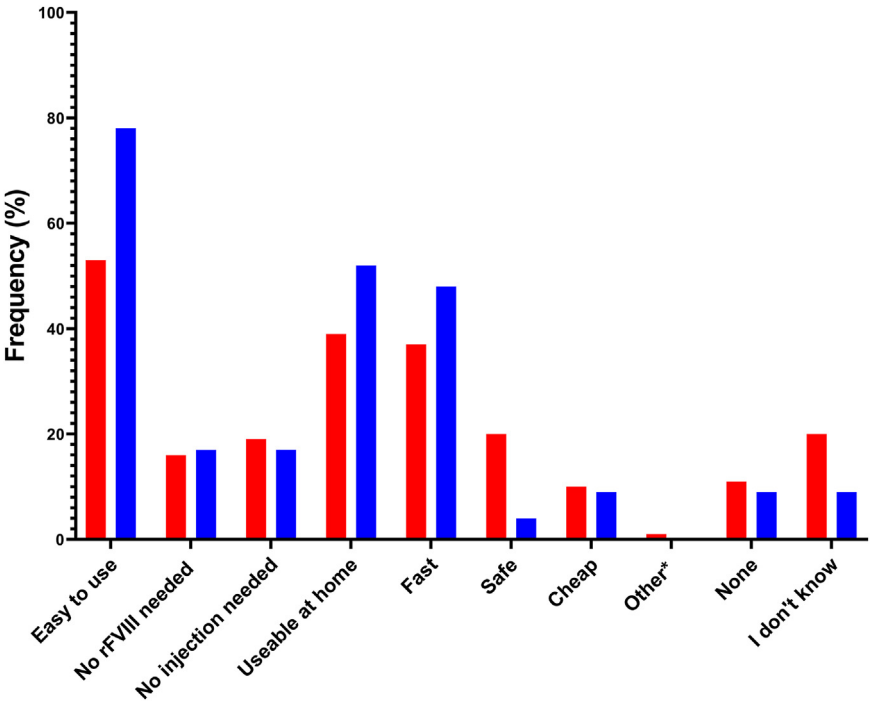

FIGURE 2 Reported advantages of desmopressin treatment in adults (red bars, *n* = 205) and children with nonsevere hemophilia A (blue bars, *n* = 23). *The other reported advantages in adults were as follows: gives me inner peace and assurance for internal examinations (*n* = 1) and handy for travel (*n* = 1).

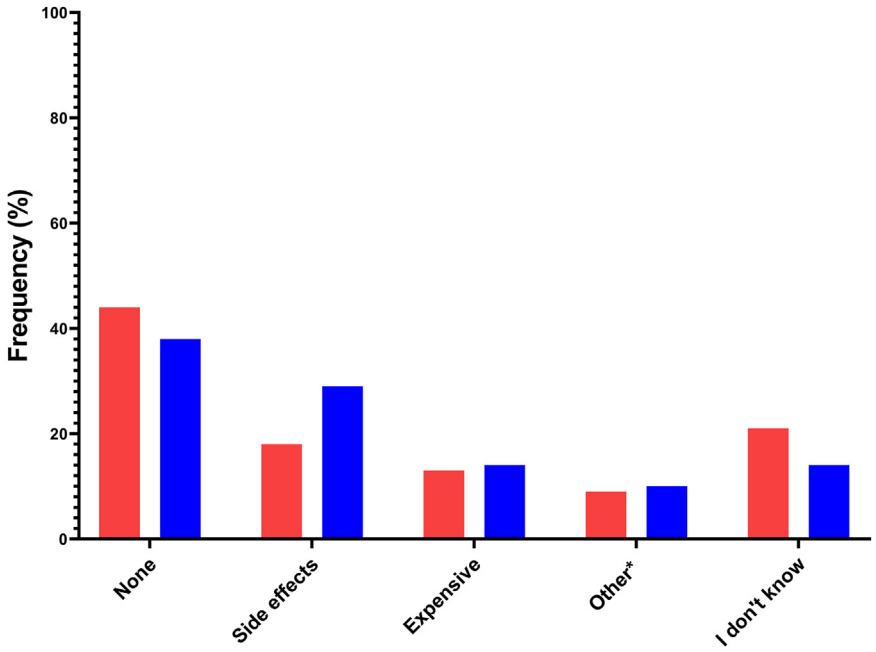

FIGURE 3 Reported disadvantages of desmopressin treatment in adults (red bars, *n* = 206) and children with nonsevere hemophilia A (blue bars, *n* = 21). *The other reported disadvantages in adults were as follows: limited shelf-life (*n* = 3), storage temperature (*n* = 2), not usable after urologic procedure because of fluid intake (*n* = 1), fluid restriction (*n* = 4), seems to evaporate (*n* = 1), not usable anymore because of a higher risk of epilepsy (*n* = 1), not usable anymore because of atrial fibrillation (*n* = 1), occurrence of ureter clots (*n* = 1), deductible for nasal spray (*n* = 1), and limited efficacy (*n* = 4). The other reported disadvantages in children were as follows: fluid restriction (*n* = 2).

4 | DISCUSSION

In our study of 706 persons with nonsevere hemophilia A, of those who reported previous desmopressin use, approximately 50% of the adults and children reported to have been ever treated with desmopressin and have undergone a desmopressin test. Additionally, 90% of the patients who had been treated with desmopressin reported that it was at least moderately effective enough to be used to prevent or treat bleedings. In 26% of the patients who had been treated with desmopressin, knowledge of desmopressin use was considered as not enough or unknown. The most reported barriers to desmopressin use were the presence of a contraindication, side effects, and high costs.

Multiple cohort studies have shown at least a partial response in 66% to 78% [13–16], up to 88% to 98% [17,18], of the studied male patients with mild hemophilia A. In our study, the patient-reported efficacy was high as well, but neither absolute desmopressin FVIII:C response nor bleeding outcome measures were available. Therefore, a direct comparison cannot be fully made.

As patients were only allowed to fill out 1 treatment modality for treatment in case of bleeding, most treatment plans listed FVIII concentrate as the preferred treatment. These data are likely an underrepresentation of the general use of desmopressin: besides (mild) bleeding, patients could be applying desmopressin prophylactically, ie, before participation in sports, as was reported to be a facilitator. Despite a seemingly lower number of persons with moderate hemophilia A who reported using desmopressin in comparison with persons with mild hemophilia A in this study, previous research has shown the merits of desmopressin in persons with moderate hemophilia A [19,20].

The most frequently reported side effects, flushing and headache, have also been reported earlier in the literature. In a study by Stoof et al. [10], the side effects of desmopressin were assessed in patients with a bleeding disorder who had just received desmopressin. Of 103 patients reporting side effects after 1 hour of i.v. desmopressin administration, itching eyes (68%), flushing (59%), headache (34%), and fatigue (40%) were reported as the most prevalent over multiple time points after desmopressin administration. However, the frequency of the self-reported side effects in our study was lower than that reported by Stoof et al. [10], which can be explained by recall bias as most patients in the present study were not included in the proximity of a recent desmopressin administration.

The most reported advantages of desmopressin were the convenience of intranasal administration and possibility of home treatment (intranasal or s.c.). The current World Federation of Hemophilia guideline states that the use of intranasal desmopressin can be difficult, possibly negatively influencing treatment. Although we did not ask explicitly if a nasal spray was easy to use, it was not reported as a disadvantage by any of our patients [1]. Interestingly, the safety of desmopressin (ie, no inhibitor formation, blood-borne diseases) and its use as an alternative to FVIII concentrate were less frequently considered as advantages than the aforementioned convenience.

The most reported disadvantage, namely side effects, was only reported in approximately 1 of 6 patients. When choosing the route of administration, it is good to realize that s.c. or intranasal administration of desmopressin results in less vasomotor side effects, such as flushing or headache, than i.v. administration [10,21]. However, at the time of the survey, s.c. desmopressin administration was not (yet) the standard of care, and therefore, s.c. desmopressin administration was not added as a survey response option. Furthermore, the use of intranasal desmopressin can be challenging because of a slower rate of absorption and lesser magnitude of response than parenteral administration, in combination with other possible limiting factors such as epistaxis or nasal blockage [22,23]. One of the other reported

disadvantages, the expensive cost of desmopressin, is related to the Dutch health care system: a yearly cumulative, minimum deductible €385 is demanded for medical care, including medication such as intranasal desmopressin. One container of intranasal desmopressin already charges this whole deductible. Persons with nonsevere hemophilia A with no other significant yearly health care costs who do not fully apply the whole deductible could consider this costly, especially in combination with the nasal spray's short shelf-life.

The knowledge of desmopressin was considered unsatisfactory or unknown by approximately a quarter of the respondents who had received desmopressin. Research on hemophilia education has shown that even a single educational intervention on the knowledge and management of bleeding temporarily improved the quality of life in persons with hemophilia A and parents of children with hemophilia A, albeit temporarily [24,25]. In other chronic disorders, such as diabetes mellitus type 2, research on (self-care) education programs has also shown improvement in disease management and quality of life, with a longer program of 5 days leading to improvement for up to 2 years [26,27]. More and frequent information and patient education on the use and self-management with desmopressin could, therefore, increase the quality of life in persons with nonsevere hemophilia A and answer possible unmet needs in this group related to our study-reported advantages of desmopressin such as home treatment. Unfortunately, however, as of the writing of this article, intranasal desmopressin is not readily available worldwide.

Our study was the first large, prospective study on patients' perspectives of desmopressin use in adults and children with nonsevere hemophilia A but was limited by some aspects of the survey. Not all patients who were included in the study reported desmopressin use (74%). In addition, patients did not always fill out questions concerning treatment (ie, management plan) and were sometimes limited to only 1 answer option, leading to missing data. This could have been caused by the use of different names for desmopressin used throughout the questionnaire (ie, DDAVP, Octostim, Minrin). As no information on ethnicity was available in the HiN6 study, we were not able to assess its influence as a sociocultural determinant on patients' perspectives on desmopressin. Recall bias could also have limited the reported number of desmopressin used in the survey. Furthermore, people who use desmopressin more often or who are more likely to use it are also more likely to fill out the survey on desmopressin. This could lead to underreporting of desmopressin use. The perceived efficacy of desmopressin could have been influenced by concomitant use of other medications, such as antifibrinolytics, partially influencing the patients' opinion in favor of desmopressin. Additionally, as these questions were part of a larger survey, less attention could have been given to this specific category of questions, leading to a less overall response. We believe that all eligible persons with nonsevere hemophilia A should be informed on desmopressin's efficacy, use, and side effects. After informing the patient (or caregiver), their perspective can be taken into account in order to decide with their health care provider whether desmopressin treatment is preferable. The main topics of discussion could be side effects, costs (if applicable), and the ability of home treatment.

5 | CONCLUSIONS

Approximately half of the persons with nonsevere hemophilia A in this subanalysis of the HiN6 study reported to have ever received desmopressin, most often intranasally, and 90% reported at least moderate effectiveness. Flushing was the most commonly reported side effect. The most frequently reported advantage was the convenience of intranasal administration and the possibility of home treatment, and the most frequently reported disadvantages were the presence of side effects and high costs. More information and more education on desmopressin from health care providers can answer the unmet needs of patients currently receiving desmopressin and desmopressin-naive persons with nonsevere hemophilia A.

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ETHICS STATEMENT

This study was approved by the Committee of Medical Ethics of Leiden University Medical Center (NL59114.058.17) and written informed consent was obtained from patients.

AUTHOR CONTRIBUTIONS

L.R. wrote the manuscript and was involved in analyzing data. M.K., S.G., L.v.V., F.H.M., H.H., M.C., K.F., S.S., C.S., M.D., P.Y., F.R., P.d.E., and J.B. designed the study, contributed to the data collection from the participating centers, and 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.V. received research grants from CSL Behring and Griffols and participated in an Advisory Board for CSL Behring and Novo Nordisk; all fees were paid to the institution. F.M. received a grant in 2022 by Sanofi for the ISTH 2022 Congress (registration and travel to the conference). 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. S.S. received a research grant from Bayer in 2021 and is a board member of the Dutch Haemophilia Centres Doctors Organisation (NVHB). J.B. has received a grant from Novo Nordisk, with payment directly to the

institution. S.G. received an unrestricted research grant from Sobi. M.K. received an unrestricted research grant from Sobi, paid to the institution, and speakers fees from Sobi, BMS, and Roche, all fees paid to the institution. P.d.E., P.Y., M.E., F.R., and J.B. have no interests to declare.

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SUPPLEMENTARY MATERIAL

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