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Adherence to on-demand treatment regimen and bleeding outcome

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ABSTRACT

Objectives: This study aims to evaluate self-reported/parent-reported adherence to on-demand therapy among persons with hemophilia.

Material and Methods: A cross-sectional survey of 55 participants receiving on-demand therapy recruited during outpatient appointments in 5 hemophilia treatment centers (HTCs) across Nigeria using the validated Hemophilia Regimen Treatment Adherence Scale-on-demand (Validated Hemophilia Regimen Treatment Adherence Scale - PRN; VERITAS-PRN) with 24 questions on six (four-item) subscales (treat, time, dose, plan, remember, and communicate). The options of VERITAS -PRN were represented in 5 Likert scale and possible subscale ranged from 4 points (most adherent) to 20 points (least adherent) and possible total score ranging from 24 (most adherent) to 120 (least adherent). The cut-off for overall adherence is put at >61 to indicate non-adherence. Information on the presence of target joints and annualized bleeding rates were collected from medical files.

Result: Of the 55 participants, 94.1% both had hemophilia A and target joints. The majority 51 (92.7%) had scores indicating non-adherence. The mean age of non-adherent and adherent participants was 19 (13.9) years and 24 (13.23) years, respectively. For the non-adherent, the overall mean score was 68.05 (8.54). Subscale scores range from 9.38 (treat) to 15.00 (remember). All subscales showed significant difference in the overall adherence between adherent and non-adherent participants with a $P < 0.05$. There was a significant association between the mean log of the number of target joints and the communicating subscale for the non-adherent group (r-0.61 $P = 0.046$).

Conclusion: The findings indicate that adherence is generally poor and there is high frequency of target joints among them. Efforts should be made to improve adherence to treatment which may reduce target joints and ultimately improve joint health.

Keywords: Hemophilia, Adherence, On-demand, VERITAS-PRN

INTRODUCTION

Hemophilia is an X-linked inherited bleeding disorder in which there is defective or decrease in the quantity of clotting factors; it usually affects either FVIII or FIX, in hemophilia A and B, respectively.[1] Depending on the residual clotting factor level, they are characterized into mild, moderate, or severe.[2,3] Clinical features in most cases are most severe in those with

the severe type in which patients bleed spontaneously without trauma.[4] In general, clinical features are mainly recurrent prolonged bleeding following injury, bleeding following tooth eruption, hematomas, and hemarthroses.[4] Hematomas and hemarthroses account for 80% of bleeding episodes.[5,6] Repeated episodes of hemarthroses lead to crippling arthropathy because of interplay between chemical irritation of the synovium by blood and release of inflammatory cytokines as well as reactive oxygen species from hem iron.[6,7] Crippling arthropathy impairs Quality of Life (QoL) of the patient, increases clotting factor consumption, and poses serious challenges on the managing team.[3,7] To treat hemophilia, there are two basic approaches: Preventing long-term complications and treating acute bleeding episodes.[5] To prevent long-term complications, prophylactic doses of clotting factor concentrates (CFCs) are given while to treat acute bleeding, on-demand/episodic approach is employed.[7,8] Challenges to treatment are more pronounced in resource-poor countries (RPCs) where total dependency on humanitarian aid donation prevents most persons with hemophilia (PWH) from being on prophylaxis therapy, comprehensive care is suboptimal, funding is grossly inadequate, and expertise for arthroscopic and radio-synovectomy is lacking.[9]

Either of these options requires huge financial expenditure, availability of and accessibility to CFCs/health personnel, commitment of the patients/caregivers to adhere to the treatment protocol, ease of getting venous access, and proximity of patients to the treatment centers among other issues. To overcome some of these problems, home treatment has been introduced in the management of patients with hemophilia. Despite the implementation of home treatment, concerns about treatment adherence persist. Expectedly, complications will be seen more in RPC among those with moderate-to-severe disease; hence the need to evaluate adherence to therapy among our patients.

Despite several efforts to improve global access to treatment among PWH with the attending commitment of huge financial and other needed resources by several stakeholders, it is still possible that adherence to on-demand treatment is not optimal.[8,10] Adherence to treatment in other chronic medical conditions such as cardiovascular diseases has also been shown to be suboptimal; ranging between 20 and 50%.[11] In chronic medical conditions, adherence to treatment has been shown to be key to therapeutic success, it improves patient's safety, decreases cost of care, decreases burden of chronic complications, and overall improves patients' QoL.[8,10,11]

Giving disparate access to CFCs, especially in some RPCs and patient's preference, on-demand treatment remains an option for the management of hemophilia. However, there is a dearth of evidence on adherence to on-demand treatment among PWH in sub-Saharan Africa. This study therefore aimed at assessing the adherence to on-demand/episodic treatment among PWH in Nigeria.

MATERIAL AND METHODS

This was a cross-sectional multicenter study carried out in five (5) HTCs in Nigeria. Adherence to on-demand treatment and bleeding outcomes was measured using a semi-structured questionnaire administered to consenting patients or their caregivers. Ethical approval from the study centers was obtained from an institutional ethical review committee with clearance number: NHREC/05/01/2008B-FWA00002458-1RBOOOO2323.

A total of 55 patients with moderate-to-severe hemophilia on on-demand treatment were recruited during the outpatient clinic using a convenience sampling method in the participating centers across Nigeria. Patients on prophylaxis therapy and those having acute bleeding episode at the time of study were exempted.

Permission to access infusion log data was sought from individuals for the purpose of this study. Participants were assured that all study-related data would be kept confidential by the study coordinator and identification would only be through an assigned unique number.

Adherence measurement

Adherence was assessed using the Validated Hemophilia Regimen Treatment Adherence Scale for on-demand (i.e., episodic) - VERITAS-PRN.[12] VERITAS scores range from 24 (most adherent) to 120 (least adherent). The 24-item questionnaire is divided into six (6) subscales: Time, Dose, Plan, Remember, Skip, and Communicate. Response options are presented as five- point Likert scales ranging from "Always" to "Never;" always reflects best possible adherence for some items and the worst possible adherence for other items. Information on the presence of target joints and annualized bleeding rate (ABR) was collected from the medical files of the participants.

Data analysis

Analysis was done using the Statistical Package for the Social Sciences version 21. Descriptive statistics were calculated for each subscale, bivariate associations using simple linear regression multivariable analysis using multilinear regression.

RESULTS

Fifty-five persons with hemophilia receiving on-demand (PRN) therapy participated in the study. The characteristics

of respondents are shown in Table 1. The majority (96.4%) of patients had hemophilia A while only 2 (3.6%) had hemophilia B). The age of the participants varied from 3 to 49 years (mean: 21,58 ± 11.41 years). Fifty-three patients (96.4%) had target joints while 2 (3.6%) did not and the average ABR was 11.94 ± 0.11.33 and ranged from 0 to 66.

Self-reported adherence

Adherence was defined as the total sum of all subscales that were <61 on the cutoff scores and non-adherence as the total sum of all subscales that were >61 based on the cutoff scores proposed by the original validation study. There was a record of 7.3% adherence among the participants. For the subscales, 87.3% of participants were more adherent in remembering their treatment followed by 69.1% reported in the communication subscale while the highest non-adherence, 76.4% was recorded in the timing subscale [Table 2].

The mean age for the adherent group was 19.33 ± 13.94 while for the non-adherent group was 24.27 ± 13.23. The mean log ABR and number of target joints are shown in Table 3. These differences in mean for age, ABR, and number of target joints were not statistically significant (P = 1.04, −0.39, and 1.22, respectively, [Table 3]).

Overall veritas PRN scores

The mean total VERITAS-PRN score for the adherence group for the total sample was 45.82 ± 6.87 with a range of 31–55 [Table 4]. Subscale mean scores ranged from 5.62 (dosing) to 12.0 (timing). While for the non-adherent group, the mean total VERITAS-PRN score was 68.05 ± 8.54. The subscale means scores ranged from 8.67 (remembering) to 15 (planning), indicating that participants reported the greatest adherence in remembering to take their CFC and least adherence in planning for the on-demand therapy.

There was a significant statistical difference in the overall VERITAS-PRN score between the adherence and the non-adherent group, as well as in all subscales with $P < 0.05$ [Table 4].

Table 1: Demographic characteristics of the participants.

Variable	*n*	Mean	SD	Minimum	Maximum
Age	55	21.58	11.41	3	49
Annualized bleeding rate	55	11.94	11.33	0	66

Table 2: Adherence status in subscales.

Variable	Frequency	
	Adherence	
Status	***n***	**%**
Adherent	4	7.3
Non-Adherent	51	92.7
Subscales	**Adherent (%)**	**Non-adherent (%)**
Treating	46 (83.6)	9 (16.4)
Timing	13 (23.6)	42 (76.4)
Dosing	29 (52.7)	26 (47.3)
Planning	17 (30.9)	38 (69.1)
Remember	48 (87.3)	7 (12.7)
Communication	38 (69.1)	17 (30.9)

Correlation analysis of self-reported adherence, ABR, and number of target joint

Association between self-reported adherence, number of target joints, and the ABR was tested with Pearson Correlation, which revealed that there were non-statistically significant associations with the subscales between the group except for communicating among the non-adherent group, with a significantly moderate negative correlation coefficient (r, −0.61 and a P = 0.046); [Table 5].

DISCUSSION

We have been able to determine the level of adherence to on-demand therapy among PWH in an African country that is still totally dependent on Humanitarian Aid donations of CFC using the VARITAS-PRN which is a validated scale to measure adherence to on-demand treatment.[12] This study reported poor adherence among the participants. There is notably a high frequency of target joint among them, an indication that they have had four or more recurrent bleeds in a particular joint in the past 6 months. Poor adherence to CFC treatment may favor the development of a target joint and subsequent hemarthrosis leading to the development of hemophilic arthropathy because target joint is actually a late indication of hemophilic arthropathy.[13] This does not support the objective of hemophilia treatment which is to prevent the development of target joint or to reduce the number of bleeding episodes before attaining the stage of chronic synovitis which technically is the target joint.[13]

O'Hara *et al.*,[14] however, reported a lower frequency of target joint of just about half of their study population which is contrary to ours despite having similar patient characteristics in terms of type of hemophilia. Our study is also in keeping with the global trend.[15]

Using the original validation study, adherence was defined as the total sum of all subscales of <61 and non-adherence as the total sum of >61. As high as 92.7% of our study cohort had scores in the non-adherence group, only as few as 7.3% were adherent which is quite low when compared to other studies

Table 3: Age, annualized bleeding rate, and number of target joints in the adherent vs. non-adherent group.

Variable	Adhere				Non-Adherence					
	Mean	SD	Min	Max	Mean	SD	Min	Max	*t* (*P*-value)	M. Diff
Age	19.33	13.94	3	40	24.27	13.23	7	49	−1.04 (0.306)	−4.93
Annualized bleeding rate (Log)	7.24	3.09	1.00	66.06	8.32	2.63	1.99	60.25	−0.39 (0.693)	−4.67
Number of target joint (Log)	2.95	1.55	1.99	6.02	2.39	1.28	1.99	3.98	1.22 (0.244)	−1.23

SD: Standard deviation

Table 4: Overall self-reported adherence.

Variable	Adhere					Non-Adherence					
	N	Mean	SD	Min	Max	N	Mean	SD	Min	Max	*t* (*P*-value)	M. Diff
Self-reported adherence												
Treating	34	6.00	1.97	4	11	21	10.48	3.43	4	17	−6.16 (<0.001*)	−4.48
Timing	34	12.00	2.85	5	17	21	13.86	2.71	8	20	−2.42 (0.020*)	−1.86
Dosing	34	5.62	1.83	4	10	21	9.38	3.32	4	15	−5.43 (<0.001*)	−3.76
Planning	34	9.53	4.34	4	17	21	15.00	2.97	10	20	−5.09 (<0.001*)	−5.47
Remembering	34	5.79	2.46	4	14	21	8.67	2.78	5	15	−3.89 (<0.001*)	−2.87
Communicating	34	6.82	2.69	4	14	21	10.67	2.79	7	16	−5.07 (<0.001*)	−3.84
Total	34	45.82	6.87	31	55	21	68.05	8.54	57	86	−10.08 (<0.001*)	−22.22

SD: Standard deviation, * Statistical significance, M. Diff: Mean difference

Table 5: Association between self-reported adherence with annualized bleeding rate and number of target joint.

Variable		Treating	Timing	Dosing	Planning	Remembering	Communicating	Sum
Annualized bleeding rate (Log)	Adherent	0.22 (0.422)	0.18 (0.512)	−0.09 (0.736)	−0.29 (0.276)	−0.02 (0.934)	0.10 (0.71)	−0.01 (0.958)
	Non-Adherent	−0.30 (0.921)	0.15 (0.630)	−0.30 (0.318)	−0.33 (0.269)	0.43 (0.141)	0.02 (0.941)	−0.06 (0.855)
	Both	0.06 (0.758)	0.16 (0.401)	−0.15 (0.428)	−0.27 (0.152)	0.16 (0.395)	0.06 (0.751)	−0.01 (0.961)
Number of target joint (Log)	Adherent	0.33 (0.381)	0.22 (0.573)	−0.25 (0.524)	0.26 (0.506)	−0.32 (0.395)	0.17 (0.658)	0.33 (0.390)
	Non-Adherent	−0.36 (0.280)	−0.42 (0.197)	−0.42 (0.194)	−0.29 (0.392)	0.11 (0.752)	−0.610 (0.046)*	−0.63 (0.039)*
	Both	−0.19 (0.417)	−0.07 (0.768)	−0.40 (0.082)	−0.08 (0.750)	−0.20 (0.392)	−0.32 (0.164)	−0.32 (0.171)

*Statistical significance

from developed countries where adherence levels of 80–87% were reported.[16] Many factors affect adherence to treatment and include availability of CFC, illness perceptions, beliefs about medication, and outcome expectations.[17] Even though the CFCs are donations from the Humanitarian Aid Program of WFH, the lack of socioeconomic support for PWH in this environment compared to those living in developed countries might be contributory to the level of adherence observed among them. Taking a closer look on the subscale, this study indicates that participants in the adherence group had the greatest adherence in dosing regimen, meaning that they were more likely to stick with their dosing regimen without increasing or decreasing it. They, however, had problems with timing of the administration of the CFC which may reflect their lack of awareness about the importance of early treatment of bleeding episodes.[18] On the other hand, this study indicated that the major issues in non-adherence to treatment are related to timing, planning, and dosing. Therefore, there is a need for further patients' education on the importance of adherence to prescribed treatment which should be planned while putting into consideration dosing and timing of the regimen.

In furtherance to the above, there was a statistically significant difference in the overall VARITAS-PRN score between the adherent and non-adherent groups in all aspects including treating, timing, dosing, planning, and remembering. This moreover supports that there is a need for HTCs to have a more encompassing and holistic approach during the education and counseling sessions on these adherence subscales.

Just as reported by Armstrong *et al.*,[15] our study found no statistically significant differences between the mean age,

Table 6: Subanalysis of the adherence subscales for age.

Variable		Age (months)		Bivariate Test
Subscales	**Adherent**	**≤18**	**>18**	**(*P*-value)**
Timing	Yes	3 (20.0)	5 (27.8)	0.699
	No	12 (80.0)	13 (72.2)	
Dosing	Yes	7 (46.7)	9 (50.0)	1.000
	No	8 (53.3)	9 (50.0)	
Planning	Yes	2 (13.3)	4 (22.2)	0.665
	No	13 (86.7)	14 (77.8)	
Remember	Yes	13 (86.7)	16 (88.9)	1.000
	No	2 (13.3)	2 (11.1)	
Treating	Yes	11 (73.3)	15 (83.3)	0.674
	No	4 (26.7)	3 (16.7)	
Communication	Yes	9 (60.0)	11 (61.1)	1.000
	No	6 (40.0)	7 (38.9)	
Overall	Yes	8 (53.3)	10 (55.6)	1.000
	No	7 (46.7)	8 (44.4)	

ABR, and the number of target joints between the adherent and non-adherent groups. Subanalysis of the subscales also showed no statistical difference between the adherence and non-adherence group for ABR, on the contrary, for target joints, communication was a significant determinant of adherence [Table 6]. During counseling, it is pertinent to emphasize the importance of good communication between the patient, doctors, and nurses of the treatment center, in case, they have questions or concerns. In addition, more effective means of communication other than physically coming to the treatment centers should be explored by the HTCs to bridge communication gaps as it affects adherence, especially in PWH with target joints. As previously suggested, establishing a good relationship between the HTC personnel with the PWH and their caregivers can increase adherence to hemophilia.[16,19]

The strength of this study lies in the fact that it is the first in Nigeria and sub-Saharan African to describe adherence to on-demand therapy in PWH. However, it is limited by its small sample size which was due to our inability to recruit more PWH during the period of the study owing to the higher number of PWH opting for and already enrolled in the prophylactic treatment regimen.

CONCLUSION

The adherence level of Nigerian PWH receiving on-demand treatment is very poor with a high frequency of target joints. Communication between patient and caregivers with the doctors and nurses of the HTCs should be strengthened. Patient education that can address all aspects of the VERITAS-PRN subsets is encouraged to improve adherence to treatment protocol which may reduce target joints and ultimately improve joint health and/or prevent future complications arising from more severe bleeding episodes.

Author contributions

TUN: Conceptualized and designed the study; TUN, HCO, YS, CEU, MO, DG, and JNO: Contributed to the interpretation of data analysis and writing up of manuscript.

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Ethical approval

The research/study was approved by the Institutional Review Board at University of Nigeria Teaching Hospital Enugu, number NHREC/05/01/2008B-FWA00002458-1RBOOOO2323, dated 14th June 2022.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Conflict of interest

There are no conflicts of interest.

Use of AI-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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