Original Article

Epidemio-clinical Profile and the Effect of Intensity of Clotting Factor Administration on Haemophilia A Patients in a Resource Limited Peripheral Medical College

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Abstract

Background : Epidemio-clinical data of the Haemophilia children in the Eastern India are scarce. Supply of clotting factor is also a major issue for a resource limited Haemophilia Treatment Centre. So, our aim was to study the epidemio-clinical profile of the Haemophilia children attending a Peripheral Medical College and the impact of intensity of clotting factor administration on the Annualised Bleeding Rate (ABR) of Haemophilia A patients to find a suitable prophylactic regimen.

Materials and Methods : This was a cross sectional retrospective hospital based single centre study on the Haemophilia patients under the age of 18 years diagnosed with clotting factor estimation and attending a resource limited Haemophilia Treatment Centre of a Peripheral Medical College between July, 2019 to December, 2019. Epidemio-clinical data were obtained. The mean ABR was compared between different groups of intensity of clotting factor administration.

Results : Haemophilia A comprised of 46 (88.46%) and Haemophilia B 6 (11.54%) patients. Family history was present in 34 (65.38%). Hemophilia was severe in 46 (88.46%). The most common first clinical presentation was bruise. Knee joint was most common joint involved. Occurrence of target joint was seen in 28 patients (53.85%). No patient could receive the full annualised dose of the prescribed prophylactic factor therapy. Episodic treatment were received by 22, prophylactic therapy by 30 patients. Comparison of ABR between the three groups of intensity of clotting factor administration was statistically significant (p value 0.002065) and comparison between intermediate level prophylactic group and low level prophylactic group was statistically not significant (p value 0.68947).

Conclusion : Given the limited supply of clotting factor, one has to settle with the intermediate or low level prophylaxis regimen and with strict compliance to regular infusions and required intervals between the infusions.

Key words : Haemophilia, On Demand Therapy, Prophylactic Therapy, Low Level Prophylaxis, Intermediate Level Prophylaxis, Target Joint.

Haemophilia A and B are congenital bleeding disorders caused by an X-chromosome linked deficiency in coagulation factors VIII or IX respectively. Severe deficiency is associated with bleeding into the joints and recurrent bleeding results in haemophilic arthropathy, disability and reduced Quality of Life. As per the recent population statistics by World Federation of Haemophilia (WFH) about 1,97,183 people are suffering from Haemophilia Globally and India contributes to 9.2% of the Haemophilia burden. Data on epidemiological and clinical profile of the Haemophilia children in the peripheral parts of West Bengal and Eastern India are scarce[1].

The bleeding is treated with intravenous Factor VIII/IX concentrate either on demand or prophylactically. In Haemophilia, prophylaxis can be defined as the administration of clotting factor concentrate in anticipation of or to prevent bleeding. On demand or episodic treatment refers to administration of replacement factor only in response to clinically evident bleeding. Now-a-days prophylactic therapy is becoming more common[1].

Editor's Comment :

- Haemophilia though rare do occur in rural community occasionally. There is little to choose between intermediate and low level prophylaxis regimen. But what is must is strict compliance to the schedule of clotting factor administration.

Haemophilias are divided into three different degrees of severity with clotting factor activity as Severe (<1%), Moderate (1-5%) and Mild (5-40%)[2].

Our aim was to study the Clinico-epidemiological profile of the Haemophilia children attending the resource limited Haemophilia Treatment Centre of a Peripheral Medical College and the impact of intensity of clotting factor administration on the Annualised Bleeding Rate of Haemophilia A Patients.

Material and Method

A cross sectional retrospective hospital based single centre study was conducted in the Paediatric Haemophilia treatment centre in a resource limited Peripheral Medical College from July, 2019 to December, 2019. Institutional Ethics Committee (IEC) approval was taken. Informed written consent was taken from the parents or legal guardian if applicable.

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All children of Haemophilia who attended Paediatrics Haemophilia Treatment Centre were study population. In 52 Haemophilia patients were included in the study.

Inclusion Criteria :

- Haemophilia patients diagnosed with clotting factor assessment.
- Age below 18 years.
- Haemophilia patients attending for prophylactic clotting factor administration and admitted for on demand factor concentrate therapy.

Exclusion Criteria :

- Patients with platelet and vascular disorders.
- Patients with clinically relevant coagulation disorders other than Haemophilia A or B.
- Patients with Hepatitis B virus, Hepatitis C virus or Human Immune Deficiency Virus infections.
- Subjects with hepatic or renal impairment.
- Patient having chronic illness or taking chronic medication.

The study was neither sponsored nor funded.

Retrospective data were obtained and recorded in a predesigned proforma by interviewing the Haemophilia children or their parents and from the Haemophilia Treatment Centre records. For statistical analysis data were entered into a Microsoft excel spreadsheet and then analyzed by SPSS (version 27.0; SPSS Inc, Chicago, IL, USA) and GraphPad Prism version 5.

Standard half life clotting factors were used in our study. Prophylactic therapy was initiated with 20 IU/kg/dose three times weekly ie, 3120 IU/kg/year. Their mean annualized clotting factor administration were calculated and the relationship with their mean Annualized Bleeding Rate was analysed.

Annualised clotting factor administration was calculated by the clotting factor administered per kg body weight during 6 months period multiplied by two.

The Annualized Bleeding Rate (ABR) was calculated as the number of reported bleeding events during six months and multiplied by two.

Determination of intensity of prophylactic clotting factor administration was on the basis of those between 3120 – 2341 IU/kg/year (More than 75% of the prescribed dose) as intermediate level prophylactic group and between 2340 – 1561 IU/kg/year (ie, between 75-50% of the prescribed dose) as low level prophylactic group.

The Annualized Bleeding Rate between the intermediate level prophylactic group, low level prophylactic group and on demand group in Haemophilia A patients were compared. One way ANOVA test was applied between them. The Annualized Bleeding Rate between the intermediate level prophylactic group and low level prophylactic group was compared by applying 't' test.

Results

Determination of intensity of prophylactic clotting factor administration was on the basis of —

*Intermediate level prophylactic group - those between 3120 – 2341 IU/kg/year (More than 75% of the prescribed dose)

Table 1 — *Epidemio-clinical profile of Haemophilia children (N=52)*

Age in years	1-5 years	13 (25%)
	6-10 years	25 (48.08%)
	11-15 years	14 (26.92%)
	Total	52
Residence	Rural	45 (86.54%)
	Urban	7 (13.46%)
	Total	52
Socio-economic status	Lower	31 (59.62%)
	Lower middle	5 (9.62%)
	Upper lower	11 (21.16%)
	Upper middle	5 (9.62%)
	Total	52
Type of Haemophilia	Haemophilia A	46 (88.46%)
	Haemophilia B	6 (11.54%)
	Total	52
Haemophilia severity	Mild	0 (0%)
	Moderate	6 (11.54%)
	Severe	46 (88.46%)
	Total	52
Family history	Absent	18 (34.62%)
	Present	34 (65.38%)
	Total	52
First clinical presentation	Bruise	30 (57.69%)
	Gum bleed	3 (5.77%)
	Joint bleed	11 (21.15%)
	Muscle bleed	4 (7.69%)
	Prolonged bleeding from wound	3 (5.77%)
	Scalp haematoma	1 (1.92%)
	Total	52
Modality of Treatment	On demand	22 (42.31%)
	Prophylactic	30 (57.69%)

Table 2 — *Epidemio-clinical profile of Haemophilia children (N=52)*

	Mean	SD	Min	Max
Age in years	8.3743	2.6583	3	14
Weight (in kg)	25.6743	9.3687	11	50
Height (in cm)	122.9061	18.4366	82	164
BMI	16.3592	1.8224	11.57	21.97
Age at presentation (in months)	19.7728	16.8940	8	72

Table 3 — *Clinical profile of joint involvement (N=52)*

		Total (N=52)
Knee joint bleeds		38 (73.08%)
Ankle joint bleeds		16 (30.77%)
Wrist joint bleeds		14 (26.92%)
Elbow joint bleeds		12 (23.1%)
Target joint		28 (53.85%)
Target joint type :	Knee	21/28 (75%)
	Ankle	5/28 (17.86%)
	Wrist	1/28 (3.57%)
	Elbow	1/28 (3.57%)
	Total	28 (100%)

Table 4 — *Effect of level of clotting factor administration on the Annualized Bleeding Rate (ABR) of Haemophilia A patients (N=46)*

Intensity of clotting factor administration	No of patients	Annualized Bleeding Rate				p-value
		Mean	SD	Min	Max	
Intermediate level prophylactic group*	13	4.77	1.30	4	8	0.002065
Low level prophylactic group**	13	6	2.58	4	12	
On demand group***	20	7.8	2.59	4	12	

**Corresponds to the intermediate level prophylactic group description (3120-2341 IU/kg/year).*
***Corresponds to the low level prophylactic group description (2340-1561 IU/kg/year).*
****Corresponds to the on demand group description (those Haemophilia A patients who were administered clotting factor based on clinically evident bleeding not on prophylaxis.*

**Low level prophylactic group – those between 2340-1561 IU/kg/year (ie, between 75-50% of the prescribed dose)

***On demand group included those Haemphilia A patients who were administered clotting factor based on clinically evident bleeding not on prophylaxis.

Discussion

Out of total 52 Haemophilia patients, 25 (48.08%) patients were of 6-10 years age, 14 (26.92%) patients of 11-15 years age and 13 (25%) patients of 1-5 years age. In a study by Manco Johnson, patients were of less than 30 months age[3]. In a study in Bangladesh[4] 22 (44%) patients were of 6-15 years and 19 (38%) patients were of 16-30 years age.

In 45 (86.54%) patients were staying at Rural area. In 31 (59.62%) patients belonged to Lower Socio-economic class, 11 (21.16%) in Upper Lower Socio-economic class, 5(9.62%) in Lower Middle Socio-economic class and 5 (9.62%) in Upper Middle Socio-economic class according to Modified Kuppuswamy's scale[5].

Haemophilia A was observed in 46 patients (88.46%) while Haemophilia B was observed in 6 patients (11.54%). In most of the earlier studies, Haemophilia A constituted around 80% of total Haemophilias[4,6,7]. In a Pakistani study, proportion of Haemophilia A was found to be low (65%) [8].

In 46 Haemophilia patients (88.46%) had Severe and 6 Haemophilia patients (11.54%) had Moderate factor deficiency. In a study in Jodhpur, 44% cases had Severe, 36% had Moderate, and 20% had Mild disease[6]. Other studies from India showed similarly high percentages of severe Haemophilia[9-11]. Striking contrast was seen in a study in Bangladesh where only 10 % of Haemophilia B had Severe disease[7]. Data from the high-income countries showed prevalence of 39%, 14% and 45% of Mild, moderate and Severe cases, respectively[1].

Family history of Haemophilia was present in 34 patients (65.38%). Similar results were obtained in a study in India where family history was present in 53% of Haemophilia A and 45% of Haemophilia B patients[9]. In a study in Bangladesh, 40% cases had family history of bleeding[7].

In 30 (57.69%) patients had bruise as the first clinical presentation,11 patients (21.15%) had joint bleed, 4 patients (7.69%) had muscle bleed, 3 patients (5.77%) had gum bleed, 3 patients (5.77%) had prolonged bleeding from wound and scalp Haematoma was present in 1 patient (1.92%). In one study, postcircumcision bleed has been found to be the most common initial bleed (51.4-62% of the case)[12]. In a study at Jodhpur, Post-traumatic bleed was the most common first clinical presentation in 36% cases[6]. In a study at Bangladesh, bruises and echymoses were the most common initial presentation in 40% of cases[7].

Knee joint bleeds were observed in 38 (73.08%) patients, Ankle joint bleeds in 16 (30.77%), Wrist joint bleeds in 14 (26.92%) and Elbow joint bleeds in 12 (23.1%). Similar findings were seen in a study at Jodhpur, where Knee joint was predominantly affected (68%) followed by Ankle joint (52%) then Elbow joint (36%)[6]. In a study at Korea, joints more frequently affected were the knee (89.0%), the Elbow (22.5%) and Ankles (21.5%)[12].

When bleeding occurs repetitively into the same joint, it is called a Target joint[13]. Target joints were present in 28 (53.85%) patients. In a study at Jodhpur, 37.5 % patients of haemophilia had developed Target joint[14]. In our study, the Target joint involved was knee joint in 21 (40.38%), Ankle joint in 5 (9.62%), Wrist joint in 1 (1.92%) and Elbow joint in 1 (1.92%) patient. In a study at Jodhpur, knee joint was the predominant Target joint in 28.57% cases[14].

22 (42.31%) Haemophilia patients received on demand and 30 (57.69%) patients received prophylactic coagulation factor therapy. In a study in Indonesia, 50% patients received on demand factor therapy and 50% patients received prophylactic factor therapy[15]. In a study in Italy, 51% patients received prophylaxis and 49% patients received on demand therapy[16].

Prophylactic therapy administered to 26 of the Haemophilia A patients were 20 IU/kg/dose thrice weekly that is equivalent to 3120 IU of clotting factor per kg per year. But none of the patients could receive the full quota of the clotting factor. These patients were divided into two subgroups. Intermediate level prophylactic group comprising of 13 patients, received more than 75% of the prescribed dose (3120-2341 IU of clotting factor per kg per year). Low level prophylactic group comprising of 13 patients, received 75-50% of the prescribed dose (2340-1561 IU of clotting factor per kg per year). On demand therapy administered to 20 of the Haemophilia A patients received 1538 IU of clotting factor per kg per year.

The Annualized Bleeding Rate (ABR) was calculated as the number of reported bleeding events in 6 months and multiplied by 2. The mean ABR in the intermediate level prophylactic group was 4.77 (SD 1.30), that in the

low level prophylactic group was 6 (SD 2.58), that in the on demand group was 7.8 (SD 2.59). The three groups were compared by applying one way ANOVA test and the result was statistically significant (p value 0.002065). Similar results were obtained by a systematic review and meta-analysis done by Carolina J Delgado-Flores, *et al*[17].

When the annualised bleeding rate was compared between intermediate level prophylactic group with that of low level prophylactic group by applying t test, the result was statistically not significant (p value 0.68947).

A study done by jiu-Mu-Zhuang, *et al* concluded that low intermediate treatment dose of prophylaxis with FVIII can significantly improve the bleeding phenotype and delay the joint injury progression, when compared with on demand treatment[18].

An article highlighted more than 90% cost of hemophilic treatment is due to clotting factor. 80% of World Haemophilia patients live in resource limited conditions. 10-20% of these are identified. Advocacy are necessary to engage the Government along with other measures[19].

Low dose FVIII prophylaxis was cost effective, efficacious and safe for the treatment of joint bleeds and consequent joint changes were observed by Verma SP, *et al*[20].

Supply of clotting factor is a major issue for a resource limited Haemophilia Treatment Centre. Issue may be with the quantity and its regularity of supply and also its cost-effectiveness. Infusions of the clotting factor should be tailored according to requirements at the level of the Haemophilia Treatment Centre and at the individual level of the patient for optimal utility in terms of affordability, feasibility and accessibility keeping in mind the interest of the children who are bleeding and crippling and becoming burden to themselves and the society.

Conclusions

Given the limited supply of clotting factor, one has to settle with the intermediate or low level prophylaxis regimen and with strict compliance to regular infusions and required intervals between the infusions. The effectiveness of these regimens should be determined through different studies in the future.

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Conflict of Interest : None.

References

1 Report on the Annual Global Survey 2015. Montreal: World Federation of Haemophilia; 2016.
2 Biggs R, Macfarlane RG — Haemophilia and related conditions: A survey of 187 cases. *Br J Haematol* 1958; **4:** 1-27. doi: 10.1111/j.1365-2141.1958.tb03830.x.
3 Manco-Johnson MJ, Abshire TC, Shapiro AD, Riske B, Hacker MR, Kilcoyne R, *et al* — Prophylaxis versus episodic treatment to prevent joint disease in boys with severe haemophilia. *N Engl J Med* 2007; **357(6):** 535-44. doi: 10.1056/NEJMoa067659. PMID: 17687129.
4 Uddin MM, Rahman MJ, Rahman MM, Sultana SA, Shah MS — Clinico-pathological study on haemophilia: An analysis of 50 cases. *J Bangladesh Coll Phys Surg* 2006; **24:** 50-3.
5 Wani RT — Socio-economic status scales-modified Kuppuswamy and Udai Pareekh's scale updated for 2019. *J Family Med Prim Care* 2019; **8(6):** 1846-9. doi:10.4103/jfmpc.jfmpc_288_19
6 Payal V, Sharma P, Goyal V, Jora R, Parakh M, Payal D — Clinical profile of haemophilia patients in Jodhpur Region. *Asian J Transfus Sci* 2016; **10(1):** 101-4. doi:10.4103/0973-6247.164269
7 Karim MA, Siddique R, Jamal CY, Islam A — Clinical profile of haemophilia in children in a tertiary care hospital. *Bangladesh J Child Health* 2013; **37:** 90-6.
8 Mohsin S, Saeed T, Hussain S, Mahmood S, Sohail S — Clinical manifestations and complications of haemophilia A in Pakistan. *Ann Pak Inst Med Sci* 2010; **6:** 168-71.
9 Pawan PK, Mahima Y, Vijai T, Manjula L — Clinicopathological features of haemophilia in a tertiary care centre of India. *J Family Med Prim Care* 2021; **10(1):** 295-9. doi:10.4103/jfmpc.jfmpc_1564_20
10 Sahoo T, Naseem S, Ahluwalia J, Marwaha RK, Trehan A, Bansal D — Inherited bleeding disorders in north indian children: 14 years' experience from a tertiary care center. *Indian J Hematol Blood Transfus* 2020; **36:** 330.
11 Kumar S, Sinha S, Bharti A, Meena LP, Gupta V, Shukla J — A study to determine the prevalence, clinical profile and incidence of formation of inhibitors in patients of haemophilia in North Eastern part of India. *J Family Med Prim Care* 2019; **8:** 2463.
12 Kim KY, Yang CH, Cho MJ, Lee M — Comprehensive clinical and statistical analysis of haemophilia in Korea. *J Korean Med Sci*. 1988; **3(3):** 107-15. doi:10.3346/jkms.1988.3.3.107
13 Conway JH, Hilggatner MW — Initial Presentation of Pediatric Haemophiliacs. *Arch Ped Adoles* 1994; **148:** 589-94.
14 Payal V, Sharma P, Chhangani NP, Janu Y, Singh Y, Sharma A — Joint Health Status of Haemophilia Patients in Jodhpur Region. *Indian J Hematol Blood Transfus* 2015; **31(3):** 362-6. doi: 10.1007/s12288-014-0465-2. Epub 2014 Nov 2. PMID: 26085722; PMCID: PMC4465520.
15 Chozie NA, Primacakti F, Gatot D, Setiabudhy RD, Tulaar ABM, Prasetyo M — Comparison of the efficacy and safety of 12-month low-dose factor VIII tertiary prophylaxis vs on-demand treatment in severe haemophilia A children. *Haemophilia* 2019; **25(4):** 633-9. doi: 10.1111/hae.13770. Epub 2019 May 2. PMID: 31044491.
16 Tagliaferri A, Feola G, Molinari AC, Santoro C, Rivolta GF, Cultrera DB, *et al* — POTTER Study Group. Benefits of prophylaxis versus on-demand treatment in adolescents and adults with severe haemophilia A: the POTTER study. *Thromb Haemost* 2015; **114(1):** 35-45. doi: 10.1160/TH14-05-0407. Epub 2015 Apr 9. PMID: 25855376.
17 Delgado-Flores CJ, García-Gomero D, Salvador-Salvador S, Montes-Alvis J, Herrera-Cunti C, Taype-Rondan A — Effects of replacement therapies with clotting factors in patients with hemophilia: A systematic review and meta-analysis. *PLoS One* 2022; **17(1):** e0262273. doi: 10.1371/journal.pone.0262273. PMID: 35030189; PMCID: PMC8759703.
18 Zhuang JM, Sun XY, Zhou X, Liu ZQ, Sun J — [Prophylactic treatment with low- and intermediate-dose factor VIII in children with severe hemophilia A: comprehensive evaluation of joint outcomes and correlation analysis]. *Nan Fang Yi Ke Da Xue Xue Bao* 2018; **38(4):** 496-501. Chinese. doi: 10.3969/j.issn.1673-4254.2018.04.21. PMID: 29735454; PMCID: PMC6765665.
19 Ghosh K, Ghosh K — Overcoming the challenges of treating hemophilia in resource-limited nations: a focus on medication access and adherence. *Expert Rev Hematol* 2021; **14(8):** 721-30. doi: 10.1080/17474086.2021.1957826. Epub 2021 Jul 29. PMID: 34278926.
20 Verma SP, Dutta TK, Mahadevan S, Nalini P, Basu D, Biswal N, *et al* — A randomized study of very low-dose factor VIII prophylaxis in severe haemophilia - A success story from a resource limited country. *Haemophilia* 2016; **22(3):** 342-8. doi: 10.1111/hae.12838. Epub 2016 Mar 14. PMID: 26987935.