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Low Dose Prophylaxis Vis-à-vis on Demand Treatment Strategies for Hemophilia: a Cost Effective and Disability Attenuatiy Careng Approach a Prospective Study in a Tertiary Care Hospital

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ABSTRACT
Hemophilia A and B are X chromosome-linked bleeding disorders caused by mutations in factor VIII (FVIII) and factor IX (FIX) genes, respectively. Hemophilia accounts for 80-85% of all hemophilia cases. To compare the effect of low dose prophylaxis versus on demand treatment for haemophilia in terms of frequency of bleeding, joint function and quality of life (hospitalization and absenteeism from work/ school). The present study was a Hospital based comparative study. This Study was conducted from 18 months at Department of Clinical Haematology Gauhati Medical College And Hospital Guwahati, Assam. By the end of 18 month follow up, clinical joint disease was seen in 77.5% cases managed by on demand treatment as compared to 20% managed by LDP ($p<0.01$). Good joint response was seen in 45% cases managed by LDP as compared to none in on demand group while none of the cases on LDP had poor response as compared to 42.5% on demand treatment ($p<0.01$). Inhibitor essay was positive in 3 cases (7.5%) manged by on demand treatment as compared to none in cases of LDP group (p-0.07). Hospital admission was required in 57.5% cases managed by on demand treatment as compared to 7.5% managed by LDP ($p<0.01$). Mean hospital stay was 2 days in LDP group while it was 3.3 days in on demand group ($p<0.01$). Mean school/ work days missed was 5.68 days in on demand group as compared to 1.43 days in LDP group ($p<0.01$). By the end of 18 months, none of the cases of LDP group showed severe disease as compared to 27.5% cases in on demand group. The improvement in LDP group cases was statistically significant (proportion of severe cases reduced from 0-85%). Concluded that low dose prophylaxis for hemophilia is more effective than on demand treatment. Cases managed by low dose prophylaxis had lower annualized bleeding rate, hospital admissions and absenteeism from work/ school and showed significant improvement in joint function. Cases managed by low dose prophylaxis were also able to maintain the factor levels and had lower risk of developing inhibitors. Present study thus recommends the use of low dose prophylaxis for hemophilia management as compared to on demand treatment.

INTRODUCTION

Hemophilia A and B are X chromosome-linked bleeding disorders caused by mutations in factor VIII (FVIII) and factor IX (FIX) genes, respectively[1]. Hemophilia A accounts for 80-85% of all hemophilia cases[2]. Consequently, the ability of the blood to coagulate gets impaired, leading to an increased risk of delayed bleeding, which in turn results in serious and life-threatening health problems. It is more frequently observed in males compared with females and may be caused by homozygosity and lionization. On the basis of clotting factor concentrations, the disease can be severe (factor level of <1 IU dL^{-1}), moderate (1-5 IU dL^{-1}), or mild (>5 IU dL^{-1}). Patients with severe hemophilia represent about half of diagnosed cases[2,3]. The common serious sites of bleeding in hemophilia include joints (hemarthrosis), muscles, especially deep compartments (iliopsoas, calf and forearm) and mucous membranes in the mouth, gums, nose and genitourinary tract, whereas life-threatening bleeding sites include intracranial, neck/throat, or gastrointestinal regions. The frequency of bleeding varies depending on the site: joints (70-80%), muscle (10-20%), other sites (major bleeds; 5-10%) and central nervous system (< 5%)[2]. The risk of mineral density is high in patients with hemophilia compared with the normal population, which may be due to severity of hemophilia, hemophilic arthropathy and the resultant immobility. Hence, the World Federation of Hemophilia (WFH) recommends regular physical activity[4].

Hemophilia A has an estimated incidence of approximately 24.6 cases per 100,000 births[4]. According to the WFH Annual Global Survey of 2018, the number of people with hemophilia around the world is approximately 400,000, with India reporting the highest prevalence (20,778), followed by the United States (17,757) and China (14,390)[2].

Prophylaxis is universally recognized as the treatment of choice for persons with haemophilia. Early prophylaxis is found to be superior to episodic treatment (ET) in reducing the risk of overall bleeding and improving joint health and quality of life (QoL)[5]. It is classified as primary, secondary and tertiary prophylaxis based on the time at which it is initiated. Primary prophylaxis is the regularly scheduled prophylaxis started before 3 years of age in the absence of any documented joint disease and before the second clinically evident joint bleed. These patients are less likely to have arthropathy. Secondary prophylaxis commences after two or more joint bleeds before the onset of joint disease. Tertiary prophylaxis is the initiation of prophylaxis after the onset of joint disease and it can be started at any age. The aim of tertiary prophylaxis is to slow the deterioration of joints, reduce pain and maintain mobility, specifically in adult haemophilia patients[4].

The objective of prophylaxis is to transition a person with severe haemophilia (factor VIII/factor IX [FVIII/FIX] <1 IU dL^{-1}) to mild or moderate haemophilia by maintaining factor levels above 1 IU dL^{-1}[6]. The major barrier in implementing this clinically effective therapy worldwide is the huge cost incurred on factors. The standard high-dose prophylactic regimen requires factor dosage of 25-40 IU kg^{-1}, thrice weekly, which is not feasible in majority of the developing countries like India. Here, on demand (OD) is still the mode of treatment. OD treatment is documented to have several potential risks such as increased bleeding rate, disability due to hemarthrosis, poor quality of life and increased chances of mortality. Several studies conducted in developed countries have confirmed the clinical efficacy of prophylaxis in Haemophilia treatment.

MATERIALS AND METHODS

Study area: Department of Clinical Haematology of Guwahati Medical College (OPD and IPD).

Study population: Patients attending OPD and IPD of dept. of clinical haematology, Gauhati Medical College and Hospital (GMCH).

Study design: Hospital based comparative study. Period of study 18 months.

Inclusion criteria:

- Severe Haemophiliacs > 3 years of Age
- Either gender
- Regular follow up for 18 months

Exclusion Criteria:

- Patient <3years
- The patients with history of inhibitors
- Patients not followed up regularly

Methodology: Study was commenced after approval from ethical committee and informed consent from patients. Study included 40 cases each in two groups of treatment:

- Cases who received on-demand treatment of plasma-derived factor infusion (Factor VIII for Haemophilia A and Factor IX for haemophilia B) - 40 cases
- Cases on low dose prophylaxis period received dose of Factor VIII 10 IU per kg body weight twice a week for haemophilia A and Factor IX 20 IU per kg body weight once weekly for haemophilia B

RESULT

Mean age of the study group was 13.26 years with 30% cases being under 5 years of age. Out of the total 80 cases, 79 (98.9%) were males while we had only one

female case (1.3%). Two third (66.3%) of the cases belonged to rural area while one third to urban area.

Out of the total 80 cases, 70 (87.5%) were of haemophilia type A while 10 (12.5%) were of type B. Family history of haemophilia was given by 27.5% cases. History of consanguinity was given by 7.5% cases.

At baseline, 41.3% cases were having moderate disease while 58.8% had severe disease. Most common involved joint was knee joint (73.8%) followed by ankle joint (21.3%). Study group was managed by one of the following two treatment (40 cases each) i.e., low dose prophylaxis and on demand treatment. Mean age of cases managed by on demand treatment was significantly more than those managed by low dose prophylaxis (19.45 vs. 7.09 years, p<0.01).

No association was observed between the type of treatment with place of residence, type of haemophilia, positive family history or history of consanguinity (p>0.05). A total of 85% cases on low dose prophylaxis had severe disease as compared to 32.5% managed by on demand treatment (p<0.01). Annualized bleeding rate was observed to be significantly more in cases manged by on demand treatment as compared to low dose prophylaxis (4.15 vs. 1.23; p<0.01) (Table 1).

By the end of 18 month follow up, clinical joint disease was seen in 77.5% cases managed by on demand treatment as compared to 20% managed by LDP (p<0.01). Good joint response was seen in 45% cases managed by LDP as compared to none in on demand group while none of the cases on LDP had poor response as compared to 42.5% on demand treatment (p<0.01). Inhibitor essay was positive in 3 cases (7.5%) manged by on demand treatment as compared to none in cases of LDP group (p-0.07). Hospital admission was required in 57.5% cases managed by on demand treatment as compared to 7.5% managed by LDP (p<0.01) (Table 2).

Mean hospital stay was 2 days in LDP group while it was 3.3 days in on demand group (p<0.01). Mean school/work days missed was 5.68 days in on demand group as compared to 1.43 days in LDP group (p<0.01).

Table 1: Association of type of treatment with family history, consanguinity, type of haemophilia and severity of haemophilia at baseline

	Treatment group			
Parameters	LDP (%)	OD (%)	Total (%)	p- value
Family history of haemophilia				
No	28 (70.0)	30 (75.0)	12 (30.0)	0.803
Yes	12 (30.0)	10 (25.0)	22 (27.5)	
Total	12 (30.0)	10 (25.0)	80 (100.0)	
Consanguinity				
No	36 (90.0)	38 (95.0)	74 (92.5)	0.675
Yes	4 (10.0)	2 (5.0)	6 (7.5)	
Total	40 (100.0)	40 (100.0)	80 (100.0)	
Type of haemophilia				
A	36 (90.0)	34 (85.0)	70 (87.5)	0.737
B	4 (10.0)	6 (15.0)	10 (12.5)	
Total	40 (100.0)	40 (100.0)	80 (100.0)	
Severity of haemophilia at baseline				
Moderate	6 (15.0)	27 (67.5)	33 (41.3)	<0.01
Severe	34 (85.0)	13 (32.5)	47 (58.8)	
Total	40 (100.0)	40 (100.0)	80 (100.0)	

Table 2: Association of type of treatment with clinical joint disease, WFH - Joint Response, Inhibitor Assay, Hospital Admissions and Severity of haemophilia at 18 month

	Treatment group			
	LDP	OD	Total	p-value
Clinical joint disease				
No	32 (80.0)	9 (22.5)	41 (51.2)	<0.01
Yes	8 (20.0)	31 (77.5)	39 (48.8)	
Total	40 (100.0)	40 (100.0)	80 (100.0)	
Wfh-joint response				
Good	18 (45.0)	0 (0.0)	18 (22.5)	<0.01
Mild	15 (37.5)	5 (12.5)	20 (25.0)	
Moderate	7 (17.5)	18 (45.0)	25 (31.3)	
Poor	0 (0.0)	17 (42.5)	17 (21.3)	
Total	40 (100.0)	40 (100.0)	80 (100.0)	
Inhibitor assay				
Negative	40 (100.0)	37 (92.5)	77 (96.3)	0.07
Positive	0 (0.0)	3 (7.5)	3 (3.8)	
Total	40 (100.0)	40 (100.0)	80 (100.0)	
Hospital admissions				
No	37 (92.5)	17 (42.5)	54 (67.5)	<0.01
Yes	3 (7.5)	23 (57.5)	26 (32.5)	
Total	40 (100.0)	40 (100.0)	80 (100.0)	
Severity of haemophilia at 18 month				
Moderate	40 (100.0)	29 (72.5)	69 (86.3)	<0.01
Severe	0 (0.0)	11 (27.5)	11 (13.8)	
Total	40 (100.0)	40 (100.0)	80 (100.0)	

Table 3: Association of type of treatment with mean Annualized bleeding rate (ABR), hospital stay and Days of School/ Work Missed

Variables	Treatment group	Number	Mean	SD	p-value
Annualized bleeding rate (ABR)	LDP	40	1.23	0.66	<0.001
	OD	40	4.15	1.75	
Hospital stay (days)	LDP	3	2.00	0.00	<0.001
	OD	23	3.30	1.15	
Days of school/WORK MISSED	LDP	40	1.43	0.96	<0.001
	OD	40	5.68	2.78	

By the end of 18 months, none of the cases of LDP group showed severe disease as compared to 27.5% cases in on demand group. The improvement in LDP group cases was statistically significant (proportion of severe cases reduced from 0-85%) (Table 3).

DISCUSSION

The present study was a Hospital based comparative study. This Study was conducted from 18 months at Department of Clinical Haematology Gauhati Medical College And Hospital Guwahati, Assam.

Haemophilia is a X chromosome-linked bleeding disorders caused by mutations in factor VIII (FVIII) and factor IX (FIX) genes, respectivel[1]. Prophylaxis is universally recognized as the treatment of choice for persons with haemophilia. Early prophylaxis is found to be superior to episodic treatment (ET) in reducing the risk of overall bleeding and improving joint health and quality of life (QoL)[5].

The standard high-dose prophylactic regimen requires factor dosage of 25-40 IU kg^{-1}, thrice weekly, which is not feasible in majority of the developing countries like India. Here, on demand (OD)/episodic treatment (ET) is still the mode of treatment. OD treatment is documented to have several potential risks such as increased bleeding rate, disability due to hemarthrosis, poor quality of life and increased chances of mortality.

The present study is an endeavour to assess the effect of low dose prophylaxis in haemophiliacs in terms of frequency of bleeding, joint function and QOL (hospitalization and absenteeism from work/school) as compared to on demand treatment.

Study included 40 cases each in two groups of treatment: Cases who received on-demand treatment of plasma-derived factor infusion (Factor VIII for Haemophilia A and Factor IX for haemophilia B) and; cases on low dose prophylaxis period received dose of Factor VIII 10 IU per kg body weight twice a week for haemophilia A and Factor IX 20 IU per kg body weight once weekly for haemophilia B.

Baseline data: In present study, mean age of the study cohort was 13.26 years with 30% cases being under 5 years of age. Overall, mean age of cases managed by on demand treatment was significantly more than those managed by low dose prophylaxis (19.45 vs. 7.09 years; p<0.01). The difference can be attributed to random sampling error. Out of the total 80 cases, 79 (98.9%) were males while we had only one female case (1.3%). Out of the total 80 cases, 70 (87.5%) were of haemophilia type A while 10 (12.5%) were of type B. Family history of haemophilia was given by 27.5% cases. History of consanguinity was given by 7.5% cases. Rural residents were 66.3% while 33.8% resides in urban area. No association was observed between type of treatment with haemophilia type (p-0.737), family history of haemophilia (p-0.803), place of residence of study group (p-0.34) or history of consanguinity (p-0.675).

Bulagouda *et al*.[8] study observed that majority (42.85%) of cases belonged to 1-5 years age group, followed by 32% cases in 5-10 years age group and the mean age of studied group was 6.8±4.5 years. Out of a total of 56 cases, 51 (91.07%) cases were diagnosed as hemophilia A while five cases (8.92%) were diagnosed as hemophilia B. The study group comprised only males indicating its X-linked recessive inheritance. Positive family history was found in 26 (46.42%) cases. Kumar *et al*.[9] study cohort includes 148 male and 2 female patients. The age of the patients ranges from 5 to 35 years and the mean age was 25 years. Family history of bleeding was observed in 97 [64.7%] cases. Forty-seven (32.3%) HB patients had a history of consanguinity. Gouider *et al*.[10] studied 77 cases of haemophilia. Out of the total 77 hemophilia patients, 66.2% (51/77) were >18 years of age. Type A and B hemophilia patients were 88.3% (68/77) and 11.7% (9/77), respectively. The percentage of hemophilia Type A patients was higher than Type B in both the age groups. The family history was present in 58.4% of the patients. In all these studies, male population was predominant similar to present study, due to the X linked inheritance.

Clinical presentation: At baseline, 41.3% cases were having moderate disease while 58.8% had severe disease. Most common involved joint was knee joint (73.8%) followed by ankle joint (21.3%). A total of 85% cases on low dose prophylaxis had severe disease as compared to 32.5% managed by on demand treatment (p<0.01). This showed that higher number of cases on low dose prophylaxis had severe form of disease.

Bulagouda *et al*.[8] observed that according to the factor level, 25 (44%) cases had severe disease, 20 (36%) had moderate and 11 (20%) had mild disease. Knee joint (67.85%) was predominantly affected by hemarthrosis followed by ankle (51.78%), elbow (35.71%), hip (12.5%) and shoulder (5.35%). Kumar *et al*.[9] observed that out of 150 cases, 102

(68%) cases were diagnosed as severe, 30 (20%) cases were diagnosed as moderate and 18 (12%) cases were diagnosed as mild. The most common initial site of bleed was knee joint [57.3%]. Gouider *et al*.[10] observed severe haemophilia among majority (80.5%) of the patients. Knee joint was observed to be as the target joint among 57.1% of the patients.

Low dose prophylaxis vs on demand treatment: A single centre experience on low dose secondary/tertiary low dose PT in children (4-17 years) with Hemophilia A and B from Tunisia was the first step placed in the implementation of low dose prophylaxis. The study used a median dose of 30 IU kg^{-1} once, twice or thrice/week for Hemophilia A and 25-35 IU/kg/week for Hemophilia B. The study concluded that low dose prophylaxis is more effective than ODT and it has to be the initiating point for prophylaxis in resource limited countries[10].

In present study, cases on low dose prophylaxis received Factor VIII 10 IU kg^{-1} body weight twice a week for haemophilia A and Factor IX 20 IU kg^{-1} body weight once weekly for haemophilia B. Aannualized bleeding rate was observed to be significantly less in cases manged by low dose prophylaxis as compared to ODT (4.15 vs. 1.23; p<0.01). By the end of 18 months, none of the cases of LDP group showed severe disease as compared to 27.5% cases in on demand group. The improvement in LDP group cases was statistically significant (proportion of severe cases reduced from 0-85). Similarly, hospital admission was required in 57.5% cases managed by on demand treatment as compared to only 7.5% managed by LDP (p<0.01). Mean school/ work days missed was 5.68 days in on demand group as compared to 1.43 days in LDP group (p<0.01).

A recent study from China, with similar dose (factor VIII concentrate 10 IU kg^{-1} twice weekly for hemophilia A and factor IX concentrate 20 IU/kg/week for B) reported that low dose secondary PT for hemophilia had significantly reduced frequency of joint bleed. There was moderate improvement in joint function, attendance in school, participation in sport and daily activities. The authors concluded that Low dose secondary prophylaxis in the context of a developing country like China is cost effective[11]. Sidharthan *et al*.[12] recently reported their clinical audit report done in eleven children with severe Hemophilia. Factor VIII concentrate was given at a dose of 20-40 IU kg^{-1} in 2 divided doses/week for Hemophilia A and Factor IX concentrate at 25-40 IU/kg/week for Hemophilia B. The study results were reduction in the bleed rate (11.27 vs. 0.91, p 0.005), reduction in hospitalization rates (12.45 vs. 2.36 days, p 0.005) and reduction in the school absenteeism (78.55 vs. 1.27 days, p 0.01) from the transition of ET to secondary/tertiary PT. Apte *et al*.[14] observed ABR during ET with that of PT as. 19 (15-32) versus 3 (3-9). The days missed were 26 (20-61) during ET and 9 (6-20) for PT. The study showed promising results in terms of ABR and days missed.

Comparison of ABR during the low dose prophylaxis regimen was compared across various studies in Tunisia, China, India and Iran[11]. The comparison with our findings is tabulated below.

In present study, after the follow up period of 18 months, we observed that clinical joint disease was present in 77.5% cases managed by on demand treatment as compared to only 20% managed by LDP (p<0.01). Good joint response was seen in 45% cases managed by LDP as compared to none in on demand group while none of the cases on LDP had poor response as compared to 42.5% on demand treatment (p<0.01). A longitudinal study named MUSFIH study was done to assess the musculoskeletal changes under episodic treatment in haemophilic children of age group 7-12 years. The study pointed that the natural course of bleeding and musculoskeletal functional decline in hemophilia are not altered by large doses of episodic treatment. Prophylaxis is the only treatment method to conserve musculoskeletal function in PwH and episodic treatment should not be the treatment option for hemophilia[15].

In present study, we also observed that inhibitor essay was positive in 3 cases (7.5%) manged by on demand treatment as compared to none in cases of LDP group. The difference was statistically non-significant (p-0.07). Apte *et al*.[14] did a study to evaluate the efficacy of FVIIIc (Eloctate) given in a dose of 20 IU/kg/week as single infusion prophylaxis regimen for severe Hemophilia A. All the study participants were inhibitor negative at start. Inhibitor was still negative in both groups of ET and PT after 50 exposure days of episodic therapy. A similar open label prospective trial was done in the rural part of eastern India. APTT based inhibitor screening was done at the baseline and at the end of 6 months. Inhibitor was absent during ET and PT period. Similarly, Abraham A wt al. study also observed that inhibitors were absent after a median of 70 exposures (range 35-90) in all study participants[16].

Thus, to summarize, cases managed by low dose prophylaxis had lower annualized bleeding rate, hospital admissions and absenteeism from work/ school and showed significant improvement in joint function. Present study thus recommends the use of low dose prophylaxis for hemophilia management as compared to on demand treatment.

CONCLUSION

Present study concluded that low dose prophylaxis for hemophilia is more effective than on demand treatment. Cases managed by low dose prophylaxis had lower annualized bleeding rate, hospital admissions and absenteeism from work/ school and showed significant improvement in joint function.

Cases managed by low dose prophylaxis were also able to maintain the factor levels and had lower risk of developing inhibitors. Present study thus recommends the use of low dose prophylaxis for hemophilia management as compared to on demand treatment.

REFERENCES

1. Mannucci, P.M. and E.G.D. Tuddenham, 2001. The hemophilias-from royal genes to gene therapy. New Engl. J. Med., 344: 1773-1779.
2. Srivastava, A., A.K. Brewer, E.P. Mauser-Bunschoten, N.S. Key and S. Kitchen *et al*., 2013. Guidelines for the management of hemophilia. Haemophilia, Vol. 19, No. 1 .10.1111/j.1365-2516.2012.02909.x
3. Dijk, K., K. Fischer, J.G. Bom, E. Scheibel, J. Ingerslev and H.M. Berg, 2005. Can long-term prophylaxis for severe haemophilia be stopped in adulthood? results from denmark and the netherlands. Br. J. Haematol., 130: 107-112.
4. Srivastava, A., E. Santagostino, A. Dougall, S. Kitchen and M. Sutherland *et al*., 2020. Wfh guidelines for the management of hemophilia, 3rd edition. Haemophilia, 26: 563-564.
5. Coppola, A., A. Tagliaferri, M.D. Capua and M. Franchini, 2012. Prophylaxis in children with hemophilia: Evidence-based achievements, old and new challenges. Seminars Thrombosis Hemostasis, 38: 79-94.
6. Nilsson, I.M., E. Berntorp, T. Löfqvist and H. Pettersson, 1992. Twenty-five years' experience of prophylactic treatment in severe haemophilia a and b. J. Internal Med., 232: 25-32.
7. Sharma, P., V. Payal, V. Goyal, R. Jora, M. Parakh and D. Payal, 2016. Clinical profile of hemophilia patients in Jodhpur region. Asian J. Transfusion Sci., 10: 101-104.
8. Bulagouda, R., S. Kulkarni, R. Hegde, S. Hegde and S. Kulkarni *et al*., 2022. Clinical profile of hemophilia b patients from karnataka. J. Family Med. Primary Care, 11: 2735-2738.
9. Kumar, S., S. Mishra, A. Panwar, D. Bhagchandani, G. Aneja, N. Verma and P. Kumar, 2016. A clinical profile of hemophilia patients and assessment of their quality of life in western uttar pradesh, India: An observational study. Med. J. Dr. D.Y. Patil Uni., 9: 320-324.
10. Gouider, E., L. Jouini, M. Achour, H. Elmahmoudi, K. Zahra, W. Saied and B. Meddeb, 2016. Low dose prophylaxis in tunisian children with haemophilia. Haemophilia, 23: 77-81.
11. Wu, R., K.K. Luke, M.C. Poon, X. Wu and N. Zhang *et al*., 2010. Low dose secondary prophylaxis reduces joint bleeding in severe and moderate haemophilic children: A pilot study in China. Haemophilia, 17: 70-74.
12. Sidharthan, N., R. Sudevan, V.N. Pillai, S. Mathew and M. Raj *et al*., 2017. Low-dose prophylaxis for children with haemophilia in a resource-limited setting in south India-a clinical audit report. Haemophilia, 23:.
13. Poonnoose, P., J.D.A. Carneiro, A.L. Cruickshank, M.E. Ekiaby and R.P.P. Bianco *et al*., 2017. Episodic replacement of clotting factor concentrates does not prevent bleeding or musculoskeletal damage - the musfih study. Haemophilia, 23: 538-546.
14. Abraham, A., S. Apte, A.S. Singh, K. Subramaniam and A. Korula *et al*., 2017. Meaningful reduction of annual bleeding rate with lower dose prophylaxis in minimally treated children with hemophilia in India. Blood, 130: 1-2.