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OUTCOME OF DOMICILIARY TREATMENT OF LOW DOSE ESCALATING FACTOR CONCENTRATE PROPHYLAXIS IN SEVERE PWH FROM LOW SOCIOECONOMIC STRATA

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ABSTRACT
Hemophilia A has prevalence of 1 patient every 10,000 male births and Hemophilia B 1 patient every 30,000 male births.1-5 Due to lack of awareness, diagnostic as well as treatment facilities, many of the patients are on cryoprecipitate/ Factor concentrate, as episodic treatment only. All severe hemophiliacs between 1-10 years were screened for inclusion and exclusion criteria and then enrolled in study after informed consent from parents. All patients were assessed for bleeding history, HJHS, FISH and CHAQ at baseline and every 3 monthly. Out of 35 patients, 7 patients were PUPs. Sixteen patients developed spontaneous breakthrough bleed during the study. There was 72.9% reduction in AJBR, 60.83% in ABR and 95.21% in school absenteeism. CHAQ score showed -68.32% improvement and the joint scores improved significantly. 18 (51.42%) patients were on home-therapy. Most of these families (82.8%) were from lower strata of society belonging to Kupuswamy classification III and IV. The study had 100% compliance. The average dose of plasma derived factor required 11.663 unit/kg/patient/dose and 1209.89 unit/kg/patient/year. **Conclusions:** Prophylaxis with low dose factor concentrate with escalation protocol can decrease the frequency of joint and other hemorrhages, reduce school absenteeism and prevent joint damage in children with severe hemophilia. Home therapy is possible in the developing countries with dedicated training even in low socioeconomic strata of society.

KEYWORDS: PWH, Factor, Episodic, breakthrough bleed, FISH, HJHS, CHAQ.

INTRODUCTION
Patients with severe hemophilia (factor level <1%) have inadequate factor VIII (FVIII) or IX levels, resulting in spontaneous and trauma-related bleeding, especially in the joints. Repeat joint bleeding eventually leads to a crippling arthropathy.1-4 Severe hemophilia A is rare, with a incidence of 1 patient every 10,000 male births and Hemophilia B 1 patient every 30,000 male births.1-5 In absence of any epidemiological studies, it is expected that there are at least 1 lakh PWH in India.[1-5]

Treatment in hemophilia is by replacement with factor concentrate which can be episodic (whenever bleeding occurs) or prophylactic.[6,7] However, prior to the availability of factor concentrate, FFP and cryoprecipitate were the mainstay of treatment. Even today they are used as and when factor concentrate are not available.

Prophylaxis is the regular infusion of clotting factor concentrates with the target of keeping factor level > 1%, in order to prevent bleeding.[8] The idea of prophylaxis came from the observation that people with moderate or mild hemophilia (who have clotting factor levels of 1% or more) rarely experience spontaneous bleeding. Prophylaxis prevents bleeding and joint destruction and should be the goal of therapy to preserve normal musculoskeletal function.[9-13]

Today, a typical adult Dutch patient with hemophilia A uses 3 × 1000 IU FVIII/week, whereas a typical adult Swedish patient uses 3 × 2000 IU or 1500 IU every other day. Both groups reported favorable long- term results, but with increasing pressure on health care budgets and a formal cost review by the Swedish authorities, it is important to assess the incremental gains of high-dose prophylaxis. The Beijing study, using lesser factor, 900-1000 unit/kg factor concentrate prophylaxis showed improvement in the joint bleeding and the quality of life in children with moderate and severe hemophilia.[14-18]

Prophylaxis is a standard of care for PWH (Patients With Hemophilia) worldwide. Due to resource constraints, in developing countries like India, factor concentrate are

given as episodic therapy. The annual bleeding frequency of patients with severe Hemophilia A ranges from 2 bleeding episodes in a year to as many as 31 bleeding episodes per year. The median value suggests that a patient with severe Hemophilia A may bleed as frequently as 11 times a year.4,5 In an epidemiological study conducted across the country, only 9 out of 149 patients were found to be free of disability. 4,5 Thus we are looking at giving PWH, the same international standard of care albeit at a lower dose and a lower frequency as per the resource constraints and its effect on the joint bleeding, joint function, school attendance, and daily activities in patients with hemophilia.

Children on episodic therapy in our centre, requirement of Factor concentrate usage were 1009.20/kg/pt/year, while in our study prophylaxis usage for factor concentrate was 1209.89 unit/kg/patient/year. In a study from South India, factor consumption for episodic treatment for 6 months was 968.24 IU/Kg and that of prophylaxis was 1077.96 IU/Kg.[19]

Though the factor requirement in prophylaxis group is only marginally higher than episodic group, outcome and compliance were significantly better in prophylaxis group at almost equivalent cost.

Home therapy 20,21 (Domiciliary treatment)
Where appropriate and possible, persons with hemophilia should be managed in a home therapy setting. Home therapy allows immediate access to clotting factor and hence optimal early treatment, resulting in decreased pain, dysfunction, and long-term disability and significantly decreased hospital admissions for complications.[20,21] Further improvements in quality of life including greater freedom to travel and participate in physical activities, less absenteeism, greater employment stability and sound mental health of patient and caregiver.

Teaching should focus on general knowledge of hemophilia; recognition of bleeds and common complications; first aid measures; dosage calculation; preparation, storage, and administration of clotting factor concentrates; aseptic techniques; performing venipuncture (or access of central venous catheter); record keeping; proper storage and disposal of needles/sharps; and handling of blood spills.

Aim of study

- To do prospective study in hemophilia A/B patients by providing factor VIII/IX concentrates prophylaxis 10 IU /kg twice weekly with escalation protocol.

Objectives

- To study outcome of bleed (Primary Outcome) in children falling between age 1-10 years
- Number of bleeds (Annual Bleed Rate and Annual Joint Bleed Rate)
- Joint status
- Functional assessment
- School absenteeism
- To train parents / guardians in administration of prophylaxis in low socioeconomic strata of society. (Secondary Outcome)

MATERIALS AND METHODS

Definition for a Joint Bleed: an unusual sensation 'aura' in the joint, in combination with any of the following:

(a) Increasing swelling or warmth of the skin over the joint
(b) Increasing pain or
(c) Progressive loss of range of motion or difficulty in using the limb as compared with baseline.

In infants and young children, reluctance to use the limb alone may be indicative of a joint/muscle bleed.

Inclusion criteria

- All children with severe hemophilia (FVIII/IX < 1% or < 1 IU/dL) with normal platelet count and negative for inhibitor and HIV/HBV/HCV.
- Patients >1 years of age or <10 years of age

Exclusion criteria

- Hemophilia A/B with inhibitor.
- Patients with other coagulation disorders (e.g. von Willebrand disease, rare bleeding disorders).
- Children with liver disease
- Children positive for - HIV/HBV/HCV

Study Design

The study was designed as a prospective study of patients of severe hemophilia A and B in a tertiary care centre in Mumbai on outpatient basis from 2015 -16 over a period of 12 months in the Department of Hematology, after approval by the Ethics committee of the hospital.

Methodology: This study was conducted in the following steps –
All children with severe hemophilia between 1-10 years of age coming to the study hospital during study period were screened for inclusion and exclusion criteria. All cases fulfilling inclusion criteria were enrolled in the study, after a written informed consent of parent or guardian. All enrolled cases were subjected to a detailed interview on a pre-designed questionnaire and joint status examination.[21-23]

The study required a total of 104 visits. Patients came to the study hospital for plasma derived factor(IMMUNATE) concentrate infusion with starting dose of 10 IU /kg twice weekly on Tuesday /Friday or Wednesday/Saturday and were observed weekly on outpatient basis throughout the study duration. Break-through bleeding history whether spontaneous/after injury and treatment taken for the same was noted. Each

monthly weight was noted to keep the doses correct.

If patient had ≥1 episodes of spontaneous breakthrough bleed at any time period, dose was increased to 15 IU / kg twice weekly and patient was assessed at each visit for spontaneous breakthrough bleeds and if patient still had bled then it was escalated to 20 IU /kg and if patient still had bled was further escalated till maximum of 30 IU/kg twice weekly.[13]

Patients were assessed for joint status Hemophilia Joint Health Score, Functional Independence Score in Hemophilia (HJHS, FISH) and Childhood Health Assessment Questionnaire (CHAQ) was administered every three monthly. The socioeconomic status of patients was assessed by Kuppuswamy scale which comprises of 5 classes – class I-V, with Class I being highest and Class V being lowest. Kuppuswamy scale is a composite score of education and occupation of the head of the family along with monthly income of the family, which yields a score of 3-29.[22]

Parental training and Home Therapy

Parental training

The parental training was started after 1 month of starting prophylaxis. Training sessions were planned for 3 months.

The parents/ guardian of the patient were trained for infusion of factor in step wise manner.

1. Tourniquet application. 2. Reconstitution of factor concentrate 3. Finding a vein 4. Inserting butterfly needle into the vein. 5. Putting syringe in the butterfly needle. 6. Infusing in slow speed.

They were trained for intravenous insertion: in step wise manner

- Artificial skin simulated veins
- Parent intravenous (butterfly needle) insertion on each other
- Intravenous cannula (butterfly needle) insertion on the patient

In each follow up for factor infusion, parents/ guardian of the patient were observed and which of the above targets they had achieved for infusion of factor was noted. Parents/ guardian of the patient were trained for infusion of factor by doctor/ staff nurse. After 8 monitored infusions by caregiver in the hospital, the patients were shifted to home based therapy.

(IMAGE 1, IMAGE 2, IMAGE 3, IMAGE 4)

Home therapy

During the entire study, the cold chain kits were utilized to maintain cold chain for home therapy patients. The patients were monitored for any spontaneous/traumatic bleed, compliance to therapy by an electronic data base in the hospital. If patient had bleed immediate factor correction was advised and given at home and patient was assessed in hospital for the same for need of any further factor correction. If no bleed, the patients were followed every monthly for weight and factor dosage and 3 monthly for joint status and questionnaire. They were asked to maintain diary in their own language, to record episodes of bleed, treatment received and any difficulties faced.

Statistical Analysis

The data was entered using MS-Excel- 2007 and analyzed using SPSS-16 software.

Following statistical tests of significance were used.

- Kolmogorov Smirnhov test – To check distribution of data
- Paired t test – For comparison of mean ABR at baseline and at the end of one year for Numerical data which is normally distributed.
- Wilcoxon signed rank test – For comparison of mean AJBR & amp; school absenteeism at baseline and at the end of one year for Numerical data which is not normally distributed.

The P value less than 0.05 was taken as statistically significant.

RESULTS

Forty two children with hemophilia of the age group 1-10 years were screened for eligibility criteria, out of which 35 were enrolled in the study (7 patients excluded-3 patients were inhibitor positive at baseline, 1pateint had F VIII >1%, 3 patients (parents/guardians) were not willing). 31 patients were of Hemophilia A (88.5%) and 4 patients of Hemophilia B (11.5%) in age group of 1-10 years with mean age of 4.580 yrs. Out of 35, 7 (20%) patients were PUPs, 8 children already had developed target joint at baseline and total 10 episodes of IC bleed were present among 7 patients at baseline(table 1). The period of study was 12 months without any adverse event and factor infusion given by peripheral IV access only.

16 patients (45.71%) developed spontaneous breakthrough bleed during the study. The total number of joint bleeds in the study was 42 episodes in 35 patients. Out of 35, 19 patients were continued on 10 unit/kg throughout the study and 16 required dose escalation: 15 unit/kg in 7 patients, 20 unit/kg in 4 patients and 25 units/kg in 2 patients and 30 unit/kg in 3 patients respectively. Of these 16 patients, 6 patients had target joints at baseline. None of the patients on primary prophylaxis required dose escalation.

In our study, 2 patients (5.71%) developed inhibitor -1 patient had inhibitor positive (11.2 BU) after 10 EDs and 1 patient had inhibitor positive after 18 ED (7.2BU) (after confirmation of two successive Bethesda titers 15 days apart) and so was excluded from the study and two patients developed transient inhibitors.(figure 1).

The AJBR (annual joint bleeding rate) reduced from 4.172 to 1.1271 after 1 year of prophylaxis i.e. 72.9% reduction in bleed rate, ABR (annual bleeding rate)

reduced 60.83% (figure 2 and table 2) and school absenteeism reduced by 95.21%.

There was significant change in the joint function scores of patients. 17 patients had FISH score ≥ 29 with 8 patients had score of 32 after 1 year of prophylaxis. The FISH score improved from 25.176 to 26.97, with 8 patients of target joint had improvement to score of 32 in 3 patients. The HJHS score improved from 12.147 to 9.15 with 18 patients had score ≤ 7. CHAQ showed 68.32% improvement from 3.482 to 1.06. (figure 3 and table 3).

All the parents were trained in infusion of factor concentrate and 18 (51.42%) patients were on home-therapy after 8 monitored infusion sessions. The study had 100% compliance to treatment. The average dose of plasma derived factor required total was 11.663 unit/kg/patient/dose and 1209.89 unit/kg/patient/year in this study.

29 out of 35 (82.8%) patients were from socioeconomic class III and IV according to Kuppuswamy scale. 42.8% middle secondary school and 37.1% educated till high school.

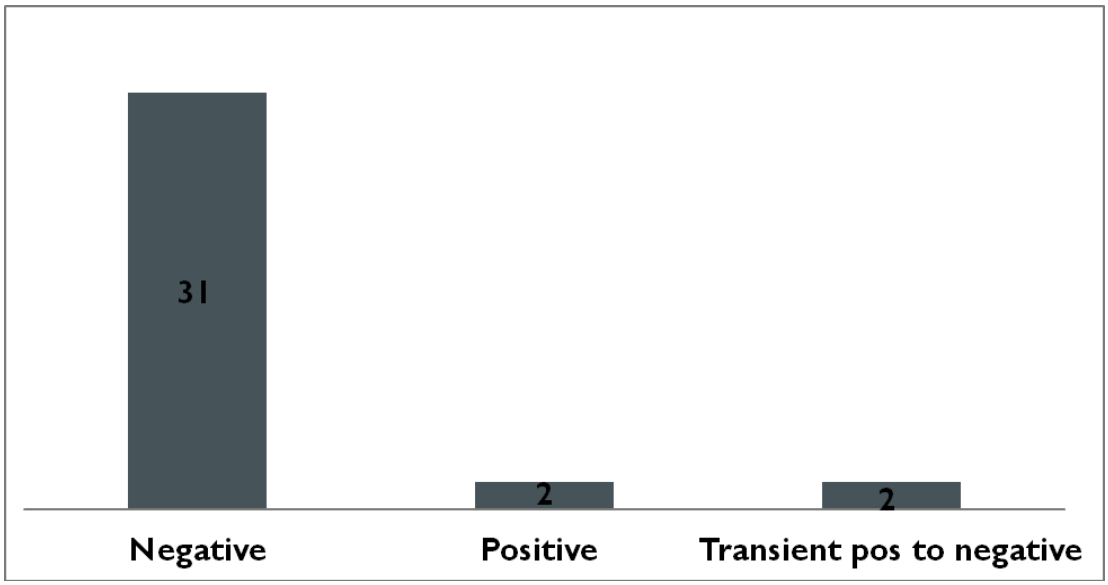

Figure 1: Inhibitor developed in the study; 2 patients having inhibitor positive (11.2 BU and 7.2 BU) and 2 had transient inhibitors.

Table 1: Baseline characteristics of patients of prophylaxis.

Variable	Values
Age at diagnosis (Months)	At birth (cephal-hematoma) - 2 years
Age at the study entry	1.0 -10 years (mean -4.580 yrs)
Diagnosis	31 Hemophilia A 4 Hemophilia B
Weight at the study entry (mean)	16.28 kg
Weight after 12 m	17.80kg
Average exposure days prior to prophylaxis	8.941 days
PUPs (Previously unexposed patients)	7
History of intracranial bleed	10 (3 episodes in 1 pt, 2 episodes in 1 pt, 1 episode in 5 pt)
Target joint at baseline	8 patients

Table 2: Shows the reduction of the annual bleeding rate and the annual joint bleeding rate after 1 year of low dose prophylaxis.

		Mean	Std. Deviation	Std. Error Mean	Significance (2-tailed)
Pair 1	**Baseline ABR**	14.471	6.9945	1.1996	**<0.0001**
	@12months ABR	6.0588	5.72046	.98105	
Pair 2	**Baseline AJBR**	4.147	4.5135	.7741	**<0.0001**
	@12months AJBR	1.2941	2.06749	.35457	

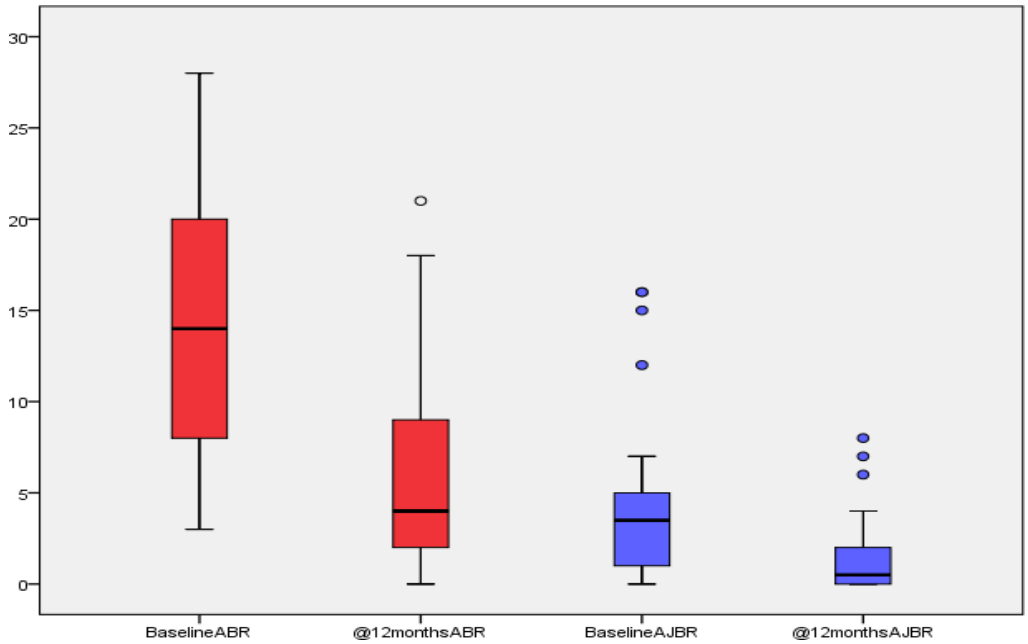

Figure 2: Shows the reduction of the annual bleeding rate and the annual joint bleeding rate after 1 year of low doseprophylaxis.

Table 3: Shows the reduction of FISH, HJHS and the CHAQ scores after 1 year of low dose prophylaxis.

		Mean	Std. Deviation	Std. Error Mean	Significance (2-tailed)
Pair 1	**Baseline FISH**	25.176	3.7211	.6382	**0.002**
	@12Months FISH	26.97	3.857	.662	
Pair 2	**Baseline HJHS**	12.147	5.9550	1.0213	**<0.0001**
	@12Months HJHS	9.15	4.091	.702	
Pair 3	**Baseline CHAQ**	3.482	3.4441	.5907	**<0.0001**
	@12Months CHAQ	1.06	1.984	.340	

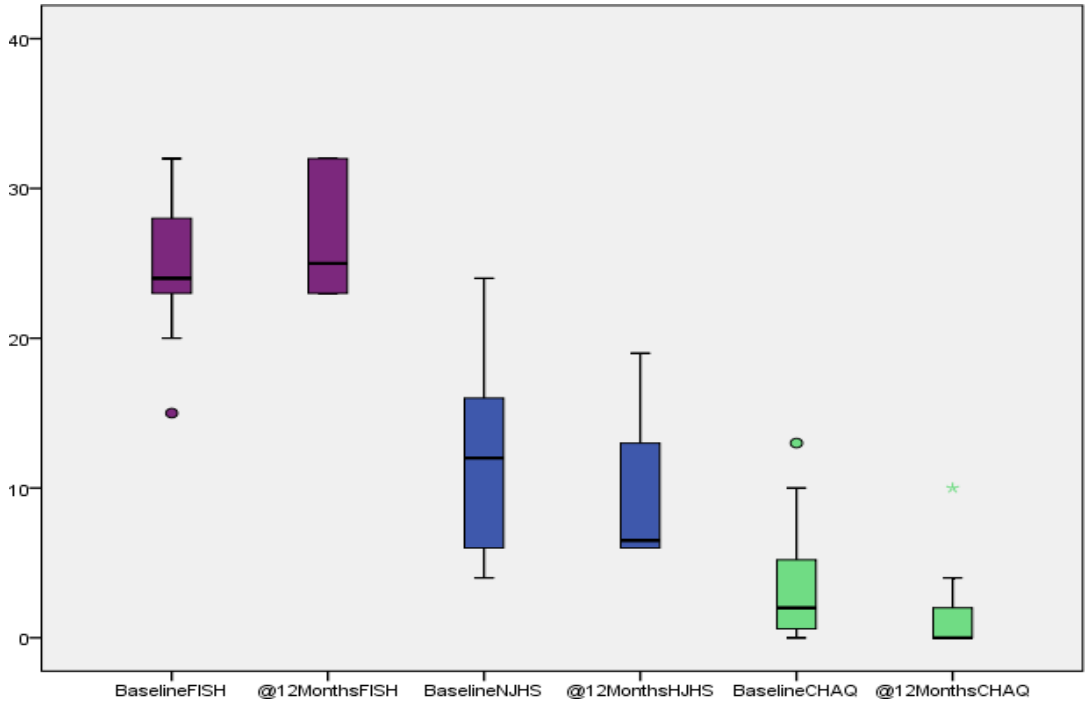

Figure 3: Shows the reduction of FISH, HJHS and the CHAQ scores after 1 year of low dose prophylaxis.

		Frequency	Percent
	A	31	88.6
	B	4	11.4
	Total	35	100.0

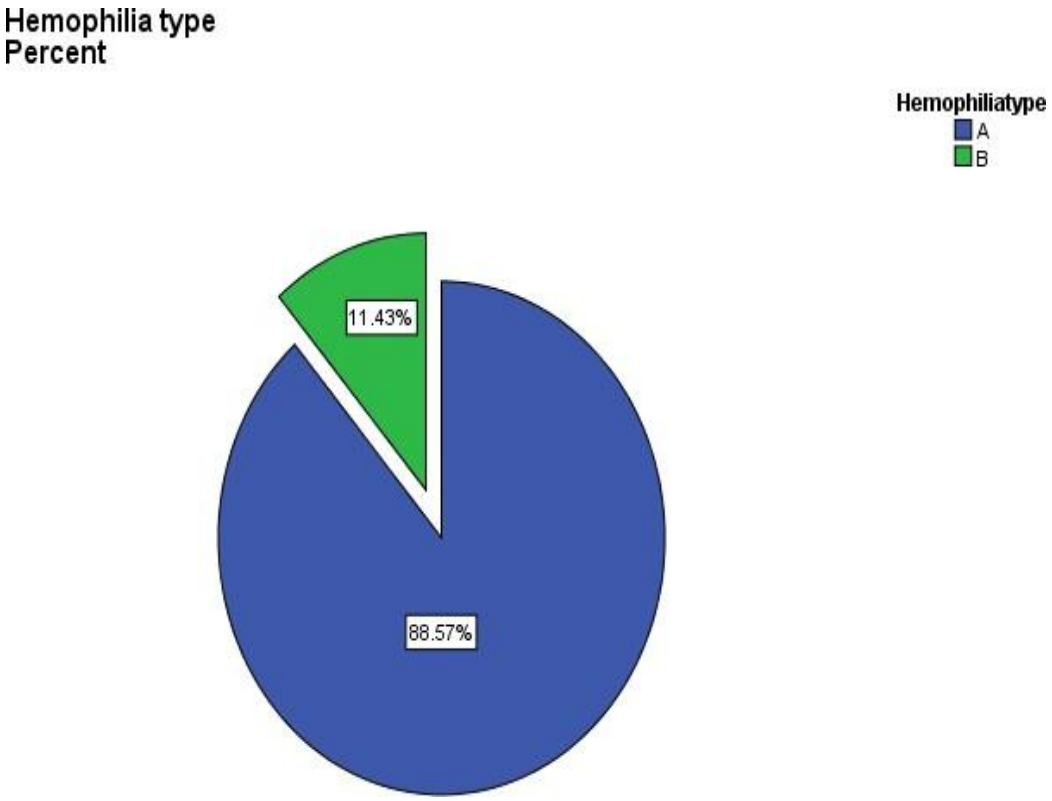

Table 4 and Figure 4- shows the frequency of types of Hemophilia.

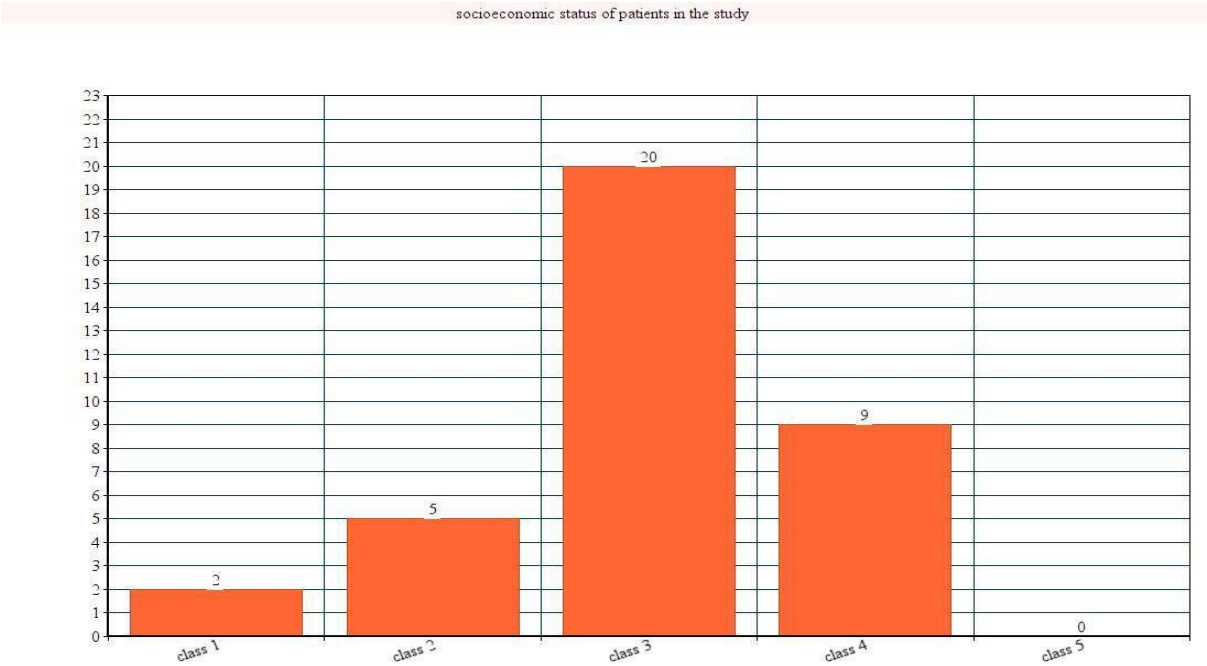

Figure 5 – shows the socioeconomic status of the patients.

The photographs show parental infusion training Parental infusion training by doctor and nurse with

1. Artificial skin with simulated veins IMAGE 1

IMAGE 2

HOME THERAPY TRAINING

IMAGE 3: Electronic database.

IMAGE 4: Monitoring Parental infusion.

DISCUSSION

In absence of any epidemiological studies, it is expected that there are at least 1,00,000 severe hemophiliacs in our country.3-5 Due to lack of awareness, diagnostic as well as treatment facilities, many of the patients are on FFP, cryoprecipitate/ factor concentrate, as episodic treatment only. Only few patients are on prophylaxis treatment. Few Indian studies have shown efficacy of prophylaxis in Indian setting.3-5 The aim of this study is to look for efficacy of low dose prophylaxis in severe hemophilia A and B patients and to study its outcome on joint status, spontaneous breakthrough bleeds, school absenteeism in children between 1-10 years of age and feasibility of domiciliary (home) treatment in low socioeconomic families.

Prophylaxis is a standard of care for PWH worldwide. Prophylaxis significantly reduces joint bleeding and prevents joint abnormality but because of the high cost it is at present not feasible in developing countries like India. Furthermore, in such scenario, many hemophilic children already have significant abnormalities in joint structure and function because of frequent joint bleeding and under treatment. The under-treatment results in an increased likelihood of repeated bleeding, school/work absenteeism, poor QoL and poor joint function and dependent life. Psychological distress and poor quality of life is widespread in parents, primarily arising from the inability to treat the child. Out of pocket and catastrophic expenditure is the major reason for limiting treatment to the affected child.

The present study showed that patients with hemophilia can have good response to relatively low dose prophylaxis of 20 IU /kg /week (with escalation protocol) with significant improvement in the frequency of joint bleeding. In these children, the resulting improvement in clinical joint function is associated with significant improvement in the QoL, with greatly improved school attendance, school sports participation and mental health.

In this study, 31 patients were of Hemophilia A (88.5%) and 4 patients of Hemophilia B (11.5%) in age group of 1-10 years with mean age of 4.580 yrs.

16 patients developed spontaneous breakthrough bleed during the study. The total number of joint bleeds in our study was 42 episodes in 35 patients. Out of 35, 19 patients were continued on 10 unit/kg throughout the study and 16 (45.71%) required dose escalation: 15 unit/kg in 7 patients, 20 unit/kg in 4 patients and 25 units/kg in 2 patients and 30 unit/kg in 3 patients respectively. In the Canadian Hemophilia Escalating Dose Primary Prophylaxis Study (CHPS), 52% required dose escalation.

Out of 35, 7 (20%) patients were PUPs, 8 children (22.85%) already had developed target joint at baseline compared to 36% in CHPS study.

In our study, total 10 episodes of IC bleed were present in 7 patients at baseline; none of these patients had recurrence during the study, despite of normal playful activity of children. None of patients developed life-threatening or organ threatening bleed during the study. This lead to major benefits to the patients and family (reduces work or school absenteeism) as well as reduces the burden on healthcare, in hospital costs of admission, beds. This reduces the direct and indirect costs of patients as well as healthcare.

The period of this study was 12 months without any adverse event and factor infusion given by peripheral IV access only while 40% of patients in CHPS study required CVC (central venous catheter) insertion.[16]

In our study, 2 patients (5.71%) developed inhibitor -1 patient had inhibitor positive (11.2 BU) after 10 EDs and 1 patient had inhibitor positive after 18 ED (7.2BU) (after confirmation of two successive Bethesda titers 15 days apart) and so was excluded from the study and two patients developed transient inhibitors. While 6.25% of patients on prophylaxis developed inhibitors in the Canadian study. 16None of the children in the South Indian study, developed inhibitors during the study period.[19]

The AJBR reduced from 4.172 to 1.1271 after 12 months of prophylaxis (P value < 0.0001) i.e. 72.9% reduction in bleed rate as compared to various high dose prophylaxis had AJBR of 1.2 in Canadian study, 0.57 in Malmo protocol (high dose regimen), 2.0 in Dutch protocol (intermediate dose regimen), and 2.6 in severe hemophilia in Beijing study on low dose prophylaxis. 14-18 Median number was 7 in on- demand therapy compared to 0.5 with low dose prophylaxis in Tunisian study whereas in South Indian study episodic treatment to prophylactic treatment (14.9 vs 0.91, p 0.005).[19,26]

There was significant reduction in the joint function scores of patients- 12.147 to 9.15 in HJHS scores with 18 patients had score $\leq$ 7 and 25.176 to 26.97 in FISH scores, 17 patients had FISH score $\geq$ 29 with 8 patients had score of 32. The HJHS score in Malmo protocol and Dutch Protocol was 4 and 7 respectively. HJHS score was 4 in Tunisian study.26 FISH and HJHS scores were either maintained or improved during the prophylaxis period in the South Indian Study.[19]

The CHAQ showed 68.32% improvement from 3.482 to 1.06 compared to 0 in Canadian study and 0.88 in Dutch protocol.[14-18]

In our study Annual bleed rate in sites other than joints (surface bleed, muscle bleed, etc.) reduced by 60.83% from 14.471 to 6.0588 (P value < 0.0001).

In the study by Kar, the number of school or workdays lost due to bleeding episodes in PWH ranged from 3.1 to 35.3 per year and 37% of patients has discontinued

education.4,5 School absenteeism per year reduced by 95.21% from 22.8 days to 1.56 days (P value: 0.011) compared to the South Indian study from 78.55 to 1.27 days, p 0.01 and to the Beijing study of 1.4 17,19 The study had 100% compliance to treatment compared to 96% in Canadian study.[14-18]

The average dose of factor required was 11.663 unit/kg/patient/dose and 1209.89 unit/kg/ patient /year in this study. This is much less compared to the high amount used in the Canadian Hemophilia Escalating Dose Primary Prophylaxis Study (CHPS) 3656 IU /kg/year, the full dose primary prophylaxis (Malmo regimen) 4000 IU /kg/year, the Dutch protocol 2100 IU /kg/year and the Beijing study 900-1000 IU /kg/year.[14-18]

The CHPS study, Malmo protocol and Dutch protocol used recombinant factor concentrate while that of Beijing study used both plasma derived and recombinant factor concentrate. Throughout our study plasma-derived (pd) intermediate purity factor concentrates was utilized.

The Cost of therapy/year/patient (US $) in this study was $ 3232 only (Rs. 2.15 lakh), compared to $272 280 in CHPS study, $297 900 in Malmo protocol, $179 600 in Dutch Protocol and $744 75 in Beijing study.14-18 In the South Indian study, the estimated cost of CFCs for duration of 6 months for episodic treatment per patient was 1314.4 USD and 1691.8USD during prophylaxis.[19]

The estimated cost of CFCs for episodic treatment per patient in our centre is $ 2981 (1.96 lakh/ patient/ year). This estimate excludes clotting factor concentrate requirements for surgery or medical emergencies and is calculated assuming each bleeding episode will be treated with only a single infusion of clotting factor concentrate. This cost is woefully underestimated as most patients would require 2-10 factor concentrate infusions depending on site and severity of bleed. Thus, the actual costs of episodic therapy would be much higher.

The outcome is much worse in terms of physical, emotional and social functioning. Thus low dose prophylaxis at an approximate cost of $ 3232 /year/patient is far more beneficial, both financially as well as medically.

This study is the most economical amongst all the protocols with bleed rates, joint status and QoL comparable to CHPS and Malmo protocol.

Home therapy

In a study from India by Kar et al showed that parents of hemophilic children were severely affected in all measures of quality of life which included physical functioning, emotional functioning, social functioning, cognitive functioning, communication, worry, daily life and family relationships as compared to control parents. Quality of life of mothers was more severely affected than that of fathers (p=0.001).

One of the highlight of our study was the training of care givers for home therapy. Though home care may be common in educated families, in our study most of the care givers (82.8%) were from class III and class IV Kuppuswamy scale and their educational status was mainly high school and middle secondary school.

So even being from developing country and with above background, 18 (51.4%) patients were on home care and our study had 100% compliance. This lead to improvement in the QoL of patients as well of their parents (in terms of emotional functioning, social functioning).

In this study, the trough levels were not monitored because the studies on prophylaxis did not change the dose depending on the trough levels and our study did not have control group, due to lack of proper follow-up of episodic therapy patients in this age group. In spite of the limitations, the current study forms the basis for a larger scale multicentre study for a longer prophylaxis period with proper controls.

CONCLUSIONS

Prophylaxis with low dose factor concentrate with escalation protocol can decrease the frequency of joint and other hemorrhages, reduce school absenteeism and prevent joint damage in children with severe hemophilia. Home therapy is possible in the developing countries with dedicated training even in low socioeconomic strata of society. There is a misconception in the minds of healthcare policy makers and healthcare workers that prophylactic therapy is astronomical and not feasible option for low socioeconomic status. However, as is clearly shown in this study and in other studies, using low dose prophylaxis is actually more economical and beneficial not only to the patient and family but also to the healthcare givers, hospital and government. Not only the Indirect costs including lost wages from missed work for those patients or parents who were employed, lost wages from working part-time or being unemployed due to hemophilia, and unpaid caregiver costs but also the Direct costs including the cost of illness for persons with all severities of hemophilia A, considering clotting factor costs, non-factor drug costs, healthcare utilization costs, and patients' are reduced.

None of the patients on primary prophylaxis required dose escalation. Thus, Primary prophylaxis as in this study can achieve best possible therapy with minimal financial burden and with minimal doses of factor concentrate.

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