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Original Research Article

Study On Feasibility and Outcome of Primary versus Secondary Prophylaxis in Haemophilia A & Haemophilia B Children Under 12 Years of Age in Tertiary Care Hospital

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Conflict of interest: Nil

Abstract

Background: There are limitations to prophylaxis in economically constrained countries due to non-affordability of clotting factor concentrate. In this resource constrained countries, the prophylaxis goals should be for improved quality of life rather than zero bleed and perfect joints.

Materials and Methods: Hospital based prospective and retrospective longitudinal study was done in Indoor & Outdoor Patients of Department of Haematology & Department of Paediatrics, diagnosed as hemophilia at Nilratan Sirkar Medical College, Kolkata, West Bengal a tertiary care hospital in Eastern India between Jan 2018 to June 2019. Type of hemophilia, APTT level, factor VIII & IX level, level of inhibitor, age at starting prophylaxis, number of joint bleeds at the starting of prophylaxis, hemophilia joint health score and assessment of quality of life. Laboratory investigations were done like level of APTT, level of factor, level of inhibitor, HBsAg, HIV 1&2, Anti HCV and X-ray of involved joint. Outcome of the prophylaxis is measured by Haemophilia joint health score (HJH). This score was done in four visits 3months apart in both primary and secondary prophylaxis cases. The quality of life was assessed by the assessment of quality-of-life score. It was done in 10 visits.

Results: Among 34 patients 27 patients are hemophilia A and 7 patients are hemophilia B. Distribution of patients (Hemophilia A 82% & B 18%). Mean age at diagnosis in case of Hemophilia A is 16.82±14.2 (months) and Hemophilia B 18.5 ±14.3. Study revealed that the comparison between mean HJH score of each visit in case of primary versus secondary prophylaxis. In first visit the mean HJH score for primary and secondary prophylaxis are 12.83+3.09 and 15.72+1.6 (P=0.03). In second visit the mean HJH score for primary and secondary prophylaxis are 10.66+3.20 and 13.04+1.73 (P=0.043). In third visit the mean HJH score for primary and secondary prophylaxis are 8.41+2.84 and 10.68+1.49 (P=0.024). In fourth visit the mean HJH score for primary and secondary prophylaxis are 6.66+3.11 and 8.86+1.45 (P=0.046). Among the 34 patients, 7 patients had developed inhibitor. All of them are hemophilia A. Study showed among the total papulation of patients' inhibitor developed in 18% of patients. It also showed that among the patients who developed inhibitor 33% patients have positive family history and 67% have negative family history.

Conclusion: So, we can conclude that the HJH score is significantly decreasing from the first visit to the subsequent visits for both primary and secondary prophylaxis. When the decreasing pattern is compared in primary and secondary prophylaxis it is seen that HJH score is decreasing more in subsequent visits in case of primary prophylaxis than secondary prophylaxis. In case of secondary prophylaxis, the assessment of quality-of-life score is significantly improving from first visit to the subsequent visits.

Keywords: Haemophilia A (Factor VIII deficiency), Haemophilia B (Factor IX deficiency), Primary Prophylaxis, Secondary Prophylaxis, Children, Haemophilia Joint Health Score (HJH), Quality-of-life.

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Introduction

The two most common and serious congenital coagulation factor deficiencies are Haemophilia A (Factor VIII deficiency) and Haemophilia B (Factor IX deficiency). Clinical findings of Haemophilia A and Haemophilia B are more or less same [1]. These two are genetically unrelated but both are inherited as sex linked recessive characters [2].

Haemophilia is an inherited single gene disorder with an incidence 1 in 10000 births for haemophilia A and 1 in 50000 births for haemophilia B [3].

Haemophilia is classified into 3 types depending on factor levels, as mild (5%-40%), moderate (1%-5%) & severe (< 1%) [4]. Spontaneous bleeding generally occurs in severe haemophilia and in moderate form prolonged bleeding occurs with minor trauma whereas prolonged bleeding occurs with major trauma and surgery in mild haemophilia [1, 4]. In haemophilia bleeding may occur at any area in the body but the hallmark of haemophilic bleeding is joint bleed i.e. hemarthrosis. Earliest joint bleed most commonly occur in ankle but in older children and adolescents hemarthrosis of elbows and knee joints are also common [1]. Repeated joint bleeds ultimately lead to disability due to chronic arthropathy with suboptimal treatment [3]. Concept of target joint: A joint in which 3 or more spontaneous bleeds have occurred within a consecutive 6 months period. This leads to haemophilic arthropathy and contracture [5].

Table 1: Approximate frequency of bleeding at different sites [6]

Site of bleeding	Approximate frequency %
Hemarthrosis	70–80
More common into hinged joints: ankles, knees, and elbows	
Less common into multi-axial joints: shoulders, wrists, hips	
Muscle	10–20
Other major bleeds	5–10
Central nervous system	<5

Long-term complications of hemophilia primarily result from chronic, untreated, or recurrent bleeding, with the most common being hemophilic arthropathy (severe, permanent joint damage) leading to arthritis, chronic pain, and limited mobility. Other serious long-term effects include muscle damage, nerve damage from deep muscle bleeds, inhibitor development against factor treatments, and risk of infections from past blood products. All these complications in the long run causes decrease in quality of life and increased morbidity [7].

Prophylaxis is considered as the optional care for haemophilia patients to prevent bleeding and to preserve joint function and thus improving the quality of life [8]. Prophylaxis is individualized to improve outcomes and cost effectiveness.

There are 3 determinants of optimal prophylaxis [8].

1. Factor dose / dosing frequency (cost/ affordability)
2. Bleeding triggers (lifestyle, physical activity, chronic arthropathy, synovitis)
3. Bleeding rates

To alter one determinant adjustment of other two determinants are required. There are limitations to prophylaxis in economically constrained countries due to non-affordability of clotting factor concentrate. In this resource constrained countries, the prophylaxis goals should be for improved quality of life rather than zero bleed and perfect joints. Central to the success of prophylaxis is comprehensive care which includes necessary professional expertise, support and counselling to educate patients, families and other healthcare professionals [9]. In this context a study is warranted in this part of our country to determine the quality of life in children with Haemophilia A & B who were given primary and secondary prophylaxis in relation to joint mobility and its effect in their social life, school activity, interaction with friends. So, this study aims to compare the outcome of primary vs secondary prophylaxis in respect to joint involvement and quality of life.

Aims & Objectives

- Feasibility of primary versus secondary prophylaxis in less than 12 years old children with hemophilia A or hemophilia B
- To study the outcome of primary versus secondary prophylaxis in the form of joint bleed (haemophilia joint health score)
- To study the improvement in quality of life after receiving prophylaxis.

Materials & Methodology

Hospital based prospective and retrospective longitudinal study was done in Indoor & Outdoor

Patients of Department of Haematology & Department of Paediatrics, diagnosed as hemophilia at Nilratan Sirkar Medical College, Kolkata, West Bengal a tertiary care hospital in Eastern India between Jan 2018 to June 2019.

Inclusion Criteria

1. Age less than 12 years of age
2. Up to one large joint bleed (large joint means elbow ankle and knee joint)

Exclusion Criteria

1. Age above 12 years
2. More than one large joint bleed
3. Children having other associated bleeding disorders.

Sample Size: The incidence and prevalence of hemophilia is low and patients qualifying criteria for primary prophylaxis is also low. One unpublished study from West Bengal has taken a study population of 30 patients. Depending on this proposed sample size was 30 but in these 12 months period data of 34 patients were collected.

All patients in indoor and outdoor with hemophilia and fulfilling the inclusion and exclusion criteria were selected for the study after taking informed consent from their caregivers.

Study Variables: Type of hemophilia, APTT level, factor VIII & IX level, level of inhibitor, age at starting prophylaxis, number of joint bleeds at the starting of prophylaxis, hemophilia joint health score and assessment of quality of life. Laboratory investigations were done like level of APTT, level of factor, level of inhibitor, HBsAg, HIV 1&2, Anti HCV and X-ray of involved joint

For statistical analysis data were entered into a Microsoft excel spread sheet and then analysed by SPSS20 and GraphPad Prism version 5. Data have been summarized as mean & standard deviation for numerical variables and count and percentages for categorical variables. Data are distributed in skewed fashion. But as they suffice the criteria of Robust Means of Equality & Levene statistics that is homogenicity of variables has not been disrupted so we perform unpaired t test, Mann-Whitney U, One-Way ANOVA, and Spearman Rank Correlation.

Results

Type of hemophilia

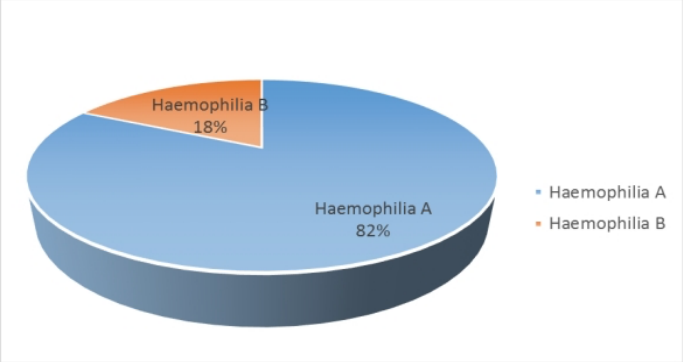

Figure 1: Distribution of hemophilia types among patients

Among 34 patients 27 patients are hemophilia A and 7 patients are hemophilia B. Distribution of patients (Hemophilia A 82% & B 18%) [Fig 1]. Among 34 patients, the percentage of male (98%) and female (2%) patients. Study depicts the family history which is positive in 26% cases and negative in 74% cases.

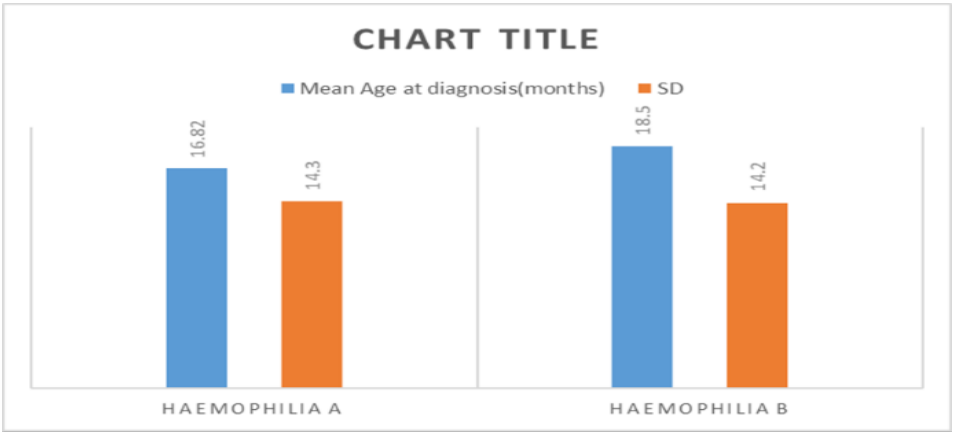

Figure 2: Mean age at diagnosis and standard deviation of both Hemophilia A & B

Figure 2 showed the mean age at diagnosis and standard deviation of both Hemophilia A & B. Mean age at diagnosis in case of Hemophilia A is 16.82±14.2 (months) and Hemophilia B 18.5 ±14.3.

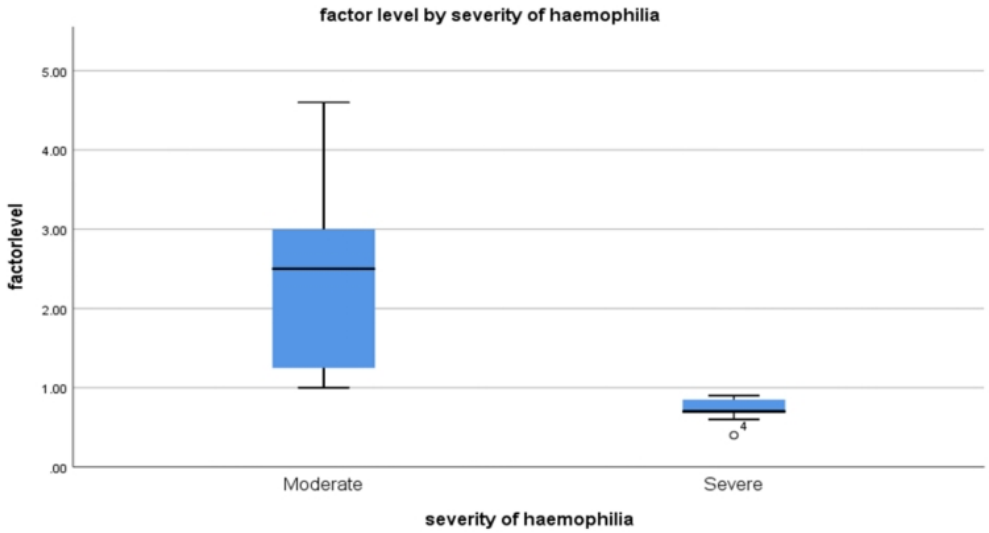

Figure 3: Showed the relation between level of factor and severity

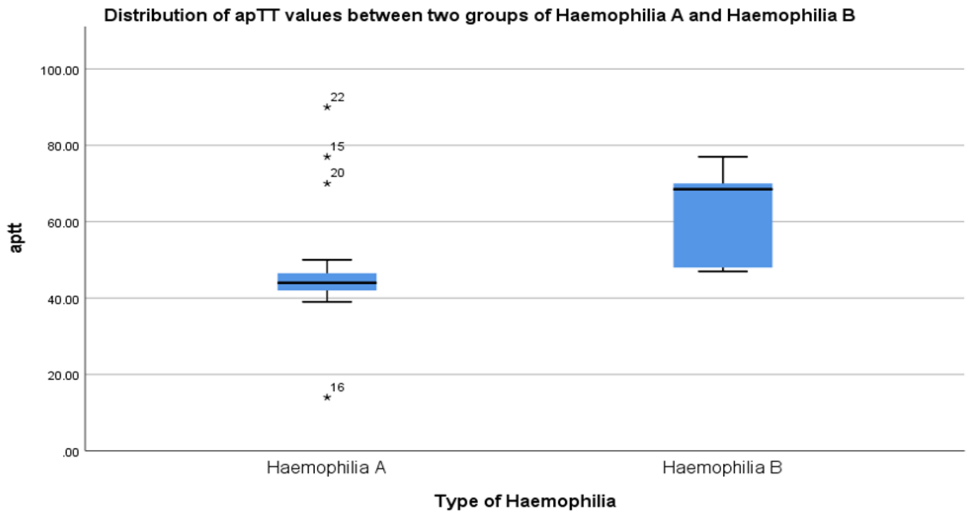

Figure 4: Distribution of apTT values between Haemophilia A and B groups

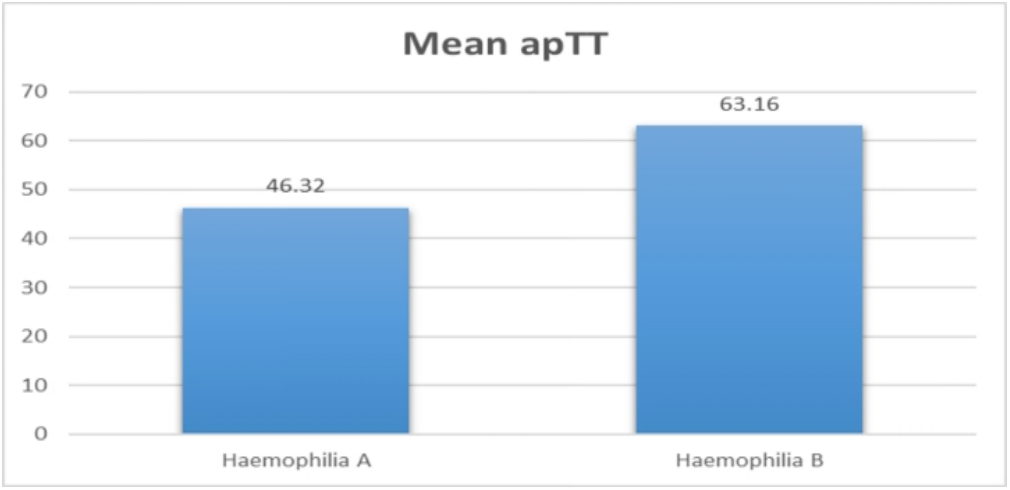

Fig 4 & 5: showed the mean APTT of hemophilia A is 46.32+13.3 and hemophilia B is 63.16+12.5. P value is 0.008.

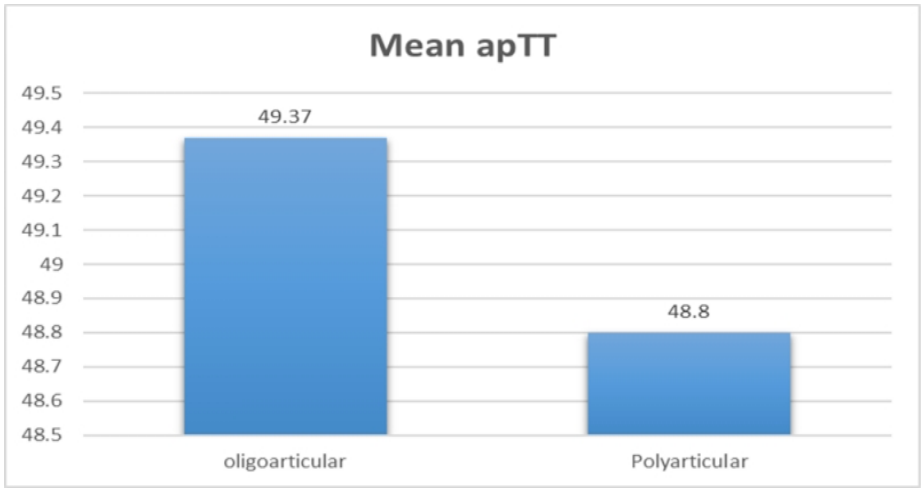

Fig. 6: Showed that the mean APTT in case of single joint bleed is 49.37+15.1 and in multiple joint bleed 48.8+11.8.

Among the 34 patients 44% were in severe category and 56 % were in moderate category.

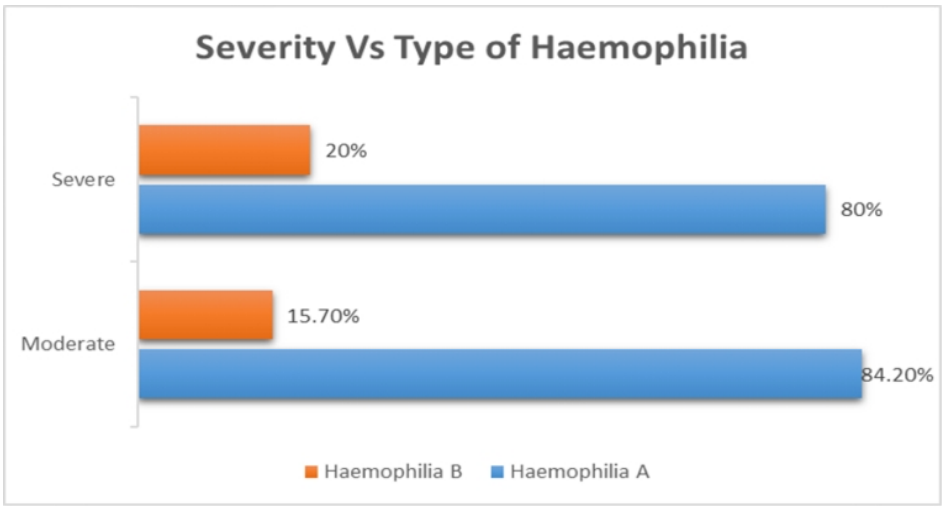

Fig. 7: showed among the severe hemophilia patients 80% were hemophilia and 84.20% were hemophilia B. Study showed the mean age in months for moderate & severe hemophilia were 6.63 and 6.2.

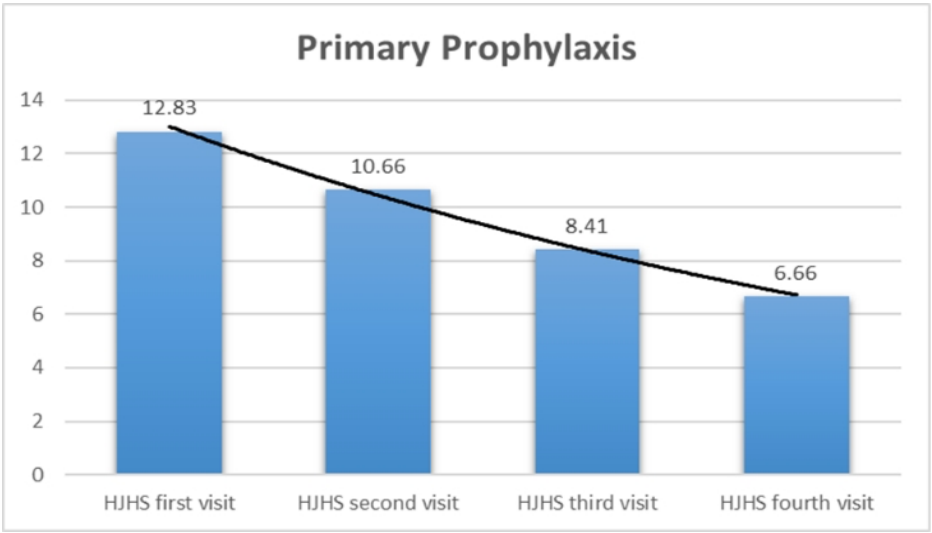

Fig. 8: showed the mean HJH score in first visit and subsequent visits in case of primary prophylaxis patients.

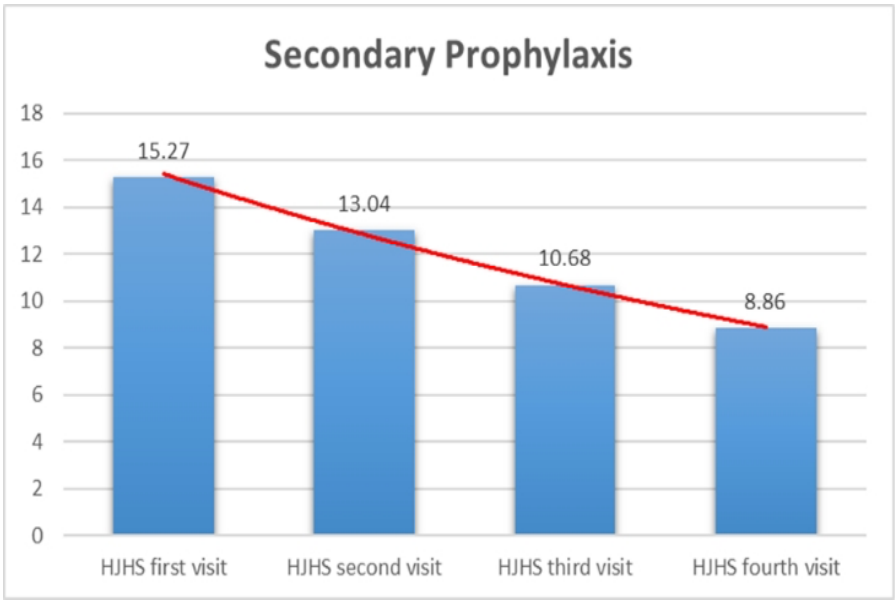

Fig. 9: showed the HJH score in first visit and in subsequent visits in case of secondary prophylaxis.

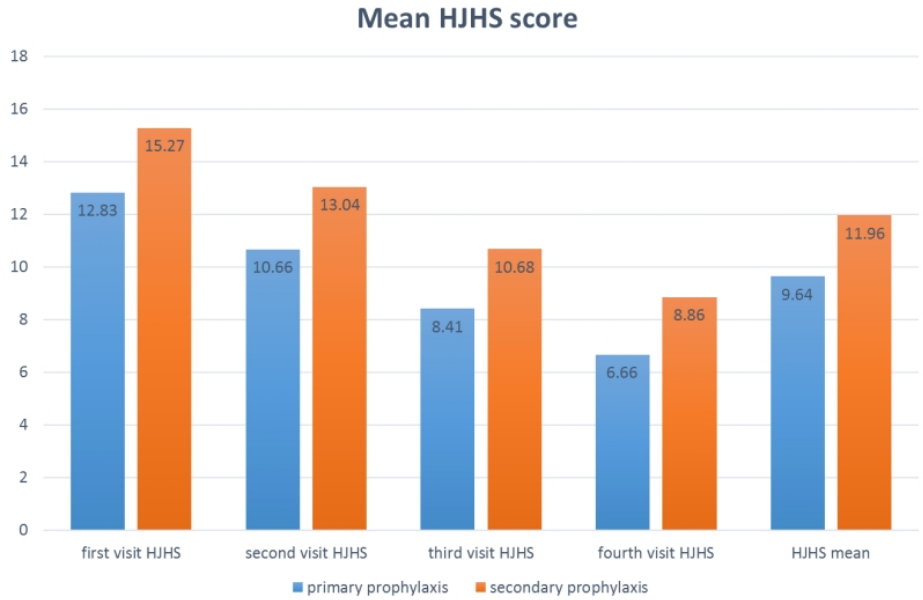

Fig. 10: showed the comparison between mean HJH score of each visit in case of primary versus secondary prophylaxis.

In first visit the mean HJH score for primary and secondary prophylaxis are 12.83+3.09 and 15.72+1.6 (P=0.03).

In second visit the mean HJH score for primary and secondary prophylaxis are 10.66+3.20 and 13.04+1.73 (P=0.043). In third visit the mean HJH score for primary and secondary prophylaxis are 8.41+2.84 and 10.68+1.49 (P=0.024). In fourth visit the mean HJH score for primary and secondary prophylaxis are 6.66+3.11 and 8.86+1.45 (P=0.046). Among the 34 patients, 7 patients had developed inhibitor.

All of them are hemophilia A. Study showed among the total papulation of patients' inhibitor developed in 18% of patients. It also showed that among the patients who developed inhibitor 33% patients have positive family history and 67% have negative family history.

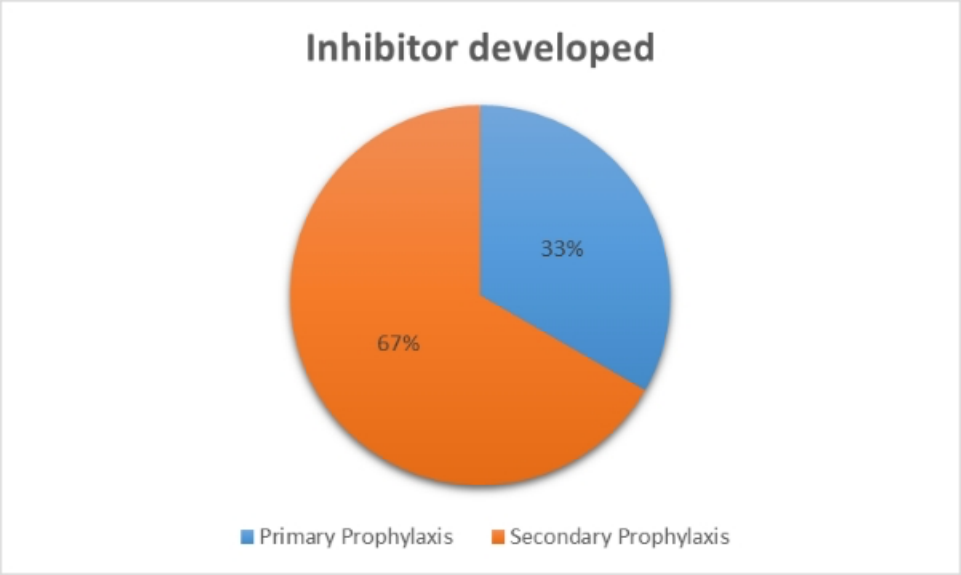

Fig. 11: Showed 33% of patients who developed inhibitor received primary prophylaxis and 67% received secondary prophylaxis.

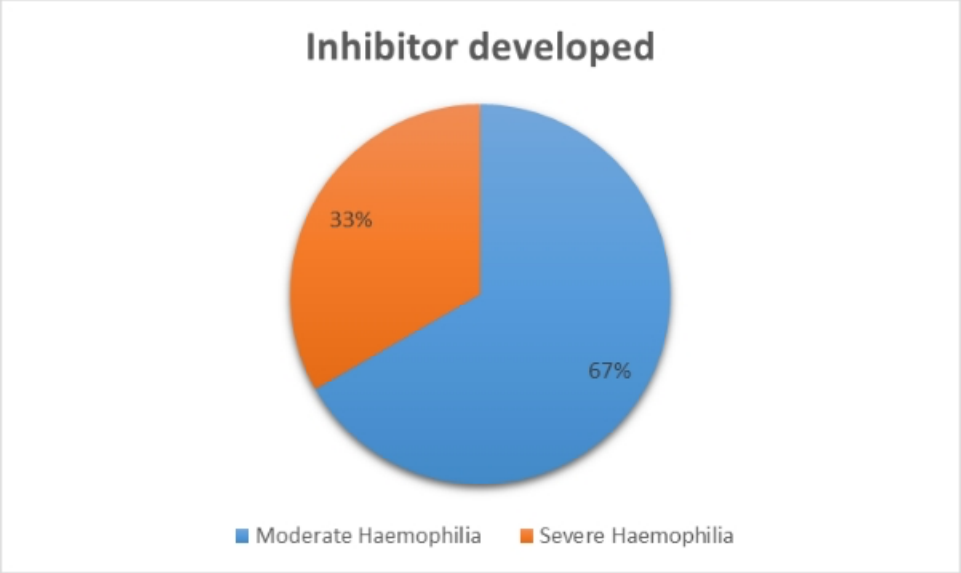

Fig. 12: Showed 33% of patients who developed inhibitor are of severe hemophilia group and 67 % are of moderate hemophilia group.

Discussion

From our existing knowledge we know that hemophilia is an important hematological problem after hemoglobinopathies though proper data especially in children is still lacking. Incidence of hemophilia A is more than Hemophilia B. Observed (calculated at 0.9 per 1,00,000) and estimated (calculated at 4 per 1,00,000 population) prevalence of haemophilia A for states and UT of India [10]. The observed and estimated prevalence of hemophilia in West Bengal is 822 & 3653 respectively [10]. As one of the important complications of hemophilia, joint bleed and permanent joint deformity mainly affects the quality of life. Prophylaxis is one of the ways to prevent recurrent joint bleed and permanent joint deformity and also improved quality of life [11]. Studies in developed countries have focused on the development of musculoskeletal scores which can be used for optimization of dose of clotting factor concentrate for maintaining joint health. In contrast, lack of treatment results in rampant disability in patients with haemophilia in India. Only one study by Kar et al [12] has measured the prevalence of disability.

This study, conducted at five centres across the country showed that of the 148 patients with severe haemophilia A, only nine were free of disability. The knee joint was affected in all of the 148 patients. Of concern was that in the age group of 5 to 12 years, only 15 per cent of patients were disability-free [12]. A significant association was

found between the socio-economic status of the patient's family and the severity of disability, suggesting the disability was most likely to be prevalent amongst the most vulnerable strata of society. Increased orthopaedic vulnerability of patients was demonstrated in another study that reported that the incidence of osteoporosis (T score: -2.5 or more) and the incidence of fractures in adult life were significantly higher in patients with haemophilia as compared to controls. In the study of Kar et al [12] a convenience sample of 148 severe haemophilia patients (FVIII < 1% of normal) above the age of 5 years were interviewed at home (34 patients), at a camp (16 patients) or at one of five haemophilia clinics (98 patients), three in Western India: Pune (n = 41 patients), Mumbai (n = 13 patients) and Kolhapur (n = 14 patients) and two centres in Eastern India: Kolkata (n = 66 patients) and Jamshedpur (n = 14 patients). Patients (or parents in case of young children) were interviewed through face-to-face interviews using a structured questionnaire and the incidence of fractures in adult life were significantly higher in patients with hemophilia as compared to controls.

In this study physical disability was measured using three parameters: mobility, functional ability and range-of-motion (ROM) measures. Twelve questions used to evaluate the effect of impairment on mobility and functional ability were selected from the World Health Organization Disability Assessment Schedule (WHO DAS II http://www.who.int/icidh/whodas/index.html) and the Arthritis Impact Measurement Scales 2 (AIMS2; http://www.cebp.nl/media/m318.pdf). Interpretation of restriction or limitation in activity was based solely on patient's evaluation and report. Each response was graded using a score of 3–1. Severe disability was defined as report of inability to perform a function and was assigned a score of 1. A patient was categorized as being affected and assigned a score of two when the patient reported that the function was possible, but was invariably associated with difficulty in performing the function. A patient was considered not disabled (score 3) when he reported no problem in undertaking any of the functions [13].

In our study, total 34 hemophilia A and B patients are included below the age of 12 years who fulfill the inclusion criteria. Among them 72% is hemophilia A and 18% is hemophilia B. Total study period was of 12 months and in this period all these patients are given prophylaxis and their outcome is measured by the Hemophilia Joint Health Score and Assessment of Quality-of-life score. These scores are compared in different visits. The mean age of this papulation is for Hemophilia A 16.82±14.2 months and for hemophilia B 18.5±14.3 months. Family history is positive in 26.5% (n=9) and negative in 73.5% (n=28) cases. The mean APTT at the time of diagnosis is for Hemophilia A 46.32±13.3 and for Hemophilia B 63.16±12.5. The P value is 0.008. In moderate hemophilia mean APTT is 50.15+12.7 & in severe hemophilia it is 48.2±16.9 (P=0.704). In first visit the mean HJH score for primary and secondary prophylaxis are 12.83±3.09 and 15.72±1.6 (P=0.03). Second visit the mean HJH score for primary and secondary prophylaxis are 10.66+3.20 and 13.04+1.73 (P=0.043). Third visit the mean HJH score for primary and secondary prophylaxis are 8.41±2.84 and 10.68±1.49 (P=0.024). Fourth visit the mean HJH score for primary and secondary prophylaxis are 6.66±3.11 and 8.86±1.45 (P=0.046). The mean value of assessment of quality-of-life score for secondary prophylaxis are for 1st visit 1.45±0.12 and for 2nd visit 6.091±0.33 and P value is 0.0001. Mean HJH score among the inhibitor developed and non-inhibitor patients are 13.04±0.73 and 10.74±2.44. and P value is 0.022.

Touré SA et al study (2023) demonstrated a total of 15 patients were included in the LDP regimen. The mean age was 6.3 years (1.5 - 10). A significant reduction was noted in the annualized bleeding rate, from 7.53 to 1.33 (p = 0.0001); the annualized joint bleeding rate passed from 3.6 to 1.4 (p = 0.001) and the proportion of severe bleeding, from 86.1% to 16.7% (p = 0.0001). The Hemophilia Joint Health Score (HJHS) moved from 9.6 to 3.4 (p = 0.0001) and the Functional Independence Score in Hemophilia (FISH) improved from 25.8 to 30.9 (p = 0.0001). School absenteeism decreased from 7.33% to 2.59%. Adherence to prophylaxis was 89.5% versus 60%. Consumption was 580 IU/kg/year versus 1254.6 IU/kg/year before and after prophylaxis, respectively. Incidence of inhibitors was 23% (3 /13 HA) [14].

Limitations of the study

There are few limitations of this study. Sample size of this study is small; it should be done in larger sample size hence the results are inadequate. Patients were attended after variable duration following prophylaxis therapy and HJH score was done in different days of prophylaxis. Patients who developed inhibitor prophylaxis has been stopped. In primary prophylaxis children who were in preschool age, assessment of quality of life cannot be done.

Socioeconomic status, cultural background, parenteral education status was not assessed in these children. Despite these limitations, the result of the study is definitely promising and warrant larger studies in this part of country to provide adequate information for planning of prophylaxis.

Conclusion

Out of these 34 patients 7 patients developed inhibitor during prophylaxis therapy. Family

history was positive in 26% cases and negative in 74% cases. Mean age at diagnosis in case of Hemophilia A is 16.82±14.2 (months) and Hemophilia B 18.5 ±14.36.

The mean value of assessment of quality-of-life score for secondary prophylaxis are for 1st visit 1.45+0.12 and for 10th visit 6.091+0.33 and P value is 0.0001. So, we can conclude that the HJH score is significantly decreasing from the first visit to the subsequent visits for both primary and secondary prophylaxis. When the decreasing pattern is compared in primary and secondary prophylaxis it is seen that HJH score is decreasing more in subsequent visits in case of primary prophylaxis than secondary prophylaxis. In case of secondary prophylaxis, the assessment of quality-of-life score is significantly improving from first visit to the subsequent visits.

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