Original Article

Study on Secondary *versus* Tertiary Prophylaxis in Hemophilia Children under 12 Years of Age in a Tertiary Care Hospital in Eastern India

Debanjana Basak[1], Prakas Kumar Mandal[2], Manik Mondal[3], Tapan Kumar Sinhamahapatra[4]

Background : Prophylaxis in hemophilia is the standard of care in developed countries for prevention of further bleeding and to preserve joint functions, thereby improving quality of life. The goals of prophylaxis are minimal or 'zero bleeds', no joint deformity and near normal life. The present study was aimed to study the outcome of secondary versus tertiary prophylaxis with a lower dose in hemophilia A and Hemophilia B children under 12 years of age.

Methods : The present prospective study was conducted over a period of 18 months. Total 34 patients were included in the study. Hemophilia A (HA) patients were started prophylaxis with recombinant Fc fusion long acting factor VIII at 15 IU.kg^{-1}.dose^{-1} twice weekly and hemophilia B (HB) with recombinant Fc fusion long acting factor IX at 30 IU.kg^{-1}.dose^{-1} once weekly. Outcome measured in terms of median annualized bleeding rate (ABR), hemophilia joint health score (HJHS) and child activity.

Results : Among 34 patients included in the study, 28 (82.3%) patients were HA and six (17.7%) were HB. Mean age of patients was 6.82 years for HA & 6.5 years for HB. Median ABR reduced from 15.6 to 1.9 bleeds/year. HJHS in case of secondary and tertiary prophylaxis at first visit were 12.83±3.09 and 15.72±1.6 and in fourth visit (at 18 months) were 6.66±3.11 and 8.86±1.45 respectively. None developed inhibitors during study. Child activity measured in terms of combined mean of school activity participation (SAP) score and daily activity (DA) score improved in secondary and tertiary prophylaxis from 1.455±0.12 and 2.46±0.11 in first visit to 6.09±0.33 and 5.39±0.23 in fourth visit respectively.

Conclusion : When compared, secondary prophylaxis is better than tertiary prophylaxis in children. In resource constraint countries where availability of CFC is an issue, prophylaxis can be individualized and the goals can be achieved by using even smaller doses.

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Key words **: Hemophilia, Children less than 12 years, Low Dose Prophylaxis, Long Acting Factors.**

Editor's Comment :

- **The standard of care in hemophilia is prophylaxis.**
- **Goals of prophylaxis are minimal or 'zero bleeds', no joint deformity and near normal life.**
- **Prophylaxis can be individualized and the goals can be achieved by using even smaller doses.**
- **Long acting factors are helpful in decreasing the frequency of administration.**

The two most common and serious congenital coagulation factor deficiencies are Hemophilia A (Factor VIII) and Hemophilia B (Factor IX), both inherited as X-linked recessive characters. Clinical manifestations of Hemophilia A (HA) and Hemophilia B (HB) are more or less same.[1] The reported incidence is 1 in 10,000 births for HA and 1 in 50,000 births for HB. Depending on how much working clotting factor is in the blood, hemophilia is classified as mild (5%-40%), moderate (1%-<5%) and severe (<1%). Bleeding may occur at any site but the hallmark of hemophilic bleeding is joint bleed (hemarthrosis). Spontaneous bleeding generally occurs in severe hemophilia, in moderate form prolonged bleeding occurs with minor trauma whereas prolonged bleeding occurs with major trauma and surgery in mild hemophilia.[1,2] Repeated joint bleeds with suboptimal treatment ultimately leads to disability due to chronic arthropathy and contracture.[1] Other than hemarthrosis, bleeding in muscle (especially psoas bleed) and CNS are also common. Different complications of hemophilia (may be related to disease- synovitis, chronic hemophilic arthropathy, pseudotumour or related to therapy - development of inhibitors & transfusion related

NRS Medical College, Kolkata 700014

[1]MD (Pediatrics), Postgraduate Trainee, Department of Pediatric Medicine

[2]DM (Clinical Hematology), Associate Professor, Department of Hematology and Corresponding Author

[3]MD (Pediatrics), Assistant Professor, Department of Pediatric Medicine

[4]MD (Pediatrics), Professor & Head, Department of Pediatric Medicine

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infections) in the long run causes decrease in quality of life (QoL) and increased morbidity. In hemophilia, prophylaxis is considered as the optional care to prevent further bleeding and to preserve joint function and thus improving QoL.[3] In this contexts, a study was conducted in children of <12 years of age with HA & HB who were given secondary and tertiary prophylaxis to determine QoL in relation to joint mobility and its effect in their social life and school activity. Thus, the study aimed to compare the outcome of secondary versus tertiary prophylaxis in respect to joint involvement and child activity.

Material and Methods

This prospective study was conducted in the Departments of Hematology & Department of Pediatrics Medicine at Nilratan Sircar Medical College, a Tertiary Care Hospital in Eastern India over a period of 18 months (January, 2018 to June, 2019).

Patients included in the study were- (a) three to 12 years of age, (b)after two or more bleeds into large joints (large joints= knees, ankle, elbow, hips and shoulders) and before the onset of joint disease documented by physical examination and imaging studies (secondary prophylaxis arm)[2], (c)after the onset of joint disease documented by physical examination and imaging studies (tertiary prophylaxis arm)[2], (d)all severe cases (factor level <1%) and moderate cases with factor level<2%, (e)previously treated patients (history of at least 50 documented EDs to FVIII or FIX in HA and HB respectively. Participants excluded from the study were : (1) Children less than three years of age and of and above 12 years, (2) children having other associated bleeding disorders, (3) history of, or currently detectable, inhibitor, (4) history of anaphylaxis associated with either FVIII or FIX.

After taking proper consent from legal guardians, a total of 34 patients were enrolled in the study. The following variable were studied and recorded for individual patients — (a) type of Hemophilia- HA or HB, (b) factor VIII & IX level at diagnosis, (c) age at starting prophylaxis, (d) number of joint bleeds at the start of prophylaxis, (e) level of inhibitor (Bethesda unit), (f) straight X-ray of involved joint(s) in selected cases. HA patients were started with low dose prophylaxis[4,5] with recombinant Fc fusion long acting factor VIII (rFVIIIFc) (ELOCTATE) at 15 $IU.kg^{-1}.dose^{-1}$ twice weekly (Monday and Friday) and HB patients started with low dose prophylaxis[6] with recombinant Fc fusion long acting factor IX (rFIXFc) (ALPROLIX) at 30 $IU.kg^{-1}.dose^{-1}$ once weekly (Friday); both for 18 months. In cases of break through bleed, they received recommended dose[2] of Coagulation Factor Concentrates (CFC) depending on site.

Outcome measured in terms of median ABR, HJHS and also child activity was measured in terms of School Activity Participation (SAP) score and Daily Activity (DA) score according to Beijing Children Hospital (BCH)[7] assessment scale.

SAP score :

- score 0 (unable to have activities beyond classes)
- score 1 (able to walk around in school yard)
- score 2 (participation in exercise drill and stretching)
- score 3 (participation in non-contact sports such as swimming or jogging)
- Score 4 (participation in contact sport such as basketball, but not in competition).

DA score :

- score 0 (wheelchair bound)
- score 1 (can work slowly)
- score 2 (walking plus one activity such as swimming or jogging)
- score 3 (walking plus two or more additional activities)
- Score 4 (no activity limitation).

Improvement in SAP score and DA score was noted as :

- poor (no change),
- mild (≤2 scores increase)
- moderate (>2 scores increase)
- Good (full increase from score 0 to 4).

School absenteeism (days/month) was also noted. HJHS and child activity score as per BCH scale[7] noted at 4 different time points- first visit (zero month), second visit (at 6 months), third visit (at 12 months) and fourth visit (at 18 months).

Statistical analysis : Data were entered into a Microsoft excel spread sheet and then analyzed by SPSS20 and GraphPad Prism version 5. Data were summarized as mean & standard deviation for numerical variables and count and percentage for categorical variables. Data were distributed in skewed fashion. But as they suffice the criteria of Robust Means of Equality & Levene statistics (that is homogenicity of variables not been disrupted), so we performed unpaired t test, Mann-whitney u test, one way ANOVA and Spearman Rho correlation test.

Observations

Among 34 patients, 28 (82.3%) patients were HA and six (17.7%) were HB. All the children included in the study were male except one female diagnosed as

HB. Definite history of another member affected in the family present in 26% cases. Mean age at diagnosis in case of Hemophilia A is 16.82±14.2 months and Hemophilia B 18.50 ± 14.36 months. Mean age of patients recruited for the study was 6.8 years for HA & 6.5 years for HB. Among the 34 patients, 15 (44.1%) patients were in severe category and 19 (55.9%) were in moderate category. Median ABR reduced from 15.6 to 1.9. Total 22 patients (HA-20 and HB-2) had a total of 38 target joints where knee joint was the most predominant site and there was resolution in all target joints. The HJH scores of each visit in case of secondary and tertiary prophylaxis are shown in Fig 1; in first visit, the mean HJH score was 12.83±3.09 and 15.72±1.6 (p=0.03) respectively. At second visit, the mean HJH score for secondary and tertiary prophylaxis are 10.66±3.20 and 13.04±1.73 (p=0.043). At third visit, the mean HJH score for secondary and tertiary are 8.41±2.84 and 10.68±1.49 (p=0.024). At fourth visit, the mean HJH score for secondary and tertiary prophylaxis are 6.66±3.11 and 8.86±1.45 (p=0.046).

During the course of study, in no case there was development of inhibitors (BU<0.6). With prophylaxis, school absenteeism (days/month) reduced by 90.3% (13.38 to 1.29). Improvement in child activity measured as combined mean value of SAP score and DA score as per BCH[7] scale was 1.455±0.12 at first visit and 6.09±0.33 at fourth visit in the secondary prophylaxis arm versus 2.46±0.11 at first visit and 5.39±0.23 at fourth visit in the tertiary prophylaxis arm (p= 0.0001).

Discussion

The term 'prophylaxis' is defined as "treatment by intravenous injection of factor concentrate in anticipation of and in order to prevent bleeding" that should be regular and continuous [defined as the intent of treating for 52 weeks/year and receiving a minimum of an a priori defined frequency of infusions for at least 45 weeks (85%) of the year under consideration].[2,8] Because of recurrent joint bleeds, there is permanent joint deformity that mainly affects the quality of life. Prophylaxis is known to prevent recurrent joint bleed and thus reduce the severity of hemophilic arthropathy and considered as the standard of care for young children in developed countries.[8,9] In contrast, lack of adequate therapy (in terms of prophylaxis) results in rampant disability in persons with hemophilia (PwH) in resource constraints countries.

With prophylaxis, in the present study, median ABR reduced from 15.6 to 1.9 (reduction by 87.8%). Mandal PK *et al*[5] earlier had studied in adultson tertiary prophylaxis with low dose rFVIIIFc and had shown a decrease in mean ABR of 3.6 bleed/year compared to 37.8 bleed/year on 'ondemand therapy'. Gulshan S *et al*[10] studied on low dose rFVIIIFc prophylaxis in children up to 12 years of age with HA and had shown a reduction in median Annual Joint Bleeding Rate (AJBR) by 85.76% (from 14.5 to 2.2bleed/year) in comparison to 'on demand therapy'. Pasi KJ *et al*[11] reported median ABR of 2.3 bleed/year in children <12 years with HB (≤2 IU/dl) who were given weekly prophylaxis with rFIXFc at a dose of 20-100 IU/Kg. Khayat CD[12] reviewed two prospective randomized studies on efficacy and safety of once-weekly prophylaxis (100 IU/kg) with recombinant factor IX (nonacog) in adolescents and adults with HB and shown reduction of ABR by 89.4%.

A target joint is defined as a major joint with three or more bleeding episodes in a consecutive 3-month period. Target joint resolution is defined as two or less bleeds in a 12 months period. In the present study, 22/34 PwH (HA-20/28 and HB-2/6) who had a total of 38 target joints at baseline achieved target joint resolution in all cases after rFVIIIFc and rFIXFc prophylaxis. O'Hara J *et al*[13] reported 551 PwH with 692 target joints and concluded thattreatment of 'target joints' should be an important target while managing hemophilia.

In the present study, total 34 children were on either secondary or tertiary prophylaxis and the outcome was measured by the HJHS and BCH assessment tool. As noted in the result section and shown in Fig 1, mean HJHS of each visit in case of secondary and tertiary prophylaxis had shown p-value of 0.03, 0.043, 0.024 and 0.046 in the first, second, third and fourth visits respectively and all were statistically significant. And there was a significant reduction in HJHS from 12.83 to 6.66 (reduction=48.1%) and from 15.27 to

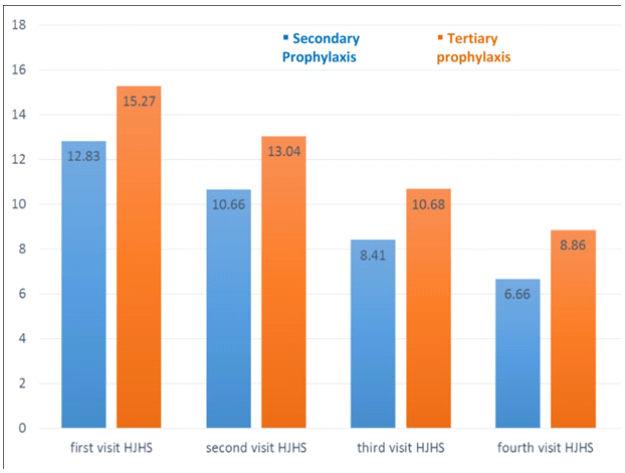

Fig 1 — Mean HJH score in first visit and subsequent visits in case of secondary and tertiary prophylaxis

8.86 (reduction=41.9%) in secondary and tertiary prophylaxis respectively. Thus, the reduction in HJHS in secondary prophylaxis (48.1%) was better than in tertiary (41.9%) prophylaxis. Payal V *et al*[14] from Jodhpur, India studied 56 cases of PwH, had shown mean HJHS of 6.78 ± 9.04 and significant positive correlation with age of patient (p=0.0001). They suggested that, prophylaxis should be tailored based on bleeding pattern and age of patients rather than clotting factor levels. When compared to 'on-demand' therapy, secondary/tertiary prophylaxis has clearly shown a significant reduction of 93.63% and 93.89% in the studies from India by Gulshan S *et al*[10] and Sidharthan N *et al*[4]. In the study from Eastern India by Gulshan S *et al*,[10] in severe HA children the mean HJHS at presentation was 8.3 that significantly reduced with regular and continuous prophylaxis. In the study by Sidharthan N *et al*[4] from South India mean HJHS at presentation was 14.9 that also significantly reduced with regular and continuous secondary/tertiary prophylaxis. Study by Kar A *et al*[15] conducted at five different centers in India measured the prevalence of disability in PwH. Their study had shown that, only nine(6.8%) out of 148 persons(aged 5-55 years) with severe HA, were free of disability. Of concern was that in the age group of 5-12 years, only 14.3% patients were disability-free. A significant association was found between the socioeconomic status of the family and the severity of disability; the study highlighted the need to provide CFCs in sufficient amounts to prevent disability.

In the present study, school absenteeism (SA) across secondary/tertiary prophylaxis groups reduced by 90.3% (13.38 to 1.29days/month). Gulshan S *et al*[10] reported a reduction in SA by 86% (17.38 to 2.42 days/month) after prophylaxis. The improvement in child activity as measured by combined mean of SAP score and DA score was statistically significant (p=0.0001) in secondary prophylaxis as compared to tertiary one. Study from China by Wu *et al*[7] showed improvement of SAP score of poor, mild, moderate and good in 25%, 75%, 0% and 0% cases respectively and in the study by Gulshan S *et al*[10] it was 5%, 57%, 38% and 0% respectively. Wu *et al*[7] showed improvement in DA score of poor, mild, moderate and good in 31.03%, 58.62%, 3.4 and 6.8% cases respectively and it was 17%, 40%, 43% and 0% respectively in the study by Gulshan S *et al*[10].

None of the cases (0/34) in the present study had shown development of inhibitors. There is no reports of development of inhibitors in recent studies from India by Mandal PK *et al*[5] with rFVIIIFc in adults and Gulshan S *et al*[10] in children <12 years. In the study on the safety and efficacy of rFIXFc by Pasi KJ *et al*[11] in the Phase 3 B-LONG (adults/adolescentse ≥12 years) and Kids B-LONG (children<12 years) studies of subjects with hemophilia B, no inhibitors were observed. In contrast to Swedish[16] protocol (25–40 IU.kg^{-1}.dose^{-1} thrice weekly) and Dutch[17] protocol (15–25 IU.kg^{-1}.dose^{-1} thrice weekly), many centers[4,5,10] in India had used low dose prophylaxis (10–20 IU.kg^{-1}.dose^{-1} twice weekly) with a significant net reduction in factor consumption with comparable outcome. Moreover, both the supplied products used in the present study were long acting preparations with extended half lifes[11,18] and that minimized number of hospital visits (notably weekly one visit for HB) and this was reflected by very good compliance in all patients.

Another important issue discussed in many of the studies on prophylaxis in hemophilia is cost that was not an issue in this study as both rFVIIIFc (ELOCTATE) and rFIXFc(ALPROLIX) they received were donated by WFH Humanitarian Aid; thus not affected the compliance of patients. The study period was long in comparison to many such other published studies.

Conclusion

CFC replacement in terms of prophylaxis is the optimal therapy for prevention of recurrent joint bleed and therefore to improve child activity. When compared, secondary prophylaxis is better than tertiary prophylaxis in children in terms of outcome such as-ABR, HJHS and child activity scores. Overall, the results are very encouraging and promising but, warrant larger studies in the study population to provide adequate information for planning of prophylaxis.

Limitations of the study :

We observed several limitations in the present study as follows —

- Small sample size (especially in case of hemophilia B); it should be done in larger sample size hence the results may be inadequate.
- In few children aged 3-6 years (ie, preschool age), there was some difficulty in assessment of child activity as per BCH assessment tools and for the reason, we had to omit the parameter of school absenteeism which is studied by many others
- Socioeconomic status, parental education status and feasibility of home based therapy that indirectly reflects the success of prophylaxis therapy, were not assessed in the present study.
- Did not measure quality of life (QoL) as measured by other study tools for kids.

Informed Consent : Informed consent was obtained from the legal guardians of all individual

children included in the study.

Conflict of Interest : No Conflicts of Interest declared by any author

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Ethics approval : The study was approved by the institutional ethical committee.

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I have had dreams and I have had nightmares, but I have conquered my nightmares because of my dreams

— **Jonas Salk, *American Physician who developed the Polio Vaccine***