Study to evaluate the effectiveness of coagulation factor concentrate prophylaxis in children with severe hemophilia

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ABSTRACT

Objective: To evaluate the effectiveness of prophylaxis with coagulation factor concentrates VIII/IX (FVII/IX) in children with severe hemophilia A/B, respectively. **Materials and Methods:** Retrospective observational study was done on children enrolled in our hemophilia clinic, who initially received "on demand" therapy and were on prophylaxis with factor VIII/IX concentrate at the time of the study. The study group consisted of 8 children. Annual hemarthrosis rate (AHR) over a period of 1-year during on demand therapy was compared with AHR during a period of 1-year on prophylaxis with FVIII/IX. **Results:** There was reduction in AHR by 87% in hemophilia A and 85% in hemophilia B during prophylaxis compared to on demand therapy. There was a significant reduction in hemarthrosis/patient/year from 2.5 to 0.3 on prophylaxis with factor concentrate compared to on demand therapy. There was also reduction in other bleeding manifestation like psoas muscle bleed, oral bleeds, epistaxis, and number of target joints involved. **Conclusion:** Prophylaxis with coagulation factor concentrate significantly reduces the AHR, and hence, decreases the disability associated with it compared to "on demand" therapy.

Key words: *Annual hemarthrosis rate, Coagulation factor concentrate VIII/IX, Factor concentrate prophylaxis, Hemophilia A/B, On demand therapy*

Hemophilia is an X-linked inherited disorder characterized by the deficiency of coagulation factors VIII/IX (FVIII/IX). World federation of hemophilia's annual global survey indicates that the number of people with hemophilia in the world is 176,211 of which 140,313 are hemophilia A and rest is hemophilia B cases. In India, there are 13,448 patients with hemophilia A and 2176 with hemophilia B, which account for 5-6% of the total, this number being only a fraction of cases since many cases go undiagnosed [1].

Severe hemophilia is defined as deficiency of coagulation factors VIII (FVIII) or IX (FIX) with circulating factor levels <1 IU/dl [2]. It manifests as recurrent bleeding into muscles and joints from an early age of life [3]. The first joint bleed in severe hemophilia generally occurs after the first 6 months of life and in the majority of cases by the second birthday [4]. The consequence of repeated bleeding into joints is the premature development of hemophilic arthropathy with chronic disability and poor quality of life (QoL) [2,5]. The treatment for bleeding in early days was with fresh frozen plasma or cryoprecipitate infusion, later with plasma-derived factor concentrates, and presently recombinant factor concentrates are being used widely [6]. Factor concentrates infused only during bleeding episodes are referred to as "on demand" therapy [7].

Various studies proved that development of arthropathy can be effectively prevented by prophylactic administration of factor concentrates, by maintaining steady level of factor VIII levels >1 IU/L [7-10]. Prophylaxis with coagulation factor concentrate was pioneered for hemophilia A in the late 1950s and in hemophilia B in the early 1970s in Sweden [6]. There are various regimens of prophylactic therapy; all intended to maintain a steady level of coagulation factors in blood to avoid bleeding and its complications and disability [5] (Fig. 1). Prophylaxis has therefore been recommended by the World Health Organization and World Hemophilia Federation since 1994 and primary prophylaxis started after the first joint bleed and/or before 2 years is now evidence-based first-choice treatment in children with severe hemophilia [6].

Although prophylaxis, in general, is expensive, resource intensive and time-consuming, the overall economic savings from improved QoL with no bleeding and bleeding related complication should be more than enough to off-set the costs of implementation [11]. While "high-dose" regimens (25-40 IU/kg 3 times a week) are considered as "gold standard" "intermediate dose" regimens (20-40 IU/kg, 2-3 times/week) have shown comparable QoL with reduction in hemoarthrosis at the expense of 2-fold higher factor consumption [6,11,12]. Even this intermediate dose regimen is clearly not affordable in developing countries. Few studies in India, China and Thailand are providing evidence that even low dose prophylaxis (8-10 IU/kg, twice a week) can have major impact on number of bleeds, QoL and full participation

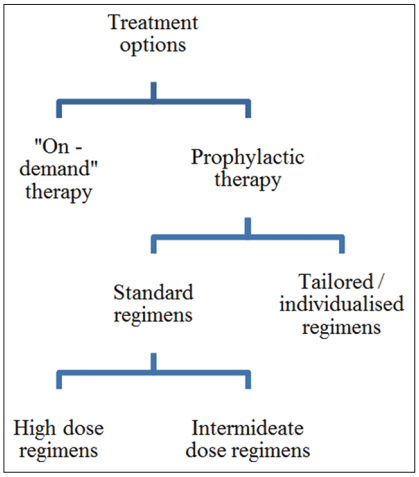

Figure 1: Treatment options

in society [12-15]. Although evidence on the benefits of low-dose prophylaxis from large clinical trials is yet to be proven, this may be the feasible way to deliver prophyaxis in developing country like ours [11]. We, at our center, started using the "intermediate regimen" due to (i) logistics of "supply-demand" and (ii) to get full patient compliance for the prophylaxis.

Very few centers in India are presently using recombinant factor VIII concentrate for hemophilia children as "on demand" therapy. "Prophylactic" therapy is yet to be implemented in most centers for this children due to financial constraints and logistics of giving this injection thrice weekly even though the benefits of this form of treatment is well established and is implemented in all developed countries. This study was undertaken to know the efficacy of intermediate dose prophylaxis with recombinant FVIII/IX concentrate in reducing the annual hemarthrosis rate (AHR).

MATERIALS AND METHODS

A retrospective observational study was conducted on children enrolled in our Hemophilia clinic of Department of Pediatrics, Employees State Insurance Corporation Post-graduate Institute of Medical Sciences and Research who initially received on "demand therapy" for 1 year and later changed over to "prophylaxis" with recombinant coagulation factor concentrate, 20 IU/kg of factor VIII/IX twice a week, for the next 1 year. Institutional Ethical Committee approval was taken for the study. Children under 18 years of age with severe hemophilia A/B (serum coagulation factor VIII/IX activity <1%) were included the study. Children with poor compliance and dropouts or those who developed inhibitors were excluded from the study. Utilizing hospital records and patients dairy, AHR of these children while on "on demand" therapy and "prophylaxis" was calculated.

RESULTS

Out of 24 children enrolled to our hemophilia clinic, 14 children fulfilling inclusion criteria were considered for the study, their records and dairies were analyzed. Of these children 2 developed

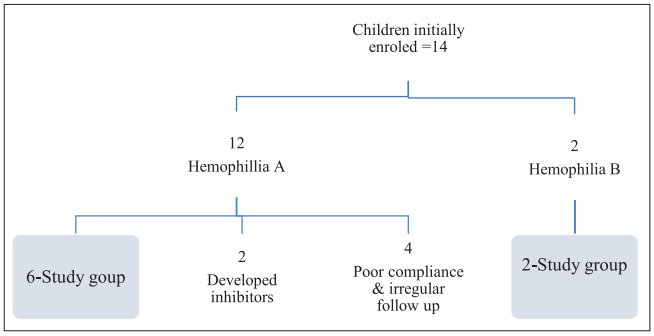

Figure 2: Study flow chart

inhibitors (suspected clinically and confirmed by biochemical estimation of inhibitor levels) [7], and 4 were irregular (noncompliant) for treatment; hence, these 6 were excluded from the study. The study group finally consisted of 8 children and among these 6 were diagnosed as hemophilia A and 2 were hemophilia B. AHR, defined as number of hemarthrosis per year requiring factor replacement therapy, for a period of 1-year during on "demand therapy" was compared with AHR for a period of 1-year on prophylaxis with FVIII/IX as shown in Fig. 2.

Age of children with hemophilia A at enrolment for prophylaxis with FVIII concentrate ranged from 4 years 1 month to 15 years with a mean of 9 years and age of children with hemophilia B for prophylaxis with FIX concentrate were aged 6 years to 7 years with a mean of 6.5 years. It was observed that AHR in children with hemophilia A/B during "on demand" therapy was significantly more than that during prophylaxis with FVIII/IX concentrate, respectively, i.e., average of 13/year during on demand versus 1.6/year during prophylaxis in hemophilia A children and average of 7/year during on demand versus 1/year during prophylaxis in hemophilia B children.

We also observed a significant reduction in other bleeding manifestation such as psoas muscle bleed, epistaxis, oral bleeds, number of target joints involvement, and decrease in school absenteeism (Table 1 and Fig. 3). There was 87% and 85% reduction in AHR in hemophilia A and hemophilia B children, respectively. Hemarthrosis rate/participant/year was 2.5 and 0.32 in on demand and prophylaxis group, respectively.

DISCUSSION

Nonrandomized as well as randomized studies have accumulated a plethora of data on prophylactic FVIII infusions in patients with severe hemophilia A/B, documenting the beneficial results of decreased bleeding episodes and later degenerative joint disease [6]. Difficulty of intravenous access in young children, lack of understanding on the part of the caregiver, fear of development of inhibitor, psychological factors, and not the least the exorbitant cost of recombinant factor therapy are some of the barriers to implement this form of therapy in severe hemophiliacs [6]. This form of therapy has not been widely practiced or standard of care in our country largely because of cost constraints. The percentage of children under 18 years on prophylaxis is estimated to be about 1%, and the majority of these children continue to receive

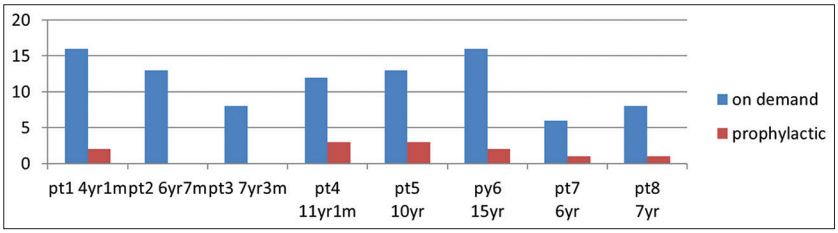

Figure 3: Comparison of annual hemarthrosis rate 1 year prior to prophylaxis (on demand) and 1 year during prophylaxis in hemophilia A (patient 1-6) and hemophilia B (patient 7 and 8) X-axis -patient (patient) and Y-axis - annual hemarthrosis rate (episodes of hemarthrosis/year)

Table 1: Comparison of AHR during "on demand" therapy versus prophylaxis with coagulation factor concentrate

Hemophilia type	Mean age at enrolment for prophylaxis (years)	Factor concentrate dose during prophylaxis	Mean AHR during		% reduction in AHR
			On demand	Prophylaxis	
A	9	20 IU/kg twice weekly	13/year	1.6/year	87
B	6.5	20 IU/kg twice weekly	7/year	1/year	85

AHR: Annual hemarthrosis rate

plasma-derived factor concentrate as "on demand" therapy [1]. As an exception to these prevailing circumstances, children with severe hemophilia of insured persons of Employees State Insurance Corporation, India, are provided with recombinant FVIII/FIX concentrate free of cost ensuring a bright future for these children.

In our study on 8 children with severe hemophilia, mean age at starting factor concentrate prophylaxis was 9 years in Hemophilia A and 6.5 years in Hemophilia B. There was 87% reduction in AHR in Hemophilia A and 85% reduction in AHR in Hemophilia B during prophylaxis compared to "on demand" therapy. Hemarthrosis rate/participant/year was 2.5 and 0.32 in on demand and prophylaxis group, respectively. Manco-Johnson et al. [16] showed annual bleed rates of 4.35 and 0.2 per year among on demand and prophylaxis group, respectively. Gringeri et al. [17] (the ESPRIT study) observed that the AHR was 5.5 and 1 in episodic/on demand treatment and prophylaxis, respectively. Verma et al. [12] showed that hemarthrosis rate among "on demand" treatment group was 0.48/patient/month (5.7/year) and prophylaxis group was 0.08/patient/month (0.96/year). Similar results have also been reported by other investigators [18-22].

At least 4 studies on children and adults from Thailand, China and India have shown superiority of low dose (~5–10 IU/kg, 2-3 times a week) prophylaxis over episodic treatment in terms of bleed reduction, and QoL, with improved physical activity, independent functioning, school attendance and community participation [12-15]. Prophylaxis can still be individualized to affordability and higher protective trough level can be achieved using smaller doses given more frequently without an increase in consumption/cost. Thus, future studies proving this low dose therapy as feasible alternative may make prophylaxis universally available in resource-poor countries like ours.

New factor preparations with extended half-life are in clinical studies. If proven effective, such factor concentrates will significantly decrease the frequency of factor infusions, thus likely increasing compliance. Gene therapy, now under investigation, constitutes a possible alternative to prophylaxis, with curative potential [6]. Our study has some limitations being a single center study involving small group and due to short duration of the study. Further large trials are needed to generalize the study results.

CONCLUSIONS

Prophylaxis with coagulation factor concentrate reduces hemorrhagic events, and hence, reduces acute and chronic complication of repeated bleeding. Thus most of the centers caring for hemophilia have started prophylaxis with Factor concentrate. In our country, because of resource constraints very few centers have started prophylaxis, ours being one such pioneering center and this study reinforces the efficacy of prophylaxis.

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