

Hemophilia is an x-linked congenital bleeding disorder caused by deficiency of coagulation factors VIII and IX in hemophilia A and B respectively, which affects males with females being asymptomatic carriers. Underlying cause is a mutation of the respective clotting factor genes. According to WFH's annual global survey, number of hemophilia patients world-wide is approximately 400,000. Reported prevalence of hemophilia in India is approximately 1.1/100000 male population which is remarkably less in comparison to western countries due to underreporting of cases. Only 10% of total cases are registered with Hemophilia federations in India. Given that incidence of Hemophilia A is one in 5000 and hemophilia B is one in 30000, the expected number of people with hemophilia (PWH) in India should be close to 100,000.

Typical phenotypic presentation of hemophilia patient is life-long bleeding tendency. Children with hemophilia start bleeding when they begin crawling, walking and running. Hemophilia patients are categorized into three categories of mild, moderate and severe hemophilia based on severity of factor deficiency. Patients with severe hemophilia have FVIII level <1% and tend to bleed spontaneously into joints and muscles, while those with moderate hemophilia have FVIII level 1-5% and rarely have spontaneous bleed.

The most common haemorrhagic manifestations in patients with haemophilia are recurrent joint bleeds followed by muscle bleeds. Commonly affected joints are elbows, knees and ankles, also known as index

joints. Recurrent bleeding in these joints in due course of time leads to progressive joint destruction, irreversible arthropathy and chronic pain. This in turn leads to loss of school days, multiple emergency visits, poor quality of life, loss of job opportunities and psychological stress among patients with haemophilia.

The current practice in India and most other developing countries is replacement of the deficient coagulation factor on episodic (demand) basis after joint bleed has already occurred (Table 1). Episodic therapy may delay progression to arthropathy but cannot prevent it. Prophylactic therapy with factor concentrates administered 2 to 3 times a week on a regular basis is the best way to prevent joint bleeds. Purpose of regular prophylactic factor replacement is to convert severe forms to milder forms. The Swedish experience demonstrates a decreasing need for orthopedic surgery in hemophilic patients who are managed from the age of 1 to 2 years (before onset of arthropathy) with a prophylactic regimen of clotting factor concentrate replacements. The doses and frequency of replacement therapy are adjusted to prevent the factor VIII levels from falling below 1% to 2% of normal, thereby converting severe hemophilia into mild or moderate disease (thus preventing spontaneous bleed). Improvements translate into decreased absence from school or work, fewer bleeds and days spent in the hospital, increased personal and professional productivity, improved overall performance status, and a healthier self-image. There is no evidence that prophylaxis begun early in childhood increases the incidence of inhibitor antibody formation.

Table 1: Definitions of regimens of factor replacement therapy in haemophilia

Episodic (on-demand treatment) CONVENTIONAL*	Treatment given at the time of clinically evident bleeding (widely practiced in India and other developing countries)
Primary prophylaxis**	In the absence of documented osteochondral joint disease, determined by physical examination and/or imaging studies, started before the second clinically evident large joint* bleed and age <3 years
Secondary prophylaxis**	After 2 or more bleeds into large joints* and before the onset of joint disease documented by physical examination and imaging studies
Tertiary prophylaxis	After the onset of joint disease documented by physical examination and plain radiographs of the affected joints
Intermittent (periodic) prophylaxis	Treatment given to prevent bleeding for periods not exceeding 45 weeks in a year

Adapted from the recommendations of the Subcommittee on factor VIII and factor IX of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis, reported in the Guidelines for the management of hemophilia from the Working Group of the World Federation of Haemophilia. *Practised in developing countries; **Practised in developed countries; ***Large joints: ankles, knees, hips, elbows and shoulders.

464 Prophylactic therapy with factor concentrates administered 2 to 3 times a week on regular basis is the best way to prevent joint bleeds. Prophylactic replacement of clotting factor has been shown to be useful even when factor levels are not maintained above 1% at all times.

Between late 1970s and 1990, children with haemophilia have been treated with prophylactic therapy using incremental doses (5–10 to 20–40 IU/kg body weight) of intermediate purity clotting factor concentrates or cryoprecipitate two to three times a week. Recently much stronger evidence on efficacy of prophylaxis was provided by randomized control trial by Manco-Johnson et al. and the ESPIRIT study by Gringeri A et al. In these studies factor VIII was used in doses of 25 IU/ kg body weight on alternate days, which involves a high amount of factor consumption and leads to high cost, resulting in unaffordability of such treatment in developing countries like India and even in some of the western countries. Following protocols are practiced currently in developed countries:

- Malmö protocol : 25-40iu/kg/dose thrice weekly
- Utrecht protocol : 15-30iu/kg/dose thrice weekly

But the optimal regimen remains to be defined.

Resource-strained countries need to have their own factor prophylaxis strategy. Very low-dose FVIII prophylaxis (10 IU/ kg body weight twice a week) may be a feasible option for prophylaxis in resource constraint countries like India as proven in one recent single-centre short-term pilot study from China.

INDIAN EXPERIENCE AT JIPMER, PUDUCHERRY

The aim of the study was to find out the efficacy, cost effectiveness and safety of very low-dose factor prophylaxis in patients with haemophilia A in Indian scenario. This study conducted in 2013 on 21 children concluded, even very low-dose FVIII prophylaxis with 10 IU/kg body weight twice a week was effective in preventing joint bleeds and overall bleeds and also was cost effective. Significantly less emergency visits, lesser days of school absenteeism were found in children. Even if the factor trough levels were not maintained above 1% in all cases, bleeding events were still prevented in all children.

ONCE WEEKLY FACTOR VIII PROPHYLAXIS IN CHILDREN WITH SEVERE HEMOPHILIA – A NEW CONCEPT

However, compliance with twice a week schedule is a limiting factor in the long run. Thus, another option for the treatment of very young children is to start prophylaxis once a week and escalate dose depending on bleeding. Low dose factor VIII prophylaxis once weekly has not been practiced earlier. Once weekly therapy is likely to have better patient compliance in long run because of significant reduction in injection pricks. In a Canadian study based on tailored dose approach, the use of once weekly prophylaxis has been found with 40% of children remaining without major bleeds for a median period of four years. However, 18% required an escalation of dose.

The same investigators from JIPMER undertook a second study hoping once weekly prophylaxis would ensure better patient compliance and thus, reduce the cost of treatment as compared to twice/thrice weekly regime (making it a very valuable option in a resource poor setting like ours). Very low-dose FVIII prophylaxis in a dosage of 20 IU kg/body weight once a week (instead of 10 IU/ kg body weight twice a week in the previous study) was given to the same group of patients belonging to the previous study.

Overall bleed, joint bleed and school absenteeism were significantly less in this once weekly low dose factor group also as compared to on-demand group (and differences were statistically significant). Further, result was not inferior to the result of twice a week schedule studied earlier.

NEWER AGENTS

Advantage – longer half life

IMPACT OF LONGER ACTING FACTOR CONCENTRATES ON INDIVIDUALIZATION OF PROPHYLAXIS

In last few years, there has been tremendous progress in developing new bioengineered factor concentrates with prolonged t_{1/2}. In comparison to currently available FIX and FVIII, longer acting FIXs have shown greatly improved PKs (3- to 5.8-fold longer t_{1/2}), while longer acting FVIIIs have shown more modest t_{1/2} prolongation (1.4- to 1.7-fold longer). The lower increase in FVIII t_{1/2} prolongation when compared with FIX is related to the dependence of FVIII clearance on the clearance of VWF, which is not altered by using the longer acting FVIII concentrates in development.

POTENTIAL BENEFITS OF LONGER ACTING FACTOR CONCENTRATES

Lower infusion frequency

- Fewer patient clinic visits or home care nurse visits when commencing patients on prophylaxis, possibly leading to earlier start of prophylaxis
- Less need for central venous line leading to some cost savings and reduced morbidity
- Allows for more convenient dosing days and times (which might improve adherence)
- Less relevance of morning administration of factor
- May allow treatment on non-work or non-school days
- Increased uptake of prophylaxis among patients not currently on prophylaxis (e.g., those with moderate hemophilia) leading to better bleed protection

In March 2014, FDA approved long awaited first long-acting factor – a long-acting factor IX concentrate, i.e. recombinant factor IX Fc fusion protein, eftrenonacog (Alprolix).

LONG-ACTING CLOTTING FACTORS (TABLE 2)

Technologies used to produce longer action

Table 2: Newer Products (Normal and Long-Acting)

Name	Company	Type of product	Mean Half-life and dose frequency	Remarks
Factor IX				
Alprolix (Eftrenonacog- α)	Biogen Idec	Recombinant, FC fusion protein	Half-life 107-111 hrs, once in 7-10 days	1 st FDA approved long acting factor (March 2014), No inhibitor develops
Idelvion	CSL Behring	Recombinant, albumin fusion protein	Very long half-life - (90 hrs), once in 2-3 weeks	FDA approved (March 2016)
Factor VIII				
Advate (octocog α)	Baxalta	Recombinant	Half-life normal, three times a week	Launched in India in July 2016.
Adynovate	Baxalta	Recombinant, pegylated	Half-life 1.4 times normal, twice a week	FDA approved (Nov 2015)
Eloctate	Biogen	Recombinant, Fc fusion protein	19 hours, 20 IU/kg body weight twice a week	1 st FDA approved long acting factor VIII (June 2014), Available in India through World Federation of Hemophilia
Kovaltry	Bayer	Recombinant, 3 rd generation full length FVIII	Slightly extended, 2-3 times a week	FDA approved (March 2016)
Novoeight (Turoctocog α)	Novo Nordisk	Recombinant, 3 rd generation full length FVIII	Half life normal, 3 times a week	Launched in India in April 2016. No inhibitor develops
Nuwig (simoctocog α)	Octapharma	Human cell line recombinant FVIII	Half-life slightly prolonged (17 hours)	FDA approved

Factor IX – Normal half-life 20 hours; Factor VIII – Normal half-life 12 hours; All factors have prolonged half-life (except Advate and Novoeight)

- Pegylation
- Fc Fusion
- Albumin Fusion

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