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REVIEW ARTICLE

Low Dose Prophylaxis in Hemophilia Care

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Abstract Hemophilia is an inherited bleeding disorder which causes impaired blood clotting. The severity of disease depends on the type of Hemophilia, level of clotting factor concentrate (CFC), phenotypic heterogeneity and the development of inhibitors. The currently accepted standard of care of this disease is prophylaxis therapy (PT) with CFC. Prophylaxis therapy for Hemophilia is given in developed countries for the last few decades. On the contrary, episodic therapy (ET) is still the mode of treatment in middle and low income countries. ET is documented to have several potential risks such as increased bleeding rate, disability due to haemarthrosis, poor quality of life and increased chances of mortality. Several studies conducted in developed countries have confirmed the clinical efficacy of PT in Hemophilia treatment. Currently, there exist several challenges for implementation of this effective treatment in resource poor nations. Low dose prophylaxis (LDP) has been developed as a solution to minimize these challenges and to provide better care for subjects with Hemophilia from low resource countries. The impact of LDP was evaluated by several recent studies and the reported clinical outcomes seem to suggest an optimistic future for this line of therapy. Several themes related to Hemophilia care like inhibitor development, tolerance, pharmacokinetics of CFCs and cost–benefit analysis of different prophylaxis regimens are currently understood poorly. These distinct elements are highly relevant to assess the actual benefits of LDP regimen in a global scale.

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Introduction

Hemophilia the congenital bleeding disorder was discovered in the eleventh century by Albucasis. The word hemophilia was derived from the Greek word "*haima*" meaning "blood" and "*philia*" meaning "friendship" [1]. In the late periods of 1940s and early 1950s we can observe the modern era of hemophilia. During the same period the two types of hemophilia such as Hemophilia A and Hemophilia B (Christmas disease) were identified [2].

The mode of inheritance is X linked recessive in nature. The chronic disease is caused by deficiency or complete absence of functional plasma clotting Factor VIII (Hemophilia A) and IX (Hemophilia B) respectively [3, 4]. The deficiency arises as a result of heterogeneous mutations of the clotting factor genes [1, 5].

Mutation in the F8C gene and F9 gene causes Hemophilia A and B respectively. About one-third of the mutation spectrums are new sporadic ones [2]. Hemophilia A represents 80–85% of the total hemophilia population [3]. Males on the maternal side are generally affected with hemophilia and females are asymptomatic carriers [2, 6]. The prevalence of hemophilia is 12.8 (per 100,000 males) for high income countries and 6.6 (per 100,000 males) in the rest of the world [3].

Symptoms and Classification

The common manifestations of the disease are simple ecchymosis, sudden bleed into soft tissues, muscle, joints or insufficient clotting of injuries with bleed. Classification

of the disease severity is according to the level of clotting factor present in the blood. If the concentration of clotting factor is < 1% of normal the disease is severe and manifest as spontaneous bleed into muscles/joints. If the presence of clotting factor is 1–5% of normal, the disease is of moderate type and manifests as occasional bleed/prolonged bleed after trauma. If the clotting factor is between 5 and < 40% of normal then it is the mild form of disease and manifests as severe bleed with major trauma/surgery [3].

About half of those affected with Hemophilia A have the severe form of the disease [7]. Life threatening hemorrhages often leads to haemarthrosis, synovial hyperplasia, chronic inflammation, fibrosis, disabilities and decline in quality of life [8].

Joint bleed is the most distinctive presentation of hemophilia. More than 90% of bleeding episodes in severe Hemophilia A and B are seen in joints and 80% of these represent haemarthrosis of the major joints such as elbow, knees and ankle [9].

History and Evolution of Hemophilia Treatment

The disease was identified as a hereditary disorder by Dr. John Conrad Otto during 1774–1844. In 1939 antihemophilic factor was discovered by Kenneth Brinkhons. Till 1960s persons with hemophilia were treated with whole blood/fresh plasma transfusions. The whole blood or plasma did not have enough FVIII or FIX proteins to stop severe bleeding and eventually these patients' experienced marked morbidity and mortality associated with the disease [10].

Judith Pool in 1964 discovered fraction cryoprecipitate which has considerable amounts of FVIII, fibrinogen and vWF. It was an extensive breakthrough in hemophilia care [2, 11]. The modern management of hemophilia truly started in the 1970s. The availability of lyophilized plasma concentrates of coagulation factors led to the widespread adoption of home replacement therapy for hemophilia. This therapy significantly resulted in the premature control of hemorrhage and the curtailment of the musculoskeletal damage [12]. The accelerated development in DNA technology in the 1980s resulted in the most significant advance in hemophilia management that witnessed the cloning of FVIII (1982) and FIX genes (1984) [11]. This development lead to the large scale industrial production of recombinant FVIII initially and FIX subsequently [13]. The major milestones in hemophilia and its treatment is given in the Table 1 [1, 2, 11, 14].

Treatment Modalities for Hemophilia

Hemophilia is treated by replacing the protein that is missing in the blood [15]. The major treatment modalities for hemophilia are episodic therapy (ET) and prophylactic treatment (PT) [16]. Table 2 presents the various options under these two treatment categories [3].

Most of the countries across the globe are using episodic therapy as the first line of management for acute bleeding events [17–19]. Dosing is accepted on the basis of uncontrolled, observational studies [15, 16]. The preferred dosage range is 5–50 IU/kg until bleeding stops [20, 21]. Episodic treatment can terminate bleeding, alleviate pain and re-establish joint motion, but will not avert arthropathy [22, 23].

Evolution of Prophylaxis Therapy

The pioneer efforts of Inga Marie Nilsson in 1956 paved the way for prophylactic treatment [24]. In this treatment mode, intravenous infusion of factor concentrate is given in anticipation of and in order to prevent bleeding [25].

The dosage for prophylaxis used by various published studies shows the accepted prophylactic dosages are 15 IU/kg thrice weekly, 25 IU/kg thrice weekly, 20–30 IU/kg thrice weekly and 50 IU/kg once weekly [26–34].

The rate of occurrence of joint bleed as well as the development of severe arthropathy are less with moderate or mild hemophilia [4, 16]. This inspired the development and initiation of the foremost prophylaxis regimen in Sweden. The objective of this new mode of treatment was to minimize the number of joint bleeds from an early age. This was done by transforming the severe form of hemophilia to a milder form. This transformation was expected to alleviate musculoskeletal impairment resulting from haemophilic arthropathy [4].

Various studies that followed this initial attempt in Sweden later proved that patients on prophylactic treatment had reduced episodes of haemorrhagic events, decline in progressive joint damage, reduction in hospitalization and days lost from work/school compared to conventional episodic treatment [33].

The results of the Swedish [34, 35] and of subsequent studies [36, 37] reported the potential benefits in terms of clinical outcomes and social well being when treated under different prophylaxis regimens. The overall favorable outcomes were reduced frequency of total as well as joint bleeds, diminution in haemophilic arthropathy assessed by clinical and radiologic scores and improvement in quality of life (QOL) of patients with hemophilia. In addition, these studies also documented better results for patient joint status on early initiation of prophylaxis compared to late initiation of the same. These reports formulated the current definitions of prophylaxis [38, 39] which is directed towards preventing joint damage/disabilities, empower normal life. In haemophilic children psychosocial development is also incorporated.

Table 1 Milestones in hemophilia [1, 2, 11, 14]

Sl no.	Year	Discovery
1	1770	Described clotting process
2	1774–1844	Identified hemophilia as hereditary disorder
3	1828	Hemophilia means—love of blood
4	1886	Rare occurrence of true hemophilia in females
5	1890	Involvement of joints
6	1905	Assembled coagulation factors
7	1934	Snake venom could accelerate the clotting of haemophilic blood
8	1937	Discovered factor VIII
9	1939	Discovered anti-haemophilic factor
10	1944	Discovered factor V
11	1952	Named anti-haemophilic factor as factor VII
12	1952	Named Christmas factor or factor IX
13	1955	Factor XII
14	1956	Prophylaxis
15	1960	Factor XIII (fibrin stabilizing factor)
16	1964	Cryoprecipitate
17	1970–1979	Lyophilized factors
		Home treatment
		Pioneer prophylaxis programs Comprehensive treatment centers
18	1977	Desmopressin
19	1982	Factor IX gene (F9) cloned
20	1984	Factor VIII gene (F8) cloned
21	1987	Safe virus inactivated plasma factor
22	1989	Recombinant factor VIII
23	1994	Immune tolerance
24	1996	Recombinant factor VII a
25	1997	Recombinant factor IX
26	2000	Gene therapy trials started
27	2000–2010	B-Domain deleted factor VIII
		rFVIII free of human and animal proteins
28	2011–2021	More factor concentrate available globally
		Longer acting recombinant clotting factors (rFVIII FC, rFVIII-Peg, glycoPEGylated factor IX)
		Fusion coagulation factors (rIX-FP)
		Emicizumab
		Gene transfer

A comprehensive Cochrane review in 2005 highlighted inadequacy of randomized controlled trials (RCTs) in comparing prophylaxis treatment (PT) and on demand treatment (ODT) for haemophilic children [40, 41]. This topic was subsequently addressed by two studies done with recombinant FVIII (rFVIII) CFC.

The Joint Outcome Study (JOS) was the first published RCT differentiating the efficacy of these two treatment options. It was a multicentric, randomized, open-label trial with 65 participants in the two arms. The age limit for participating in the study was < 30 months. The participants were randomly assigned to prophylaxis (n = 32) or episodic therapy (n = 33). The primary endpoint of this study was the extend of prevention of joint damage. Joint damage were enlisted as those started prior to or at the time of the second joint bleed (between 6 and 30 months of age). The extend of joint damage was evaluated at the age of 6 years by radiography and/or by magnetic resonance imaging (MRI). For 93% of children in the prophylaxis arm and 55% that of episodic arm had normal index joint structure ($p = 0.006$). This study reported a sixfold decline in risk of joint damage in children under Prophylaxis with 25 IU/kg rFVIII on alternate days versus children under intensive episodic treatment (40 IU/kg, then 20 IU/kg at 24

Table 2 Hemophilia treatment modalities [3]

Protocol	Definition
Episodic ("on demand") treatment	Treatment given at the time of clinically evident bleeding
Continuous prophylaxis	
Primary prophylaxis	Regular continuous treatment initiated in the absence of documented osteochondral joint disease, determined by physical examination and/or imaging studies, and started before the second clinically evident large joint bleed and age 3 years
Secondary prophylaxis	Regular continuous treatment started after 2 or more bleeds into large joints and before the onset of joint disease documented by physical examination and imaging studies.
Tertiary prophylaxis	Regular continuous treatment started 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

and 72 h and alternate days till recovery). The study concluded that in young children with severe factor VIII deficiency, prophylaxis with recombinant factor VIII can reduce the occurrence of joint/any type of hemorrhage as well as the risk of joint damage considerably emphasizing the efficacy of prophylaxis treatment [28].

The second RCT was ESPRIT study (Evaluation Study on Prophylaxis: a Randomized Italian Trial). In this trial, 40 patients of age < 7 years (median 2 years) with no bleed/joint damage (negative clinical and radiologic scores) at the time of study entry were randomized to receive either 25 IU/kg rFVIII 3 times/week or Episodic therapy (25 IU/kg rFVIII until complete healing). The results of the study were significant reduction in bleeding frequency and low Pettersson scores for children under PT compared to those on episodic therapy for a long-term follow-up of 10 years [29].

The JOS and ESPRIT study results contributed essential evidence for considering PT as the treatment of choice in haemophilic children [4].

Another RCT named SPINART trial compared the standard PT and ET with rFVIII-FS in the age group 12–50 years. The dosage for the regimen was 25 IU/kg 3 times/week for PT and the same dose when needed for ET. The study concluded that adolescent children receiving rFVIII-FS prophylaxis had significantly lower total/joint bleeding episodes compared to ET [30].

The recently published POTTER trial compared long-term late secondary PT (recombinant FVIII-FS 20–30 IU/kg thrice weekly) with ET in severe hemophilia A patients in the age group of 12–55 years. The benefits reported were reduction in bleeding frequency, improvement in joint status and Health related quality of life (HRQoL) [30, 41]. Patients under PT had minimal frequent monitoring, less need for joint surgery and a better quality of life [42].

Several studies comparing PT and ET concluded as PT improved life expectancy and quality of life of patients with hemophilia A in high income countries [43–46].

The Swedish high dose approach supposed to be the most effective PT regimen recommends initiation of prophylaxis with once weekly infusion followed by twice-weekly infusions and finally to three infusions per week as full prophylaxis, based on the availability of adequate peripheral veins or on the frequency of bleeding. The dose used was 25–40 IU/kg. In the Utrecht study, Dutch intermediate and Swedish high dose prophylactic regimens for persons with severe hemophilia (factor VIII/IX < 1 IU/dL) were compared for a period of 5 years. The observational study was done by following the cohort prospectively for standardized outcome assessment. The cost of the treatment was collected retrospectively. Intermediate dose prophylaxis used less factor concentrate (2100 IU/kg/year) compared to Swedish high dose (4000 IU/kg/year). Evaluating the clinical outcome measures, bleed rate was higher and joint health was slightly lower for the intermediate dose where as social participation and quality of life were similar. The annual total cost for Swedish high dose prophylaxis was 66% higher than intermediate dose Utrecht approach and the incremental benefits were limited. The study concluded that without compromising safety many patients may get better outcomes under PT. The study also suggested prophylaxis has to be tailored individually [32].

The Canadian approach consists of once-weekly infusions at a dose of 50 IU/kg started between 1 and 2 years of age, with a clinical follow-up of every 3 months. In patients experiencing three bleeds in the same joint or four total bleeds in a period of 3 months, the prophylaxis dose recommended is an infusion of 30 IU/kg twice weekly or 25 IU/kg every other day [34].

It can be concluded that prophylactic treatment in severe hemophilia is very effective but is limited by cost issues [32].

For a child weighing 50 kg the annual cost of prophylaxis is estimated as $300,000 [45]. Currently ET is the commonly practiced treatment strategy for hemophilia in

Table 3 Change in bleed rate—episodic therapy versus prophylaxis therapy [52–54, 56–58]

Study	Bleed rate		Duration and type of bleed	*P* value
	ET	PT		
Gouider et al. [52] Tunisia	7 (0–50) median and range	0.5 (0–120 median and range)	Bleed rate per year	
Wu et al. [53] China	9.9 (mean)	1.7 (mean)	Joint bleed for 12 weeks	
Tang et al. [54] China	2.4 ± 1.9 (mean ± SD)	0.5 ± 0.8 (mean ± SD)	Joint bleed/month	< 0.01
Verma et al. [56]	0.787 ± 0.46 (mean ± SD)	0.185 ± 0.18 (mean ± SD)	Overall bleeds/patient/month	< 0.05
India	0.48 ± 0.34 (mean ± SD)	0.08 ± 0.13 (mean ± SD)	Joint bleeds/patient/month	< 0.05
Sidharthan et al. [57] India	11.27 ± 6.29 (mean ± SD)	0.91 ± 1.64 (mean ± SD)	Over all bleeds for 6 months	0.005
Eshghi et al. [58]	5.60 ± 1.83 (mean ± SD)	1.86 ± 1.52 (mean ± SD)	Mean ABR	0.000
Iran	2.04 ± 1.54 (mean ± SD)	0.88 ± 0.81 (mean ± SD)	Mean annual joint bleed rate	0.000

developing countries and PT the standard of care in developed nations. Even though PT is accepted as the standard of care, in US only 19% of children receive primary prophylaxis, and a wide variability is reported in European countries with Sweden having highest figures for prophylaxis (73%). In many countries outside Northern Europe during 1990s, primary prophylaxis was implemented in large scale. This was mainly due to the expanded availability of safer rFVIII products [47]. Latest recommendation in the treatment of hemophilia states that prophylaxis should be the standard of care for all PwH at any age and has to be continued throughout the life [48–50].

Clotting factor concentrate cost appears to be the crucial barrier in preventing the widespread use of prophylaxis. The cost for these are prohibitive in many developing countries [51, 52].

Evolution of Low Dose Prophylaxis

A single centre experience on low dose secondary/tertiary low dose PT in children (4–17 years) with Hemophilia A and B from Tunisia was the first step placed in the implementation of low dose prophylaxis. The study used a median dose of 30 IU/kg once, twice or thrice/week for Hemophilia A and 25–35 IU/kg/week for Hemophilia B. The median follow up period was 5 years. The study reported significant reduction in bleed rate after initiating prophylaxis (7 vs. 0.5), stable FISH, HJHS and satisfactory QoL during PT compared to ET period. The study concluded that low dose prophylaxis is more effective than ET and it has to be the initiating point for prophylaxis in resource limited countries [53].

A recent study from China reported that low dose secondary PT for hemophilia A with factor VIII concentrate 10 IU/kg twice weekly and for hemophilia B, factor IX concentrate 20 IU/kg/week had significantly reduced frequency of joint bleed. There was moderate improvement in joint function, attendance in school, participation in sport and daily activities. The authors concluded that Low dose secondary prophylaxis in the context of a developing country like China is cost effective [54]. Another multicentric study from China reported PT use is limited in economically constrained nations due to the ill-affordability of clotting factor concentrates [55]. All studies done on children and adults from Thailand, China and India in comparing low dose PT (5–10 IU/kg 2–3 times/week) versus episodic treatment concluded that there is an improvement in outcome measures such as bleed reduction, physical activity, independent functioning, school attendance and community participation [55, 56].

A randomized controlled trial was conducted in India on very low dose factor VIII prophylaxis (10 units/kg body weight on 2 days a week versus episodic group receiving factor concentrate in standard recommended doses) in children of 1–10 years of age with severe hemophilia A. This trial reported that there were no significant complications in PT group and the compliance was 98%. The study concluded as low-dose FVIII prophylaxis is cost effective, efficacious and a safe method of preventing joint bleeds and consequent joint damages [57].

We recently reported our clinical audit report done in eleven children with severe Hemophilia A (n = 8) and B (n = 3). These children were started with low dose prophylaxis using plasma derived CFCs for a period of 1 year. In this study, Factor VIII concentrate was given at a dose of 20–40 IU/kg in 2 divided doses/week for Hemophilia A

and Factor IX concentrate at 25–40 IU/kg/week for Hemophilia B. The study results were reduction in the bleed rate (11.27 vs. 0.91, p 0.005), reduction in hospitalization rates (12.45 vs. 2.36 days, p 0.005) and reduction in the school absenteeism (78.55 vs. 1.27 days, p 0.01) from the transition of ET to secondary/tertiary PT. The study concluded that the new regimen is feasible and promising in resource limited settings [58].

A recently published study done at Hemophilia Comprehensive Care Centre in Iran compared the efficacy of low dose escalating prophylaxis (LDEP)regimen with that of ET. Twenty-five PwH with severe hemophilia (Haem A: n = 20, Haem B: n = 5), < 15 years of age and factor level < 1% were studied for 6 months with ET and 3 years for LDEP with plasma derived CFCs. The dose escalation schedule was 25 IU/kg/week to 25 IU/kg twice a week/thrice a week for Hemophilia A. The same for Hemophilia B was 30–50 IU/kg/week to twice a week. The results obtained were significant reduction in annual total bleed/joint bleed rate, mean days of hospitalization. The researchers concluded that low dose, low frequency prophylaxis with escalating criteria according to patient phenotype is ideal for countries with CFCs use of 2.5–3 units/capita. This will result in annual joint bleed rate < 1. The yearly consumption of CFCs is comparable to ET so that there is no additional burden to PwH. In the back ground of all these benefits the new regimen is a necessity for low and middle income countries [59].

A longitudinal study named MUSFIH study was done to assess the musculoskeletal changes under episodic treatment in haemophilic children of age group 7–12 years. The study pointed that the natural course of bleeding and musculoskeletal functional decline in hemophilia are not altered by large doses of episodic treatment. Prophylaxis is the only treatment method to conserve musculoskeletal function in PwH and episodic treatment should not be the treatment option for hemophilia. The study has proved that children with ABR > 3 per year are more prone to get musculoskeletal functional decline [60].

ABR during the low dose prophylaxis regimen administered in Tunisia, China, India and Iran are given in Table 3 [53–59]. All these studies substantiated that the subsequent consequences of joint bleed and over all bleeds such as muscular deformities and skeletal dysfunctioning can be prevented/reduced by low dose prophylaxis regimen.

There are few short Indian studies related to Low dose prophylaxis in hemophilia. The objective of one study was to evaluate the efficacy of FVIIIc (Eloctate) given in a dose of 20 IU/kg/week as single infusion prophylaxis regimen for severe Hemophilia A in 34 children of age group 5–11 years. All the study participants had more than 50 exposure days during episodic therapy and were inhibitor negative. All of them were in regular physiotherapy schedule till the end of study period. The outcomes measured after 1 year were annual bleed rate, number of school days lost due to hemophilia, physiotherapy scores such as HJHS and FISH, inhibitor status. The ABR during ET with that of PT was 19 (15–32) versus 3 (3–9). The days missed were 26 (20–61) during ET and 9 (6–20) for PT. The HJHS and FISH didn't show much change. Inhibitor was nil during ET and PT. The study showed promising results in terms of ABR and days missed [61].

An open label prospective trial was done in the rural part of eastern India using historical data as control in 15 children with Hemophilia A of age < 15 years. Recombinant FVIII in the dose of 15 IU/kg/week was administered for 6 months. APTT based inhibitor screening was done at the baseline and at the end of 6 months. The mean age of the study participants was 9.47 years (range 3–15 years). The ABR during ET and PT were 23.73 versus 1.87 ($p < 0.001$). Inhibitor was absent during ET and PT period. Ped QL score and days of school absenteeism reduced markedly during PT compared to ET. CFC used on ET was 1235 IU/kg/year and that during PT was 821 IU/kg/year [62].

A prospective evaluation study regarding the effectiveness of low dose prophylaxis in minimally treated 26 children with severe hemophilia of age group 3–7 years was conducted for a period of 8 months. At the time of study entry, all the participants were inhibitor negative and their HJHS score was < 5. PT was given with plasma derived FVIII (KLOTT) in a dose of 10–15 IU/kg twice weekly. The median age was 5 years. The median of exposure to CFC during ET was 4 (range 0–314). The median annualized bleeding rate (AdBR) during ET was 3 (range 1–5) and that at PT was 0 (range 0–3). There were no target joint development, no muscle/CNS bleed during PT period. The inhibitors were absent after a median of 70 exposures (range 35–90) in all study participants [63].

A retrospective observational study was done in 8 children < 18 years with severe hemophilia A (n = 6) and B (n = 2) to evaluate the effectiveness of PT with CFCs. All were inhibitor negative during baseline. Annual hemarthrosis rate (AHR) was observed for a period of 1 year ET and 1 year PT. The CFC dose during PT was 20 IU/kg of factor VIII/IX twice a week. AHR was reduced to 87% in Hemophilia A and 85% in Hemophilia B during PT. The reduction in hemarthrosis/patient/year was 2.5–0.3 from ET to PT. There was reduction in all types of bleed as well as target joints involved [64].

All these short studies were recommending the replacement of ET with low dose PT for long term so that reduction in bleeding and improvement in musculoskeletal outcome could be achieved significantly. This in turn will improve the quality of life and social performance of

Table 4 Comprehensive view of different prophylaxis studies [28–34, 42, 53, 55–59]

Name of the study/year of publication/ sample size	Study design	Duration	Age	Factor level	Type of factor used	Dose/kg	Frequency	Outcomes comparison (ODT vs. PT)					
								ABR/JB	HJHS	FISH	SA/work (p value)	HV/ stay	QoL
Canadian study (tailored dose escalation regimen) (2006) 56	RCT (open labelled)	2 years	1–2.5 years	< 2%	Recombinant CFC	50 IU 30 IU 25 IU	1–3/weeks	NA	NA	NA	NA	NA	NA
								NA	NA	NA	NA	NA	NA
Joint outcome study (2007) 65 (32PT and 33 ODT)	RCT (open labelled, multicentric)	9 years	12 months–30 months	< 2%	Recombinant CFC	25 IU	3/weeks	ABR17.69 ± 9.25 versus 3.27 ± 6.24 JB 4.89 ± 3.57 versus 0.63 ± 1.35	NA	NA	NA	NA	NA
Esprit (2011) 45	RCT	10 years	1–7 years	< 1%	Recombinant CFC	25 IU	3/weeks	JB 0.52 versus 0.20	NA	NA	NA	NA	NA
Spinart (2013) 84	RCT (open labelled, parallel group, multinational)	1.7 years	12–50 years	< 1%	Sucrose formulated Recombinant CFC	25 IU	3/weeks	27.9 versus 0	NA	NA	NA	NA	NA
Dutch intermediate dose and Swedish Regimen (2013) 128 (78 Dutch/50 Swedish)	Multicentric, observational study	5 years	14–37 years	< 1%	Recombinant CFC	Dutch 2100 IU/ kg/year (15 IU) Swedish 4000 IU/ kg/year (25 IU)	3/weeks	ABR 1.3 versus 0	>10 points for Swedish regimen	NA	similar	NA	similar
China (2013) 66	RCT, Multicentric (15 centres)	12 weeks	< 18 years	Severe and moderate Hem A	RFVIII-FS	10 IU	2/weeks	JB 2.4 ± 1.9 versus 0.2 ± 0.5	NA	NA	NA	NA	NA
Potter (2015) 58	RCT (open labelled)	5 years	12–55 years	< 1%	Sucrose formulated Recombinant CFC	20–30 IU	3/weeks	JB 16.80 versus 1.97	NA	NA	P < 0.0001	NA	Better
Tunisia (2016) 55	Single centre observational study	1 year	< 15 years			20–30 IU	1/week	ABR 7 versus 0.5	NA	NA	NA	NA	NA

Table 4 continued

Name of the study/year of publication/sample size	Study design	Duration	Age	Factor level	Type of factor used	Dose/kg	Frequency	Outcomes comparison (ODT vs. PT)				
								ABR/JB	HJHS	FISH	SA/work (*p* value)	HV/stay	QoL
India	RCT	11.5 months	< 18 years	Severe	Plasma derived FVIII	10 IU	2/weeks	JB	NA	NA	25 versus 3	9 versus 1	NA
(1) Verma et al. (2016)								0.48 ± 0.34 versus 0.08 ± 0.13					
21	Clinical audit	1 year	5–11 years	< 1%	Plasma derived FVIII	10–20 IU	2/weeks	ABR	4.18 versus 1.18	28.82 versus 31.85	43.18 versus 1.27	11.55 versus 1.82	
(11 PT, 10 ODT)								11.27 ± 6.29 versus 0.91 ± 1.64					
(2) Sidharthan et al. (2017)													
11													
Iran (2017)	Observational study	1 year	< 15 years	< 1%	Plasma derived FVIII	25 IU	1–3/weeks	ABR	NA	NA	NA	0.64 versus 0.24	NA
25								5.60 ± 1.83 versus 1.86 ± 1.52					

PT prophylaxis therapy, *ODT* on demand therapy, *ARB* annual bleed rate, *JB* joint bleed, *HJHS* Hemophilia Joint Health Score, *FISH* Functional Independence Score in Hemophilia, *SA* school absenteeism, *HV* hospital visit, *QoL* quality of life

patients. The major findings evolved from the studies are shown in Table 3.

Areas Needing More Exploration

Inhibitor Development Tolerance

One of the major complications of hemophilia treatment is the development of inhibitors. Patient immune system, genetic factors, environmental risk factors interact together for the inhibitor development. Evidence shows that 95% of inhibitor occurrence is in the first 50 exposure days. The role of early prophylaxis and low dose prophylaxis to prevent the development of inhibitors has to be studied further in detail [59, 63, 64].

Pharmacokinetics

In patients with severe hemophilia, sustaining high factor levels for a long time is difficult because of short half-life of infused FVIII (6–25 h). When the trough level is < 1% there is more susceptibility for bleeding events. If the factor infusions are divided into 2 or 3 times/week, the trough level can be maintained. Even though all these parameters are kept under permissible values the bleeding tendency differs in the same cohort. This can be explained by the heterogeneity in pharmacokinetics. More studies are needed to explore the details like distribution of coagulation factor in human body, pathophysiology of storage of factor, utilization of factor under different situations in individuals under prophylaxis etc. [34, 65, 66].

Conclusion and Recommendations

Advancement in medicine has made hemophilia a well-defined monogenic disorder with efficacious and safe treatment. The post period of wide spread blood borne HIV transmission made a strong drive towards safe replacement therapy. We can see that studies across the world have proven the potential benefits of low dose prophylaxis regimen in persons with severe hemophilia. Even though cost of treatment during prophylaxis increases due to consumption of CFCs, it is evident that decrease in bleed rate, preventing destruction of joint and its function and improvement in quality of life can be achieved through low dose prophylaxis regimen.

Many studies have shown that the yearly consumption of CFCs during PT is comparable to ODT. It has been estimated that 70–80% of people with hemophilia across the globe and those living primarily in the developing world has inadequate or no treatment [67, 68]. This

discrepancy is due to the unavailability and/or unaffordability for factor concentrates [69, 70]. Therefore low dose prophylaxis may be considered as an initial step for prophylaxis regimen, particularly in resource limited settings.

Currently, there appears to be the need for unified national registries, multi centric randomized control trials, long term follow up of patients under prophylaxis of all age groups, studies on tolerance in inhibitor development, studies examining pharmacokinetics of factors infused and cost–benefit analysis of different prophylaxis regimens. These multi-pronged approaches are pertinent to establish the actual benefits of low dose prophylaxis regimen on a global scale.

A comprehensive view of different prophylaxis studies is shown in Table 4.

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Compliance with Ethical Standards

Conflict of interest The authors stated that they had no interest which might be perceived as posing a conflict or bias.

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