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Low Dose Prophylaxis (LDP) in Haemophilia- by Using Extended Half- Life (EHL) Factor Concentrates

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Abstract

Objective: To assess the effectiveness of low dose prophylaxis in Haemophilia, as compared to episodic treatment

Methodology: In this prospective cohort study 21 patients with severe Haemophilia A, registered with Haemophilia Treatment Centre Rawalpindi, were enrolled. According to Low Dose Prophylaxis (LDP) protocol, patients were started on a uniform dose of extended half life (EHL), recombinant, Factor VIII concentrate (Eloctate) ,250 IU, intravenous, once weekly, escalated to twice weekly if a patient experienced more than two spontaneous bleeds in three months, and thrice weekly if bleeding continued after initial dose escalation. Twenty one patients, receiving episodic treatment (treatment as per requirement of bleeding episode) were also included. Primary outcome was the total spontaneous bleeds. Secondary outcome was presence of factor VIII inhibitors. All the patients were assessed every four months for spontaneous bleeds. Inhibitors were screened in serum six monthly. Patients were followed for twenty four months and Annulized Bleeding Rate (ABR)was calculated.

Results: Eleven patients were on once weekly, nine on twice weekly and one thrice weekly infusions. Age range was two to nine years (mean 4.07 years). Low dose prophylaxis dose per Kg of body weight per week was calculated by multiplying the number of times the dose was given in a week with 250 IU and the result divided by the body weight in Kg. Mean Annualized Bleeding Rate (ABR), during study period was 0.07, which is significantly less as compared to episodic treatment group ($p < 0.001$). Development of inhibitors was not found in any patient on prophylactic treatment. In prophylactic group majority (91.66%) did not showed any bleeding episode during treatment period.

Conclusion: Low Dose prophylaxis significantly reduces Annualized bleeding Rate(ABR) and production of inhibitors, as compared to those who are on episodic treatment .

Key Words: Haemophilia, Low Dose Prophylaxis, Extended Half- Life Factor Concentrates, Inhibitors, Annualized Bleeding Rate

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Introduction

Approximately 400,000 people globally are affected by haemophilia, and only 25% receive adequate treatment.[1] The key to a successful long-term outcome in patients with haemophilia is an efficient prophylaxis that prevents bleeding in joints. Prophylactic therapy is given in developed countries from the last two decades. On the contrary, episodic therapy (ET) is still the mode of treatment in middle- and low-income countries.[2-4] In developing and underdeveloped countries the freedom to adjust the determinants of management are impaired by lack of resources and affordable products. Without prophylaxis haemophilics suffer tremendous disability, leaving them with crippling arthropathy, and unable to integrate fully to society. Many become wheel-chair bound, unable to attend school or secure gainful employment.[5]

Efficient prophylaxis requires taking into account the available resources (clotting factor concentrate type, trough levels, etc), the bleeding trigger (activity level, chronic synovitis, already existing arthropathy, etc) and most importantly the number of acceptable bleeds, especially joint bleeds. In an ideal setting the number of spontaneous bleeds should be minimized in order to prevent the manifestations of arthropathy.[6]

According to International Society of Thrombosis and Hemostasis (ICTH) definitions, primary prophylaxis begins in the absence of documented joint disease and before the second clinically evident joint bleed and before the age of three years. Secondary prophylaxis commences after two or more joint bleeds. Once joint disease appears prophylaxis needs modifications. Tertiary prophylaxis is defined as treatment initiation after the onset of joint disease at any age of patient.[6-9]

Current approaches improving prophylaxis outcomes include best use of availability of factor concentrate and

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individualization of treatment regimens with respect to dose intervals, and type of concentrate, considering trough levels and bleeding triggers. [6,10] World Federation of Haemophilia (WFH) recommends short- term intermittent prophylaxis for patients with moderate or severe haemophilia A or B and who experienced a life-threating bleed, such as intracranial haemorrhage. [11]

Lack of appropriate treatment for recurrent bleeding results in intra-articular changes that culminate in progressive joint destruction, irreversible arthropathy, chronic pain and overall deterioration of disability. Loss of opportunities, school absenteeism, frequent hospital visits, poor quality of life (QoL), stress and economic burden are other drawbacks associated with the disease.[4,11,12]

Methodology

Twenty-one patients with severe Haemophilia A, registered with Haemophilia Treatment Centre Rawalpindi, were enrolled in the study. According to Low Dose Prophylaxis (LDP) protocol, patients were started on a uniform dose of extended half life, recombinant, Factor VIII concentrate (Eloctate), 250 IU, intravenous, once weekly, escalated to twice weekly if a patient experienced more than two spontaneous bleeds in three months, and thrice weekly if bleeding continued after initial dose escalation. Eleven patients were on once weekly, nine on twice weekly and one thrice weekly infusions. Low dose prophylaxis dose per Kg of body weight per week was calculated by multiplying the number of times the dose was given in a week with 250 IU and the result divided by the body weight in Kg.

Twenty-one patients, receiving episodic treatment were also included. Inferential statistics (Mann-Whitney test) was applied to compare prophylactic group with and on-demand group. Primary outcome was the total spontaneous bleeds; Secondary outcome was presence of factor VIII inhibitors. All the children were assessed every four months for spontaneous bleeds. Inhibitors were screened in serum six monthly. Patients were followed for twenty four months and Annulized Bleeding Rate (ABR) was calculated. This study was sponsored by World Blood Diseases Registry (WBDR) grant. Factor concentrates were donated by World Federation of Haemophilia (WFH) Aid Program.

Results

Mean Annualized Bleeding Rate (ABR), during study period was 0.07, which is significantly less as compared to episodic treatment group. Development of inhibitors was not found in any patient on prophylactic treatment. Occurrence of bleeding episodes was also significantly less as compared to those who were on episodic treatment (Table I). Age range was two to nine years (mean 4.07 years). To compare inhibitors production between two groups, exact binomial test was applied, which revealed a significant difference between both groups. The incidence of inhibitor formation in the group given Factor VIII on demand is 1 out of 21, which is approximately 4.76%. In contrast, in the group given Factor VIII eight as prophylaxis, there were no reported cases of inhibitor formation. (Table II)

Table I: Low Dose Prophylaxis in Haemophilia- Treatment outcome.

Variable	Prophylactic Group (n=22)	Episodic treatment Group (n=22)	p-value
Mean Annualized Bleeding rate (ABR)	0.07	6.0	<0.001*
Inhibitor production	Nil	3.5%	
Patients without bleeding	22/24	Nil	<0.0001*

Table II: Inhibitors in low dose prophylaxis versus on demand therapy patients. (Binomial Test of Proportions)

		Category	N	Observed Prop.	Test Prop.	Exact Sig. (2-tailed)
Inhibitor	Group 1	developed	1	0.05	0.50	0.000
	Group 2	None	41	0.95		
	Total		42	1.00		
Factor 8	Group 1	On-demand	21	0.51	0.50	1.000
	Group 2	Prophylaxis	21	0.49		
	Total		42	1.00		

Discussion

Episodic treatment (ET) can terminate bleeding, alleviate pain and re-establish joint mobility, but unlikely to avert arthropathy.[13] Now, prophylactic treatment (PT) is

considered as optimal care for haemophilia patients to prevent bleeding and to preserve joint function.[5,14] For patients with haemophilia with severe phenotype (many patients with moderate haemophilia with a severe phenotype), the WFH recommends prophylactic treatment .[9]

Prophylaxis with acceptable results needs to be initiated very early (≤ 36 months).[15,16] Studies reported a significant decline in risk of joint damage in children under prophylaxis, receiving recombinant factor VIII concentrates versus children under intensive episodic treatment.[17,18] Several trials on prophylaxis have shown that it effectively prevents recurrent joint bleeding which would lead to arthropathy and disability ,compared to on-demand treatment.[2,4,10.11,13,17-25] With optimized prophylaxis the expected outcome is that children with hemophilia will reach adulthood with normal joint function and live a full and active life in the absence of bleeding events. [9,12]

Low Dose Prophylaxis (L.D.P) has been developed as a solution to minimize these challenges and to provide better care for subjects with haemophilia from low resource countries. The impact of L.D.P is evaluated in several studies. LDP regimens, in patients with severe haemophilia A, with a dose of 10 to 15 IU/kg, 1 or 2 times per week, ensure better outcomes. Studies reported acceptable results in majority (85%), even with factor levels low than 1%. Recognized benefits of lower dose infusion frequency are fewer clinic visits, less need for CAVADs, less burdensome infusion schedules (dosing, days and times), fewer infusions on work/school days and many others. This allows replacement therapy with annual consumption similar to episodic treatment but with a much lower rate of spontaneous bleeds.[3,4,9,22,26-31-34]

Studies comparing episodic with prophylactic therapy in haemophilia A revealed that approximately thirty to forty percent of patents in episodic group were hospitalized during study period, as compared to that none in prophylactic group. Studies also demonstrated a significant reduction in the total number of bleeding episodes, joint bleeds and improvement in joint function in low-dose prophylxis group, as compared to porophylactic group.[14,17,18,32]

Canadian Hemophilia Primary Prophylaxis Study (CHPS) was pioneer in tailoring prophylaxis and was able to produce adequate preservation of joint status using less factor.[35] In patients on prophylactic therapy regimens Total Gilbert Joint Scores improves better , as compared with on-demand therapy, and is likely to eliminate surgical/orthopedic intervention which may be required in long run.[9,36] Better treatment adherence is also witnessed in paediatric prophylactic groups, as parents follow regimens of children more regularly. The adults, being independent in many ways, show less adherence. [1,37-39]

In long-acting F-VIII concentrates fusion of biologically active protein, to Fc domain of human IgG, facilitates binding of the protein to the neonatal Fc receptor (Fc-Rn). This Fc-Rn is expressed in many cell types throughout life. Once the Fc-fusion protein binds to Fc-Rn , it becomes protected from lysosomal degradation .When Fc-fusion proteins and IgG are taken up from circulation into cells by endocytosis, they interact with Fc-Rn enodosomes and are redirected back to plasma . This naturally occurring recycle pathway prolongs the half lives of various biologics, including recombinant F-VIII. Similar extended half-life products are now under study with PEGylation of recombinant F-VIII.[40,41]Currently there are four main EHL Factor-VIII therapies available, which can be categorized into two main groups i.e., Fc-fusion treatments and PEGylated (conjugation of F-VIII proteins with polyethylene glycol (PEG) treatments. Ultra low F- VIII replacement therapies are also in development, but their impact on the treatment landscape remain to be seen.[40-44]

A wide variability is reported even in developed world for the availability of primary PT. Clotting factor concentrates cost appears to be the crucial barrier in this regard. Even in United States of America approximately 19% of children receive primary prophylaxis and a wide variability is reported.[3,45]

It is required to explore pharmacokinetics and acceptable trough levels, as studies reveal adequate bleeding control even at a low level.[38-40,46] Using longer-acting coagulation factors with different pharmacokinetic profiles is likely to further individualize treatment by maintaining adequate trough levels with fewer infusions.[6] Genotypically different mutations ,most importantly F8/F9 gene mutations , splice site mutations and some small deletions, can be held responsible for a disease phenotype, with reduced frequency of spontaneous bleeds. Analysis revealed that specific cohort of patients

can have a non-bleeding status even with low factor level. [5,6,31.40]

In present study none of the patients developed inhibitors against F-VIII. Most of the studies substantiate this finding. [24,47] Evidence shows that 95% of inhibitor occurrence is in the first fifty exposure days. Limited factor exposure in prophylactic regimens can be assumed as a factor for low inhibitor occurrence in haemophlics on prophylactic regimens. [6,9,22,24,40]

It is widely accepted that keeping trough levels about 1% should be a minimum, as few joint bleeds occur about this level. The mean F-VIII used during prophylaxis is found to be lower as compared to the on-demand arm, though not significant statistically. But, it translates into overall reduction in cost of therapy in long run. [5,40,48]

Individual dosing based on differences in pharmacokinetic handling of coagulation factors has the potential to optimize clinical efficacy of these expensive therapies. Time spent in a therapeutic window or a 'normal' and safe zone between trough and peak thresholds, are now regarded as important concepts to define effective prophylactic regimens for individual patients.[12,30] PK parameter such as incremental recovery area under the concentration – time cure (AVC) , clearance (CL) and subsequently t- ½ are now considered surrogate efficacy endpoints for F-VIII replacement therapies.[12] There is a significant variation between patient's coagulation factor pharmacokinetics.. Wide inter-patient variability in PK, lifestyle and physical activity levels, the ability to adjust F-VIII levels and to provide appropriate bleeding protection to suit a given situation may be crucial factor in the treatment decision – making process.[37,46]

Conclusion

1. Low dose prophylaxis, in haemophilia, is cost-effective, efficient and safe method for preventing joint bleeds and hence delaying joint damage.
2. Adherence to treatment recommendations and follow up is an ongoing challenge, common to long term medical conditions, like haemophilia.
3. Long acting recombinant Factor VIII concentrates (with extended half-life). It makes possible prophylaxis-adherence an achievable goal, even in financially-constraint set up.
4. Prophylactic regimens can achieve a non-bleeding status even with low trough levels of factors
5. Particular attention is required to tailor individual treatment regimens in accordance to pharmacokinetics of factor, preferred life style and daily physical activities, including sports
6. Central to the success of prophylaxis are clinics with comprehensive care that provide the necessary professional expertise, support and counselling, to educate patients, families and other health care professionals, and to support research for improved haemophilia care.

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