

IMPACT OF LOW DOSE PROPHYLAXIS ON HEALTH RELATED QUALITY OF LIFE IN CHILDREN WITH HEMOPHILIA AT A TERTIARY CARE CENTRE IN SOUTH INDIA

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Abstract

Background: This study aimed to assess the impact of low dose standard half-life clotting factor concentrate (CFC) prophylaxis on health related quality of life (HRQoL) in children with severe hemophilia A and B. It evaluated changes in functional independence, joint health, and overall quality of life before and after initiating prophylaxis. **Materials and Methods:** This prospective observational study was conducted with seven children (ages 8 to 14) with severe hemophilia A or B receiving low dose CFC prophylaxis at the Integrated Centre for Hemophilia and Hemoglobinopathies at Kanyakumari Government Medical College. Children were administered standard half-life CFC twice weekly for hemophilia A and once weekly for hemophilia B. HRQoL was assessed using the Functional Independence Score in Hemophilia (FISH), Pediatric Hemophilia Activities List (PAED HAL), and Hemophilia Joint Health Score (HJHS) 2.1 before and six months after prophylaxis. Parental questionnaire was used to assess perceived changes in fear of injuries, school performance, and participation in outdoor activities. **Result:** The study showed significant improvements in both HJHS (Reduction from 5.42 ± 2.92 to 2.28 ± 1.74) and FISH scores (Increase from 23.28 ± 7.28 to 30.42 ± 1.84). In the PAED HAL domains, activities in all domains showed improvement with statistically significant improvement observed in arm function. Parental reports revealed significant reductions in fear of injuries, improved outdoor activity and better school performance after six months of prophylaxis. **Conclusion:** Low-dose CFC prophylaxis significantly improves joint health, functional independence, and HRQoL in children with hemophilia. These findings suggest that low-dose prophylaxis should be implemented in resource-constrained settings to enhance patient outcomes.

INTRODUCTION

Individuals living with hemophilia tend to have quality-of-life (QoL) issues that affect their physical, psychological, social, and economic well-being. Some individuals limit activities due to the potential risk of a bleeding incident, whereas others are limited in terms of mobility and functional status due to permanent and painful joint damage. Disease severity has also been shown to impact QoL among individuals with hemophilia A and B, where individuals with severe hemophilia report poorer

QoL than those with mild-moderate hemophilia. Clotting Factor Concentrate replacement therapy is the mainstay of hemophilia treatment. For patients with severe phenotype hemophilia A or B in countries with healthcare constraints, the World Federation of Hemophilia (WFH) strongly recommends prophylaxis (even when the only option is using lower factor doses) over episodic factor therapy to reduce hemarthroses and other spontaneous and breakthrough bleeding and better preserve joint function.^[1]

For those countries with healthcare constraints where prophylaxis may potentially be instituted gradually, it is most essential to initiate prophylaxis in young children since prevention of target joint development may offer marked long-term joint health benefits. This prospective observational study aimed to assess the impact of low-dose standard half-life clotting factor concentrate (CFC) prophylaxis on health-related quality of life (HRQoL) in children with severe hemophilia A and B.

MATERIALS AND METHODS

Seven children with severe hemophilia A and B without inhibitors receiving hemophilia prophylaxis at the Integrated Center for Hemophilia and Hemoglobinopathies (ICHH) functioning at Kanyakumari Government Medical College were included in the study. The criteria for initiation of prophylaxis included severe hemophilia and negative inhibitor status at initiation of prophylaxis. Children less than 18 years of age with severe Hemophilia A and Hemophilia B receiving low dose standard half-life prophylaxis with a minimum compliance of 80% with negative inhibitor status were included in the study. Exclusion criteria included children with less than 80% compliance and positive inhibitor status. Low dose factor prophylaxis was provided with standard half-life clotting factor concentrate at the dose of 10 to 20 IU per Kg twice weekly for Hemophilia A and 20 to 40 units/Kg once weekly for Hemophilia B. Children were initiated on a fixed dose of 250 IU for children weighing less than 25 Kgs and 500 IU Factor VIII for children with weight between 26 to 50 Kg twice weekly (Wednesday and Saturday) for hemophilia A and 500 IU Factor IX once a week (every Saturday) for hemophilia B children weighing less than 50 kg. Recombinant factor VIII in hemophilia A children and plasma derived factor IX in hemophilia B children was used. In view of frequent spontaneous bleedings, dose was escalated from 250 IU to 500 IU for one child after 21 weeks of prophylaxis.

After obtaining informed consent, data were collected from the parents using a predesigned questionnaire. The data collected included demographic details, clinical details and details regarding fear of physical injuries, outdoor activities, school performance, perception of usefulness of treatment. Joint health of the children with hemophilia was assessed using Hemophilia Joint Health Score 2.1 (HJHS 2.1) before and six months after initiation of prophylaxis. Health related Quality of Life of the seven children were assessed using Functional Independence Score in hemophilia (FISH), Paediatric Hemophilia Activities list Questionnaire (PAED HAL) before initiating prophylaxis and after 6 months of prophylaxis.

FISH score (Functional Independence Score in Hemophilia) includes the assessment of eight activities: eating, grooming, dressing, chair transfer,

squatting, walking, step climbing and running. Each activity is graded from 1 to 4 according to the amount of assistance required to perform the activity. The maximum possible score is 32.

Paediatric Hemophilia Activities list childrens / teenagers version (V0.11) is an activities questionnaire for children and teenagers aged 8 to 17 with hemophilia. It consists of 53 items across 7 domains – sitting/standing/kneeling, function of legs, function of arms, use of transportation, self care, household task, leisure activities and sports. This list describes a number of activities that can cause problems for children and teenagers with haemophilia. Children were asked to answer the questions according to their experiences. For each of the activities, they were asked to indicate whether they had problems with the activity in the past month as a result of hemophilia. This questionnaire takes about 10 minutes to complete

HJHS 2.1 (Hemophilia Joint Health Score 2.1)—includes assessment of eight joint parameters (joint swelling, duration of swelling, muscle atrophy, crepitus on motion, flexion loss, extension loss, joint pain and strength) of six joints (bilateral knee, ankle and elbow joints). It is sensitive enough to pick up the subtle early signs of joint damage. The individual joint score ranges from 0 to 20. Global gait was assessed separately for a score of 0–4. Total joint scores for all six joints and global gait score were then combined for a total score ranging from 0 to 124. A higher score indicates worse joint health.

RESULTS

Average FISH score before starting prophylaxis 23.28 ± 7.28 improved to 30.42 ± 1.84 after prophylaxis. This improvement was statistically significant (P value < 0.05). [Table 2] Average HJHS score 5.42 ± 2.92 before prophylaxis significantly reduced to 2.28 ± 1.74 ; two of the children had joint score of 0 at the end of six months with complete resolution of arthropathy as shown in [Table 2].

Average PAED HAL score before and after hemophilia prophylaxis in various domains are shown in [Table 3]. The activities in all the seven domains showed improvement with maximum effect in self care and leisure/sports activities. However, of the seven domains, only improvement in the function of the arms was statistically significant (P value < 0.05).

Parents were asked to score the fear of physical injuries, involvement in outdoor activities and school performance in a Likert scale from 1 to 5. A significant reduction in the scores were observed after 6 months of prophylaxis [Table 4]. All the 7 children reported increased outdoor activities after prophylaxis. 5 out of 7 children (71.43%) reported improvement in school performance after prophylaxis. And all the parents felt that prophylaxis was beneficial to their children.

Table 1: Demographic characteristics and prophylaxis details.

Case number	Hemophilia Type	Age (In Years)	Sex	Type of prophylaxis	Indication for initiation of prophylaxis
1	A	8	Male	Secondary Prophylaxis	Recurrent Joint Bleeding
2	A	8	Male	Secondary Prophylaxis	Recurrent Joint Bleeding
3	A	10	Male	Secondary Prophylaxis	Recurrent Joint Bleeding
4	A	13	Male	Secondary Prophylaxis	Recurrent Joint Bleeding
5	B	14	Male	Secondary Prophylaxis	Recurrent Joint Bleeding
6	B	12	Male	Secondary Prophylaxis	Recurrent Joint Bleeding
7	B	9	Male	Secondary Prophylaxis	Recurrent Joint Bleeding

Table 2: FISH score and HJHS 2.1 (Before and after prophylaxis)

Case number	FISH SCORE		HJHS	
	Before prophylaxis	After prophylaxis	Before prophylaxis	After prophylaxis
1	10	28	7	3
2	16	29	2	0
3	31	32	10	5
4	22	32	8	4
5	27	32	6	2
6	31	32	2	0
7	26	28	3	2
Mean	23.28	30.42	5.42	2.28
SD	7.28	1.84	2.92	1.74
P Value (Paired t test)	0.0298 (<0.05)		0.0013 (<0.05)	

Table 3: Scores in PED – HAL domains (Before and after prophylaxis)

Case Number	SIT/ KNEEL/ STAND		LEG		ARM		TRAN SPORT		SELF CARE		HOUSE HOLD TASK		LEISURE ACTIVITIE S/ SPORTS	
	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After
1	19	47	24	46	18	31	4	8	22	53	3	14	4	9
2	36	45	34	51	23	31	3	5	27	45	8	10	38	55
3	54	59	61	64	34	36	12	12	53	54	17	18	5	5
4	33	39	36	34	18	25	12	16	41	46	3	14	10	30
5	48	48	66	66	25	30	18	18	36	39	12	10	34	31
6	50	55	54	58	35	36	17	18	52	54	10	12	46	55
7	51	53	60	64	36	36	18	18	53	53	10	12	50	54
Mean	41.57	49.42	47.85	54.71	27	32.14	12	13.57	40.57	49.14	9	12.85	26.71	34.14
SD	11.7	6.23	15	10	7.32	3.83	5.87	4.952	11.8	5.43	4.59	2.58	18.36	19.9
P Value (Paired t test)	0.0676 (>0.05)		0.0912 (>0.05)		0.0253 (<0.05)		0.0616 (>0.05)		0.0958 (>0.05)		0.0913 (>0.05)		0.0601 (>0.05)	

Table 4: Parental Questionnaire (Before and after prophylaxis)

Case Number	FEAR OF PHYSICAL INJURIES		OUTDOOR ACTIVITIES		SCHOOL PERFORMANCE	
	Before Prophylaxis	After Prophylaxis	Before Prophylaxis	After Prophylaxis	Before Prophylaxis	After Prophylaxis
1	5	5	1	3	2	4
2	5	5	3	4	3	4
3	5	5	1	3	3	3
4	4	4	2	3	1	2
5	4	4	3	4	2	2
6	3	3	2	3	2	3
7	5	5	2	3	2	4
Mean	4.43	4.43	2.00	3.29	2.14	3.14
SD	0.79	0.79	0.82	0.49	0.69	0.90
P Value (Paired t test)	0.0029 (<0.05)		0.0004 (<0.05)		0.0378 (<0.05)	

DISCUSSION

For over two decades, prophylaxis has been the standard of care in most well-resourced countries but was seldom undertaken in resource-constrained countries as it was deemed to not be affordable at the

doses conventionally used. In the early 2000s, several observational studies demonstrated the benefits of low-dose factor prophylaxis over episodic factor replacement therapy, without a dramatic increase in cost. This shift in perspective resulted in low dose factor prophylaxis being increasingly recognized as

the preferred way of managing patients in resource constrained countries.^[2]

In this study, we assessed the impact of Low dose clotting factor prophylaxis on HRQoL in children with hemophilia six months after starting prophylaxis. A statistically significant improvement was observed in joint health, with the Hemophilia Joint Health Score (HJHS) and FISH scores both improving. Furthermore, the PED HAL score, which measures HRQoL across various domains, showed improvement in all areas, particularly in arm function, which was statistically significant. Notable reductions in fear of physical activity, enhanced school performance, and greater participation in outdoor activities were also reported. These findings align with previous research, which highlights the positive effects of prophylaxis on joint health and overall well-being.

In line with the validation of the HJHS by Feldman et al., our study demonstrated the effectiveness of HJHS in assessing joint health, especially in children receiving prophylactic treatment.^[3] Similar improvement in HJHS were observed by J A Aznar et al study in their study.^[4] Positive effect of FVIII prophylaxis on patient-reported measures of pain over time was observed in patients with severe hemophilia A by Pasi et al (2022).^[5]

The improvement in joint health and HRQoL with low-dose prophylaxis observed in our study mirrors findings from studies in Tunisia, Pakistan, and India. For instance, Gouider et al. reported similar improvements in HJHS, FISH, and HRQoL among Tunisian children,^[6] while a cohort study in Pakistan demonstrated superior outcomes in the low-dose prophylaxis group in terms of annual bleeding rates and joint bleeding compared to on-demand treatment.^[7] In India, personalized low-dose prophylaxis resulted in significant reductions in annual bleeding rates and improvements in joint health, as evidenced by changes in HJHS and FISH scores.^[8]

Our findings also support the results of Alvarez et al., who demonstrated that recombinant factor VIII/IX prophylaxis reduced annual bleeding rates and improved HRQoL across several domains, particularly in sports and leisure activities.^[9] The significant improvement in the sports and leisure domain in our study further emphasizes the importance of prophylaxis in enhancing the quality of life. The self-care domain also showed meaningful improvement, as assessed through the PED HAL scoring system, which corroborates findings from previous studies.^[6-9]

In contrast, the study by Gomber et al. at New Delhi,^[10] comparing twice-weekly versus thrice-weekly low-dose factor VIII prophylaxis in hemophilia A children found no significant differences in bleeding rates or clinical scores between the two regimens. Our study, which included twice-weekly prophylaxis for hemophilia A and once-weekly for hemophilia B children, produced similar results, reinforcing the idea that low-dose

prophylaxis, regardless of frequency, offers considerable benefits in terms of bleeding control and joint health.

Finally, while this study focused on children with hemophilia without inhibitors at the start of prophylaxis, research by Oldenburg et al. highlights the benefit of Emicizumab prophylaxis in individuals with hemophilia A and inhibitors, which was associated with a significantly lower rate of bleeding events compared to no prophylaxis.^[11] This underscores the importance of personalized treatment approaches for hemophilia patients, tailored to their specific needs and circumstances.

CONCLUSION

This study shows positive impact of prophylaxis with low dose standard half-life clotting factor concentrate on quality of life in children with hemophilia. An improved outcome with hemophilia prophylaxis in terms of annual bleeding rate, joint health and independent functioning was observed. In conclusion, this study along with evidence from other studies, supports the use of low-dose prophylaxis as an effective strategy for improving joint health and HRQoL in children with hemophilia, particularly in limited resource countries.

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