Research Article

Comparison of effect of Prophylaxis Therapy and On Demand Therapy on Joint Bleeding Episodes in Children With Hemophilia in Moewardi Hospital, Surakarta

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ABSTRACT

Background: Factor replacement therapy is the primary treatment in children with hemophilia. Factor replacement is classified into two categories, prophylactic treatment and on-demand treatment. The administration of these two therapies may vary in any hemophilia center based on the availability and stakeholder policies.

Aim: This study compares characteristics and analyses groups of children with hemophilia treated prophylactically and those who received on-demand therapy.

Methods: All children with hemophilia registered in Dr. Moewardi Hospital were included in this study. All subjects were provided information about prophylaxis treatment. The prophylactic group received a factor replacement therapy of 10-15 IU/kg/time; for patients with hemophilia A given three times a week and patients with hemophilia B given twice a week. The number of bleeding events and joint bleeding in 6 months was recorded. In addition, inhibitor testing was carried out in both groups. Subjects were observed for six months.

Results: In this study, it was noted that there were significant differences between the prophylactic group and the on-demand treatment group in terms of the number of joints affected and the frequency of bleeding. In the prophylactic group, the tendency for the number of joints to be involved was found in 2 locations, whereas those who did not receive prophylaxis had one joint involvement, with $p = 0.022$ ($p < 0.05$). The prophylactic group's frequency averaged 16.00 +6.20 per year, while those who did not receive prophylaxis averaged a bleeding frequency of 24.28 +10.57 with $p = 0.048$ ($p < 0.05$). There was no significant correlation between the frequency of bleeding with the subject's BMI ($p = 0.195$) and the severity of hemophilia ($p = 0.823$). This study also found a correlation between the number of affected joints with age, where the younger the age, the more joints' location were affected with $p = 0.042$ ($p < 0.05$).

Conclusion: Prophylactic therapy was effective in reducing joint bleeding episodes and bleeding frequency in children with hemophilia.

Keywords: Children, hemophilia, prophylaxis vs. on-demand treatment

INTRODUCTION

Hemophilia is an X-linked coagulation disorder due to inadequacy of coagulation factor VIII (hemophilia A) or factor IX (hemophilia B). It should be speculated that hemophilia in youngsters with a background marked by simple wounding in youth, unconstrained dying (seeping without an obvious reason), particularly in joints, muscles, and delicate tissues. The order of hemophilia depends on the fair and square of figure VIII or IX plasma. The rate of seeping in hemophilia patients differs relying upon the area of the dying. When joint bleeding reaches 70-80% frequency, muscle region goes from 10-20%, and other significant bleeding reaches 5-10%. Intracranial bleeding can happen in hemophilia patients in fewer than 5% of the occurrence.[1–3]

WFH prescribes prophylactic treatment in hemophilia patients to forestall joint harm or repetitive bleeding occasions. The prophylactic measurements of hemophilia patients in a few examinations shift even inside one country; thus, the ideal portion of preventive treatment has not been settled globally. Not all youngsters with hemophilia receive prophylactic treatment because of different components, including the accessibility of restricted and brought together coagulating factors, the significant expense of thickening elements so as it will be hard for agricultural nations to provide coagulating factors from makers, to the trouble of wellbeing admittance that children with hemophilia can reach. The rules for prophylactic treatment are isolated into three; primary,

secondary, and tertiary prophylaxis. Primary prophylaxis can generally be applied in developing nations due to the guardians' readiness; thus, youngsters with hemophilia can be treated from the beginning. In developing nations, tertiary prophylactic treatment is, for the most part, applied to hemophilia patients. The association of musculoskeletal problems can be seen toward the start of treatment. It is believed that prophylaxis can decrease bleeding rates or injury to joints and muscles to advance children's personal satisfaction.[1,4–6]

METHODS

A prospective cohort study was conducted in a pediatric facility of Dr. Moewardi Hospital, Surakarta, between February 2019 and December 2019. The cases were collected from all subjects with hemophilia less than 18 years of ages who were followed up regularly in the pediatric center. All pediatric patients with hemophilia were included in this study. Subjects who received prophylactic treatment were gathered into one group and compared with the group who received on-demand treatment. The inclusion criteria for the prophylactic group were ready to be administered low-dose prophylactic injection (10-15 IU/kg/times) three times a week for hemophilia A and two times a week for hemophilia B. The two groups were then monitored for a half year and investigated depending on the frequency of joint bleeding episodes, the utilization of blood coagulating factors, and the degree of joint bleeding during the half-year. If the prophylactic group has bleeding under monitoring, the prophylactic administration is temporarily stopped and resumed two weeks after the bleeding is controlled. The level of joint bleeding was assessed utilizing the HEAD-US score, which a board-certified musculoskeletal radiologist scored. The ethical approval was acquired from the ethics committee of the Faculty of Medicine of Sebelas Maret University and Dr. Moewardi Hospital, Surakarta, Indonesia. Authorization to gather information was allowed from clinic specialists.

The research data obtained will be analysed and presented in narratives, tables, and graphs. SPSS-based statistical software (version 22) was used for data analysis. Age, age at first diagnosis, joint bleeding incidence were presented as mean, median, standard deviation, minimum and maximum values, and percentages. Consumption of factor VIII is described as mean ± standard deviation (SD). Mann-Whitney test was performed on statistical analyses of baseline data (age, age at first diagnosis, age at first FVIII exposure, duration of diagnosis to initiate routine prophylactic treatment, first-time treatment, and FVIII consumption). The analysis was carried out on two variables, which were assumed to be related. Hypothesis testing uses the Pearson test when the data distribution was normal; meanwhile, the Spearman test was applied when the data distribution was abnormal. The difference was considered statistically significant when $P < .05$.

RESULTS

This study was conducted on 45 pediatric patients aged 1-18 diagnosed with hemophilia at Dr. Moewardi Hospital, Surakarta. In this study, joint ultrasound examinations were performed to assess joint abnormalities in subjects at the start of the course. Examination results that supported the presence of hemophilia arthropathy were noted. The patient underwent a low dose of protocol-based prophylactic therapy. When the patient arrived at the clinic, the patient delivered weekly monitoring containing complaints on arrival and the number of factors administered that day. We compared the results of joint ultrasound at the start and at the end of the study to see the progression of hemophilic arthropathy. The results of the characteristics of the research subjects were as follows.

Table 2 explains that patients with a lower BMI with an average bleeding frequency of 21.53 +8.85 times, patients with a normal BMI with an average bleeding frequency of 24.93 +11.70 times, and patients with an excess BMI with an average bleeding frequency of 48.00 + - times, thus there is a tendency that the higher the BMI score, the more frequent the bleeding is. The p-value = 0.195 ($p > 0.05$), which means no significant correlation between BMI and bleeding frequency. Patients with a mild degree of hemophilia have an average bleeding frequency of 22.86 +5.64 times, patients with moderate degrees of hemophilia have an average bleeding frequency of 23.19 +11.46 times, and patients with a mean degree of hemophilia have an average bleeding frequency of 24.00 + 0.00 times; thus there is a tendency that the heavier the degree of hemophilia, the greater the frequency of bleeding. The p-value = 0.823 ($p > 0.05$) means no significant correlation between the degree of hemophilia and the frequency of bleeding.

Table 1. The baseline characteristics of the study subjects

Variable	Prophylaxis		Total (n=45)	p-value
	Yes (n=6)	No (n=39)		
Age[1]	10.83 ±4.07	10.05 ±4.77	10.16 ±4.65	0.706
Age at diagnosis[2]				0.482
< 3 years old	4 (66.7%)	20 (51.3%)	20 (51.3%)	
> 3 years old	2 (33.3%)	19 (48.7%)	19 (48.7%)	
First bleeding episode[2]				0.642
< 3 years old	5 (83.3%)	35 (89.7%)	40 (88.9%)	
> 3 years old	1 (16.7%)	4 (10.3%)	5 (11.1%)	
BMI[3]				0.986
Below normal	4 (66.7%)	26 (66.7%)	30 (66.7%)	
Average	2 (33.3%)	12 (30.8%)	14 (31.1%)	
Overweight / Obese	0 (0.0%)	1 (2.6%)	1 (2.2%)	
Type of hemophilia[2]				0.286
A	4 (66.7%)	33 (84.6%)	37 (82.2%)	
B	2 (33.3%)	6 (15.4%)	8 (17.8%)	
The severity of hemophilia [3]				0.103
Mild	0 (0.0%)	7 (17.9%)	7 (15.6%)	
Moderate	5 (83.3%)	31 (79.5%)	36 (80.0%)	
Severe	1 (16.7%)	1 (2.6%)	2 (4.4%)	
Clotting factor consumption within six months (IU)	18333.3 ±3881.6	24782.1 ±18518.4	23922.2 ±17401.0	0.776

Note: [1]Independent t-test (Numeric data is normally distributed); [2]Chi-Square test (Nominal data); [3]Mann-Whitney test (Ordinal data or numerical data not normally distributed) [3]

Table 2. Correlation between BMI and the severity of hemophilia with bleeding frequency

Variable	n	Bleeding frequency	p-value
BMI			0,195
Below normal	30	21.53 +8.85	
Average	14	24.93 +11.70	
Overweight / Obese	1	48.00 + -	
The severity of hemophilia			0,823
Mild	7	22.86 +5,64	
Moderate	36	23.19 +11,46	
Severe	2	24.00 +0,00	

Note: Spearman Rank (numeric ordinal data)

Table 3. Correlation between age and the number of affected joints

Affected joints	n	Age	p-value
None	2	1 + 0,00	0,042
One area	23	12.61 +3.86	
Two areas	19	8.47 +3.53	
Three areas	-	-	
Four areas	1	4.00 + -	

Note: Spearman Rank correlation (numeric ordinal data)

Table 3 explains that patients with no joints were affected with a mean age of 1 + 0.00 years, patients affected by 1 location with a mean age of 12.61 +3.86 years, and patients with two joint sites. With a mean age of 8.47 +3.53 years and one patient with four affected joint locations with a mean age of 4 years, there is a tendency that the older the age, the more joint areas are affected. The p-value = 0.042 (p <0.05), indicating a significant correlation between age and joint profile.

Table 4. Effect of prophylactic therapy on bleeding frequency, joint profile, and cost of therapy

Variable	Prophylaxis		p-value
	Yes (n=6)	No (n=39)	
Bleeding frequency	16.00 +6.20	24.28 +10.57	0,048*
Affected joint			0,022*
None	0 (0.0%)	2 (5.1%)	
One area	1 (16.7%)	22 (56.4%)	
Two areas	4 (66.7%)	15 (38.5%)	
Three areas	0 (0.0%)	0 (0.0%)	
Four areas	1 (16.7%)	0 (0.0%)	
Cost of therapy within six months (million Rupiahs)	81.79 +19.97	107.30 +68.25	0,763

Note: Mann-Whitney test (ordinal data or numerical with abnormal distribution data)

Based on table 4.4, it is identified that the frequency of bleeding in the prophylactic group averaged 16.00 +6.20 times per year while those who were not prophylactic had an average bleeding frequency of 24.28 +10.57 times per year with a value of p = 0.048 (p <0.05), which means that there is a significant difference between prophylaxis and the amount of bleeding. Therefore the hypothesis, which states, "The administration of low doses of prophylactic therapy can reduce the incidence of bleeding and joint bleeding in hemophilia patients," is proven

DISCUSSION

This study was conducted on 45 pediatric patients who checked up routinely as patients at the pediatric outpatient clinic Dr. Moewardi Hospital, with a hemophilia diagnosis, both A and B. This study shows that low-dose prophylaxis with blood clotting factor replacement effectively reduced the number of affected joints and non-joint bleeding in children with severe hemophilia.

Previous studies in individuals with hemophilia concluded that repeated bleeding in the joints resulted in arthropathy, which would damage the surrounding tissue with clinical manifestations of pain experienced by the patient. Recent studies, including in vitro studies and animal studies, have provided findings of arthropathy's complexity in hemophilia patients. Although the exact mechanism of hemophilic arthropathy has not been fully elucidated, it has been suggested that iron resulting from the breakdown of hemoglobin released from erythrocytes after repeated bleeding in the joints resulting in inflammatory synovitis leading to cartilage damage and bone destruction. Many inflammatory mediators are involved in this process, and angiogenesis, induced by growth factors such as vascular endothelial growth factor (VEGF), is a characteristic sign of synovitis and joint damage at the cellular level. Evidence from in vitro studies shows that joint cartilage in children may be more prone to damage than adult joint cartilage.[5–7]

Previous studies on low-dose prophylaxis have been carried out in developing countries due to limited or difficult access to factor replacement drugs. Thailand started a prophylactic program on six hemophilia A children aged 11 to 16 years with clotting factor levels between 1 and 3.5% with the administration of 8-10 IU / kg BW at a frequency of 2 times a week for one year, and bleeding and absences were found. In a Canadian study of children with hemophilia, prophylactic therapy was modified according to individual needs. This study was started in children under three years of age (primary prophylaxis) and was monitored if the child had joint bleeding; the prophylactic dose would be increased as needed. This study used three doses of prophylaxis in stages. The first stage used a dose of 50 IU/kg administered once per week. The second stage used a dose of 30

IU/kg twice a week. The third stage used a dose of 25 IU/kg administered every other day. The criteria for increasing the doses were observed should joint bleeding occurred more than three times in 3 months with fixed prophylactic doses. In the existing policy system, provision of clotting factor replacement therapy, both prophylactic and on-demand, must be carried out in Dr. Moewardi Hospital. The condition of the house distance was the most significant inhibiting factor.[8–14]

MRI is the standard modality for evaluating hemophilic arthropathy; however, it is expensive, requires sedation in children, and is not widely available. Joint ultrasound is an alternative to MRI modalities where ultrasound is cheaper, faster, and does not require sedation in pediatric patients. Joint ultrasonography has a sensitivity and specificity of nearly 100% for the diagnosis of hemophilic arthropathy events. Meta-analysis and systematic reviews also support that joint ultrasound is a more affordable modality compared to MRI. A joint radiologist performed the joint ultrasound examination in this study. The level of accuracy of the analysis will increase according to the experience of the examiner. Therefore, it is recommended that joint ultrasound operators have received further training or education; thus, the sensitivity and specificity will increase. The HEAD-US assessment differs from other scoring systems due to the additional synovial hypertrophy score, which results in changes in cartilage and bone structure. The advantage is that it can observe the condition of 6 joints at once, namely the elbows, heels, and knees. The higher the score, the more severe the structural deformity is. None of the patients in this study had a score of 0 because all patients in this study did not receive prophylactic therapy under the previous three years of age. This study only focused on the joints that the child most complained about.[15,16]

In this study, no correlation between the BMI of children and frequent bleeding events was found. In other studies, few have compared BMI to the frequency with which bleeding occurs. Difficult access to clotting factors is a significant obstacle in pediatric hemophilia patients in developing countries. Therefore, policymakers' regulation is the optimal approach so that all hemophilia patients can be treated with the appropriate clotting factors.[17–21]

Several limitations of this study include the small number of subjects receiving prophylactic therapy due to various factors such as; not all parents can escort their children to take prophylactic injections because prophylactic treatment must be done in Dr. Moewardi Hospital. Afterward, ultrasound assessment can only be performed on one of the more massive joints; thus, the other joints' condition cannot be monitored. In addition, the joint ultrasound specialist operator is only one person; therefore, the patient has to wait about 3 to 4 weeks from the joint ultrasound's initial schedule.

CONCLUSION

Prophylactic therapy can reduce the frequency of recurrent bleeding in patients with hemophilia. Joint ultrasonography is a modality that can be used to monitor the progression of hemophilic arthropathy. However, if there has been a severe degree of hemophilic arthropathy, six months of monitoring has not been able to describe a significant difference. From this conclusion, suggestions are proposed: It is necessary to socialize children with hemophilia for prophylactic therapy as early as possible. It is essential to monitor regularly, especially for joint ultrasonography in hemophiliacs in which hemophilia arthropathy has not yet occurred clinically. Finally, there needs to be an approach to policymakers; thus, the family can handle that factor replacement drugs, and they do not have to come to the hospital to receive prophylactic therapy.

CONFLICTS OF INTEREST

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