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Original Article

The prevalence of factor VIII inhibitor in patients with severe hemophilia-A and its clinical characteristics

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ABSTRACT

Background Hemophilia is a hereditary blood-clotting disorder due to factor VIII deficiency. Up to this date, the administration of factor VIII in preventing and managing bleeding has been the main treatment. One of the complications, which may occur due to repeated administrations of factor VIII, is the formation of factor VIII antibody (factor VIII inhibitor).

Objective To find out the prevalence of severe hemophilia-A with factor VIII inhibitor and its clinical characteristics.

Methods A cross-sectional descriptive study was performed on children with severe hemophilia-A at the National Hemophilia Care Centre, Cipto Mangunkusumo Hospital, Jakarta, Indonesia, in June-August 2004.

Results Out of 45 children studied, 16 had factor VIII inhibitor with average inhibitor titre of 1.15 Bethesda units (BU) (range 0.15-15 BU). Most of them (12 patients) had inhibitor titre <5 BU. Chronic arthropathy was found in 17 out of 45 (37%) children with severe hemophilia-A, consisting of nine patients from positive inhibitor group and 8 patients from negative inhibitor group. Thirty-nine patients (86%) used an on-demand treatment pattern, among whom 15 had positive inhibitor. Among patients receiving prophylactic treatment pattern, only one had positive inhibitor. There were 39 patients (86%) treated using cryoprecipitate, among whom factor VIII inhibitor was found in 12, while among those treated with factor VIII concentrate, the inhibitor was positive in 4/6. The average amount of factor VIII transfused in positive and negative factor VIII inhibitor groups was similar.

Conclusion The prevalence of factor VIII inhibitor in severe hemophilia-A patients was 35%. Chronic arthropathy occurred more often in patients with positive factor VIII inhibitor. Factor VIII inhibitor was found more frequently in patients with an on-demand treatment pattern and in those using factor VIII concentrate **[Paediatr Indones 2005;45:177-181].**

Keywords: *severe hemophilia-A, factor VIII inhibitor, prevalence*

Hemophilia is an X-linked hereditary blood clotting disorder, which manifests only in males.[1-3] Hemophilia-A results from factor VIII deficiency, while hemophilia-B is a consequence of factor IX deficiency.[2,4] The disease causes prolonged bleeding, with mild to severely life threatening bleeding manifestations.[1-3] Based on clinical symptoms and factor VIII activity, hemophilia-A is classified into mild, moderate, and severe.[2,3] In severe hemophilia-A, the activity of factor VIII is less than 1%, in moderate hemophilia the activity is around 1-5%, and in mild hemophilia it is around 2-25%. To date, the administration of factor VIII to prevent and manage bleeding has been the main treatment for hemophilia-A. Complications of disease and treatment may occur, and one of them, which may occur during repeated factor VIII administrations, is the formation of antibody against factor VIII, called factor VIII inhibitor.

The prevalence of severe hemophilia-A with factor VIII inhibitor varies, ranging from 2 to 40%.[5] Some factors were postulated to play a role in the presence

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of the inhibitor, such as genetic factors, inflammation or septic condition during factor VIII administration, race, type of factor VIII given, amount of T-cell receptors, factor VIII treatment pattern, and age at first factor VIII administration.[6-10] The presence of factor VIII inhibitor in severe hemophilia-A patients makes bleeding management more complex and, consequently, more costly.[11,12] In general, the level of inhibitor is classified into high and low titres.[5,6] An inhibitor titre of =5 Bethesda units (BU) is regarded as high and often gives anamnestic responses with repeated administration of factor VIII,[5,11,13] while a low inhibitor titre (<5 BU) usually shows no anamnestic reaction with the administration of factor VIII and indicates good response to a conventional dose of factor VIII.[5,13]

This study was aimed at finding the prevalence of severe hemophilia-A with factor VIII inhibitor and describing its characteristics.

Methods

This cross-sectional study on severe hemophilia-A patients at the National Hemophilia Care Centre, Cipto Mangunkusumo Hospital, Jakarta, was performed during June-August 2004. Subjects were hemophilia-A patients aged =18 years old in whom severe hemophilia-A (<2% of factor VIII activity) had been diagnosed, who were willing to be involved in the study.

Subjects were recruited by consecutive sampling. Measurement of factor VIII inhibitor was conducted using Bethesda assay,[14] by mixing plasma of hemophilia patient with normal plasma at a concentration of 1:1, and placing the mixture in an incubator for 1-2 hours at a temperature of 37ºC. The presence of factor VIII inhibitor would result in a longer aPTT (>8 seconds), while a shorter aPTT indicated that there was no inhibitor in the patient's plasma.[5,6,15] One Bethesda unit was defined as the amount of inhibitor required to inhibit 50% of factor VIII activity in normal plasma.[13,15] The study was approved by the Committee of Medical Research Ethics, Medical School, University of Indonesia. Informed consent was obtained from the subjects' parents prior to the study.

Results

There were 45 patients enrolled in the study, of whom 16 (35%) had positive factor VIII inhibitor (**Table 1**). The average inhibitor titre in this study was 1.15 BU (range 0.15-15 BU). Among 16 patients with positive inhibitor, 4 had high inhibitor titres (=5BU), of which 2 had inhibitor titres of <10 BU (6.05 BU and 7.5 BU, respectively) and 2 others had titres of >10 BU (11 BU and 15 BU, respectively); the rest had low inhibitor titres (<5 BU).

Table 1 indicates that the average age of all subjects was 12 years old (range 3-17 years). The average age of patients with positive inhibitor was 12 years old (range 5-17 years), while the average age patients without inhibitor was 10 years old (range 3-17 years). Hemarthrosis was the most frequent type of bleeding, which occurred in both the positive inhibitor group (13/16) and negative inhibitor group (23/29). Chronic

Table 1. Characteristics of study subjects

Characteristics	Positive inhibitor (n=16)	Negative inhibitor (n=29)	Total (N=45)
Median age in years (range)	12 (5-17)	10 (3-17)	12 (3-17)
Age			
• 0-5 years	2	2	4
• 6-12 years	8	15	23
• 13-18 years	6	12	18
Most frequent type of bleeding			
• Hemarthrosis	13	23	36
• Gum bleeding	2	2	4
• Cutaneous bleeding	1	3	4
• Epistaxis	0	1	1
Chronic arthropathy			
• Present	9	8	17
• Absent	7	21	28

arthropathy was found in 17 patients, nine in the positive inhibitor group and eight in the negative inhibitor group (**Table 1**).

Thirty-nine patients who used an on-demand treatment pattern, while only 6 used a prophylactic treatment pattern. In the on-demand group, positive inhibitor was found in 15/39, while in the prophylactic group it was found in 1/6. The patient in the prophylactic group with positive inhibitor had an inhibitor titre of 1 BU; this patient had factor VIII concentrate as prophylactic treatment. Patients in the negative inhibitor group mostly used cryoprecipitate (**Table 2**).

To treat bleeding, 39 patients used cryoprecipitate and 6 used factor VIII concentrate. In the cryoprecipitate group, positive inhibitor was found in 12 out of 39 patients, while in the factor VIII concentrate group, it was found in 4 out of 6 (**Table 2**). Among 4 patients with positive inhibitor who used factor VIII concentrate, 3 patients had an inhibitor titre of <5 BU (0.15, 0.3, and 1 BU, respectively) and 1 had a titre of 7.5 BU. The average amount of factor VIII per kilogram body weight between the positive inhibitor and the negative inhibitor groups had no significant difference (19.3 IU/kg vs. 19.1 IU/kg).

Discussion

Prevalence of factor VIII inhibitor

In this study, positive factor VIII inhibitor was found in 16 patients (35%). The prevalence of factor VIII inhibitor in this study was higher than that in studies by El Alfy *et al*[16] and Kavakli *et al*.[17] The difference between these studies, apparently, was caused by different methodologies that were applied. In our study, determination of the presence of inhibitor was done only once, hence we were not able to rule out the presence of transient inhibitor.

El Alfy *et al*[16] obtained a low prevalence, 10%, of inhibitor among severe hemophilia-A patients who received cryoprecipitate. The study was a prospective study and the Bethesda assay examination was conducted every six months in order to rule out any transient inhibitor. The peak inhibitor titre reported in this study was 18.6 ± 9.0 BU. In a study among hemophilia-A patients in Turkey, Kavakli *et al*[17] obtained a prevalence of factor VIII inhibitor of 21%.

Type of bleeding

Hemarthrosis was the most frequent type of bleeding that occurred in hemophilia-A patients. Thirteen out of 16 patients in the positive inhibitor group and 23 out 29 patients in the negative inhibitor group had hemarthrosis. In most patients (44/45), bleeding manifestations were spontaneous bleeding with or without mild trauma. This matched the typical clinical appearance of severe hemophilia-A. Hemarthrosis is a typical bleeding manifestation found in severe hemophilia, especially in patients receiving no maintenance treatment or prophylactic factor VIII treatment.[2,4] Another frequent bleeding manifestation is muscle hemorrhage, which occurs mainly on thighs, buttocks, and arms. Bleeding may also occur on gums, the tongue, and teeth as they erupt.[2,4] In this study, gum bleeding was found in 2 patients; one from the positive and negative inhibitor group each.

Chronic arthropathy

Hemarthrosis in severe hemophilia-A patients usually occurs more severely and more often than in moderate

Table 2. Characteristics of factor VIII treatment

Characteristics	Positive inhibitor (n=16)	Negative inhibitor (n=29)	Total (N=45)
Treatment pattern			
• On-demand	15	24	39
• Prophylactic	1	5	6
Type of treatment			
• Cryoprecipitate	12	27	39
• Factor VIII concentrate	4	2	6
Mean amount of factor VIII received in IU/kg (range)	19.3 (9.4-25.8)	19.1 (13.7-31.1)	19.1 (9.4-31.1)

and mild hemophilia patients. Repeated hemarthrosis in the same joint will cause permanent joint damage (chronic arthropathy) and often leads to several mobility disorders. Chronic arthropathy is most frequently found in the knee joint, although it may affect other joints, such as the ankle, elbow, waist, wrist, shoulder, and even the spine.[2-4]

In this study, chronic arthropathy was found in 9 out of 16 patients in the positive inhibitor group and 8 out of 29 in the negative inhibitor group. As of yet, we could not find any literature concerning the possible relationship between factor VIII inhibitor with chronic arthropathy, but the presence of inhibitor often causes insufficient response to conventional dose of factor VIII treatment. In this study, the average amount of factor VIII received per kilogram body weight were not significantly different between the positive and negative inhibitor groups. Therefore, the presence of inhibitor can be assumed to play a role in reducing the effectivity of factor VIII treatment and contributing to the incidence of chronic arthropathy in the positive inhibitor group. Another reason, which may have contributed to this incidence, is the inappropriate frequency of factor VIII administration. Factor VIII should be given every 12 hours, if an acute bleeding were to occur. However, due to financial limitations, in our patients factor VIII could only be administered once.

Chronic arthropathy was found in 16 out of 39 patients in the on-demand treatment group and 1 out of 6 patients from the prophylactic treatment group. The patient having chronic arthropathy in the prophylactic group used cryoprecipitate treatment, although in an insufficient dose of 13.7 IU/kg, while the other patients in the same group received approximately 24 IU/kg. The result of this study supported a statement by Lusher *t al* that the prophylactic treatment pattern can prevent joint and musculoskeletal disorders early.[18] A study by Nilsson *et al*, as quoted by Lusher *et al*[18], revealed that among 15 patients aged 4-12 years old, none suffered from hemarthrosis and chronic arthropathy after receiving prophylactic treatment. Despite its financial drawbacks, the prophylactic treatment pattern is beneficial and furthermore reduces the number of absences in school and work attendance, reduces costs of hospitalization and interventional orthopaedic treatment, as well as improves the self-confidence of patients by preventing chronic arthropathy.[3,4,18]

Risk factor for the presence of inhibitor in severe hemophilia-A patient

Several risk factors were assumed to influence the presence of factor VIII inhibitor, yet several studies have not shown consistent results. These factors were genetic, race, type and pattern of factor VIII treatment, history of the presence of inhibitor in the family, age at initial treatment, and any inflammation which occurred during administration of factor VIII. Genetic factors were the most studied and have been proven to affect the presence of factor VIII inhibitor.[610]

Pattern and type of factor VIII treatment

The pattern and type of factor VIII treatment applied in the management of hemophilia-A patient has been mentioned in many studies as one of the factors affecting the presence of factor VIII inhibitor.[7,11,17] Thirty-nine hemophilia-A patients in this study received on-demand treatment and only 6 received prophylactic treatment. In the group receiving on-demand treatment, positive inhibitor were found in 15/39, while in the prophylactic treatment group only 1/6 had positive inhibitor, with a titre of 1 BU. In all patients with positive inhibitor, factor VIII was administered in concentrate form. According to the World Federation of Hemophilia (WFH), the best management for hemophilia is administration of prophylactic factor VIII since a young age at a dose of 20-25 IU/kg, 2-3 times a week.[19] In this study, the prophylactic treatment pattern apparently had a role in the absence of inhibitor. However, the presence of such a role needs to be confirmed by further study.

The administration of cryoprecipitate as prophylaxis was also done in studies by El Alfy *et al*[16] and Kavakli *et al*,[17] only the objective of cryoprecipitate administration in those studies was to induce immune tolerance. El Alfy *et al*[16] used cryoprecipitate for immune tolerance induction at a dose of 25 IU/kg three times a week for 1-4 months if inhibitor titre was <40 BU and 50 IU/kg if inhibitor titre was >40 BU. Immune tolerance induction at the mentioned dose gave satisfying results with the disappearance of inhibitor in 8 out of 10 patients. The same result was obtained by Kavakli *et al.*[17] In this study, immune tolerance in-

duction was given two times a week at a dose of 25 IU/kg for 1-4 months. Immune tolerance induction in this study was successful in 4 out of 7 patients with positive inhibitor.

Kavakli *et al*[17] obtained a lower prevalence of factor VIII inhibitor in hemophilia patients receiving fresh frozen plasma compared to patients receiving factor VIII concentrate. In this study, 7 out of 23 patients who received factor VIII concentrate had positive inhibitor, while none of 10 patients receiving fresh frozen plasma had positive inhibitor. According to Kavakli *et al*,[17] the lower amount of factor VIII contained in fresh frozen plasma than in concentrate products might explain the higher occurrence of factor VIII inhibitor in patients receiving concentrate.

El Alfy *et al*, in their study of 100 severe hemophilia-A patients receiving cryoprecipitate, obtained a lower prevalence of factor VIII inhibitor (10%). El Alfy considered the low purity factor in cryoprecipitate to be the cause of lower prevalence. According to Vermeylen,[7] hemophilia patients receiving factor VIII products with low purity factor had a lower prevalence of factor VIII inhibitor. Vermeylen suspected that residual or protein contaminants within the cryoprecipitate act as immunomodulator, reducing the risk of inhibitor formation.

In conclusion, the prevalence of factor VIII inhibitor in severe hemophilia-A children aged less than 18 years was 35%. Most patients with positive inhibitor had a low titre (<5 BU). Chronic arthropathy was more frequent in those with positive inhibitor. Positive inhibitor was more prevalent in patients receiving on-demand treatment and in those treated using factor VIII concentrate.

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