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Original Article

Short-term intermittent prophylaxis post-intracranial hemorrhage in children with hemophilia

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Abstract

Background Intracranial hemorrhage (ICH) is one of the major bleeding events causing mortality and long-term morbidity in children with hemophilia, especially those who receive on-demand therapy.

Objective To evaluate the outcome of children with hemophilia after ICH receiving short-term intermittent prophylactic treatment.

Methods This retrospective study was conducted in the Department of Child Health, Dr. Cipto Mangunkusumo Hospital, Jakarta. Children ≤ 18 years of age with hemophilia presenting with ICH between 2015-2020 were included. We recorded patients' demographics, type and severity of hemophilia, the presence of factor VIII (FVIII) inhibitor, brain CT scan, treatment, and outcomes of these patients. Patients who received short-term intermittent prophylaxis using clotting factor concentrate (CFC) post-ICH episodes were observed for ICH recurrence.

Results There were 19 episodes of ICH experienced by 18 patients, consisting of 16 patients with hemophilia A and 2 with hemophilia B. Patients' median age was 4 years (range 0-16 years). Hemophilia was classified as severe in 13 patients, moderate in 4 patients, and mild in 1 patient. Thirteen episodes were preceded by head trauma. The most common clinical manifestation was seizures (13.2%). The most common type of ICH was subdural hematoma. Two patients died and 2 patients had neurological sequelae during hospitalization. The median dose of short-term intermittent prophylaxis using CFC (n=16) was 20 IU/kg of FVIII twice a week and 30 IU/kg of FIX twice a week, for a median duration of 8 weeks (range 5-12 weeks). One patient who did not adhere to the prophylaxis regimen had recurrent ICH at a similar location 6 months after the first episode.

Conclusion Our findings suggest that short-term intermittent prophylaxis is important to prevent the recurrence of ICH in children with hemophilia. **[Paediatr Indones. 2022;62:174-9 DOI: 10.14238/pi62.3.2022.174-9].**

Keywords: *hemophilia; prophylaxis; intracranial hemorrhage*

Intracranial hemorrhage is a life-threatening bleeding event that may result in long-term morbidity in children with hemophilia. Children with hemophilia have a greater risk of intracranial hemorrhage (ICH) than the general population, with estimated prevalences of 3.5-4% of neonates, and 3-10% of children over age 1 to 17-year-old with hemophilia.[1,2] The mortality rate of hemophilia patients with ICH is 20-25%.[3,4] A prior study in Dr. Cipto Mangunkusumo Hospital reported 13 ICH episodes in 11 children with hemophilia between 2007-2010, with a mortality rate of 7.6% and neurological sequelae (epilepsy) documented in one patient.[5]

The incidence of ICH is lower in children with hemophilia who are treated with prophylaxis compared to those treated on-demand.[6] Prophylaxis is the regular administration of clotting factor concentrate (CFC) aimed to maintain hemostasis in order to prevent bleeding, whereas episodic replacement therapy (also known as on-demand

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therapy) is the administration of CFC only at the time of bleeding.[7,8] However, prophylactic treatment is very costly. In Indonesia, an emerging country, CFC is mostly given as on-demand treatment due to limited budget and resources. *The World Federation of Hemophilia* recommends short-term intermittent prophylaxis for patients with moderate or severe hemophilia A or B, who have experienced a life-threatening bleed, such as ICH. Short-term intermittent prophylaxis is defined as administration of CFC either factor VIII (FVIII) or factor IX (FIX), given twice to three times weekly, with a dose 10-25 IU/kg. Short-term intermittent prophylaxis is important during the first 3-6 months following ICH, to minimize the risk of recurrence during these periods.[6,8] In this study, we aimed to evaluate the outcome of children with hemophilia receiving short-term intermittent prophylaxis after ICH.

Methods

This retrospective cohort study was conducted in Dr. Cipto Mangunkusumo Hospital, Jakarta. All children with hemophilia ≤18 years of age with ICH presenting between January 2015 to December 2020 who received short-term intermittent prophylactic treatment were enrolled in this study.

Data were obtained from the medical registry of the Hematology-Oncology Division, Department of Child Health, Dr. Cipto Mangunkusumo Hospital, and from patients' medical records. We recorded patients' demographics, type and severity of hemophilia, the presence of factor VIII (FVIII) inhibitor, brain CT scan, treatment, and the outcome of these patients. Patients who received short-term intermittent prophylaxis using CFC post-ICH episodes were observed to have the occurrence of recurrent ICH. This study was approved by the Ethics Committee of the Universitas Indonesia Medical School/Dr. Cipto Mangunkusumo Hospital.

Results

Between 2015 and 2020, 197 children with hemophilia were registered, comprising 157 hemophilia A and 40 hemophilia B patients. Nineteen separate episodes of ICH were identified in 18 patients, of which 16 had hemophilia A and two had hemophilia B. The majority of patients with ICH had severe hemophilia (72.2%). The median age at presentation was 4 (range 0-16) years. Subjects' characteristics are shown in **Table 1**.

All patients with ICH received supportive treatment; none required neurosurgical intervention. Clotting factor concentrate was administered for a median duration of 12 (4-19) days in subjects with hemophilia A without FVIII inhibitor, and 14 (10-16) days in subjects with hemophilia B. The doses and durations of CFC are summarized in **Figure 1**. During hospitalization, 16 patients clinically improved while

Table 1. Subject characteristics

Characteristics	(N=18)
Type of hemophilia,n	
Hemophilia A	16
Hemophilia B	2
Severity of hemophilia, n	
Mild	1
Moderate	4
Severe	13
Age at occurrence of ICH, n*	
0-4 years	11
5-9 years	3
10-14 years	4
15-18 years	1
FVIII inhibitor, n**	
Negative	15
High titer	1
Low titer	0
Clinical manifestations, n	
Seizure	12
Vomiting	8
Headache	6
Hematoma	4
Loss of consciousness	2
Hemiparesis	2
Lethargy	2
Blurred vision	1
Site of bleeding, n (N=18)	
One site:	13
Subdural	6
Epidural	2
Intraparenchymal	4
Pons	1
Multiple sites:	6
Subdural, subarachnoid, intaparenchymal	2
Epidural, subdural	2
Epidural, subdural, subarachnoid	1
Subdural, subarachnoid	1
Head trauma, n	
Yes	
No	

*) There were 19 total occurrences of ICH in 18 patients
**) Only 16 patients underwent FVIII inhibitor examination

2 patients died due to ICH. Neurological sequelae of epilepsy and hemiparesis with visual acuity loss were documented in two patients.

There was one severe hemophilia A patient with a history of positive FVIII inhibitor during previous treatment and a family history of positive FVIII inhibitor. Initial FVIII inhibitor screening done at the time of diagnosis of ICH was negative. This patient was treated with FVIII concentrate according to the protocol for ICH. However, on the 12th day of hospitalization, he experienced severe headache, his hemoglobin level had declined to 3.5 g/dL, and his FVIII inihibitor level titre had increased (112.8 BU). We then performed a repeat brain CT scan, which revealed worsening epidural hemorrhage and cerebral edema, with midline shift. Due to the lack of access to hemostatic bypassing agents, this patient was given higher doses of FVIII concentrate at a dose of 60 IU/kg every 12 hours. The patient was also treated with intravenous methylprednisolone and cyclophosphamide for inhibitor eradication. He showed clinical improvement in the observation that followed. FVIII inhibitor levels were closely monitored and became negative five months after discharge.

Sixteen patients received short-term intermittent prophylaxis at a median FVIII dose of 20 (range 8-35) IU/kg twice a week and a median FIX dose of 30 (range 30-50) IU/kg twice a week (**Figure 2**). The median duration of prophylaxis administration was 8 weeks (5-12 weeks). One moderate hemophilia B patient experienced recurrent subdural hematoma six months after the first bleeding episode. It occurred in the left parietal region, and patient was hospitalized for 14 days. After the first bleeding episode, patient received short-term intermitten prophylactic at a dose of 30 IU/kg twice a week. However, due to the patient's lack of compliance, prophylactic treatment was discontinued after 6 weeks of treatment. He experienced the second episodes of ICH, with more extensive bleeding, located in the left frontoparietotemporal region, and caused subfalcine herniation.

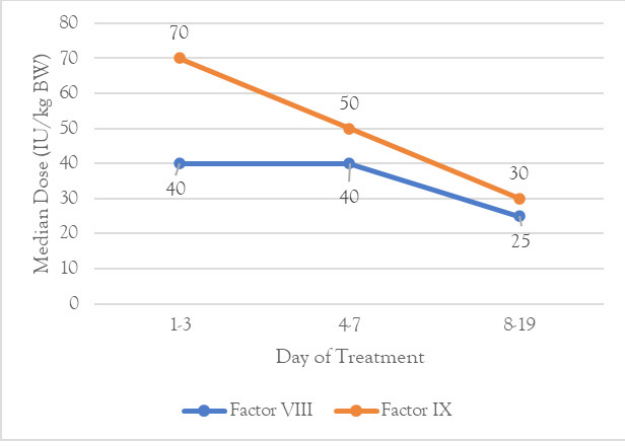

Figure 1. Dose and duration of clotting factor concentrate administration

Discussion

In our hospital, from 2015 to 2020 there were 19 episodes of ICH in 18 out of 197 patients (9.6%). The incidence rate was higher compared to that reported from 2007 to 2011 in the same center, which was 7.1%. Prophylactic clotting factor administration is recommended as standard treatment for hemophilia patients, because it has been shown to reduce not only the number of joint bleeding episodes, but also the risk of major bleeding, such as ICH, compared to on-demand treatment. A previous study reported 29 cases of ICH in hemophilia patients aged 0 to 22 years registered in 33 European hemophilia centers. Out of the 29 cases, 24 occurred in children treated with on-demand therapy, three in children receiving partial prophylaxis, and two in those receiving full prophylaxis. This finding suggests that prophylaxis is highly protective against ICH.[6] The high incidence of ICH in our center is likely to be associated with the on-demand treatment still prevailing in Indonesia.

A retrospective cohort study in children with inherited bleeding disorders conducted in the United Kingdom between 2003 and 2015 reported ICH in 54 children with hemophilia. The median age at presentation was five months (range 0-15 years). Of the 54 children with hemophilia, 51 were classified as severe. Although the prophylactic treatment had commenced before the age of three years in children with severe hemophilia in the UK, the age distribution in the study reflected that earlier onset of prophylaxis was associated with greater reduction in the risk of ICH.[3] Our subjects were also mostly children with severe hemophilia, but in contrast to the aforementioned study, all received on-demand treatment, and the median age was 4 years.

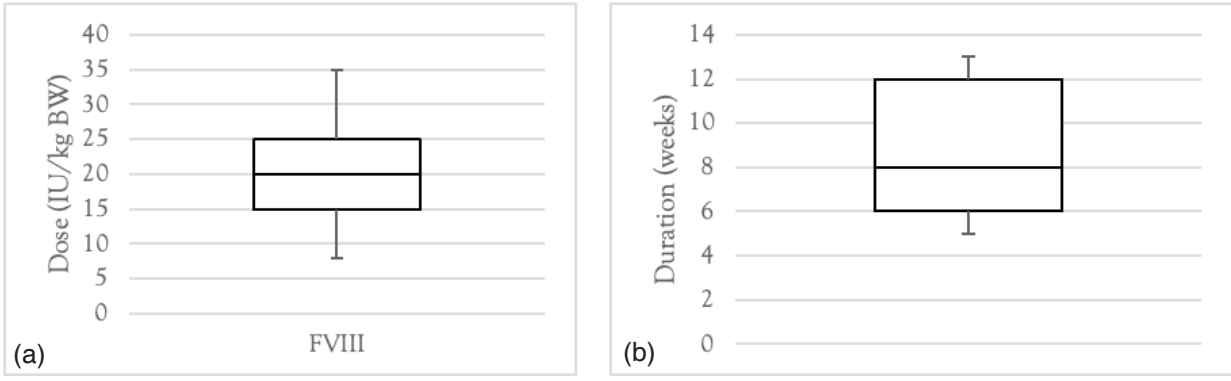

Figure 2. (a) Dose of FVIII prophylaxis in IU/kg; (b) duration of short-term intermittent prophylaxis

The main predisposing factor for ICH is head trauma which is more commonly seen in children than in adults. According to our findings, 13/19 episodes (68.4%) had a history of head trauma prior to ICH. Similarly, a South Korean study reported that traumatic ICH accounted for 58.4% of cases; spontaneous ICH accounted for the remaining cases. Other known predisposing factors for ICH are HIV and HCV infections and the presence of FVIII/FIX inhibitors.[7,9] Comorbidities such as HIV or HCV infection were not observed in our study, but one patient with severe hemophilia A was known to have a high titre of FVIII inhibitor.

The most common symptoms of ICH in our study were seizures (63.2%), vomiting (42.1%), and headache (31.6%). A retrospective study from China reported that headache was the most common chief complaint in children aged >3 years, whereas symptoms in children <3 years of age were atypical, such as sleepiness, irritability, or vomiting.[1] The clinical manifestations of ICH include severe or sudden headache, vomiting, seizures, irritability, somnolence, or loss of consciousness. Hemophilia patients who present with these symptoms, despite the absence of head trauma, should be treated as soon as possible for ICH, and immediately referred for further investigation.[1,8]

Radiology examination is a reliable and valuable diagnostic tool primarily used to confirm the diagnosis of ICH. The most frequently performed examination in our center is non-contrast computerized tomography examination (CT scan). CT scan can reveal the location and volume of bleeding, as well as the presence of skull fractures, cerebral edema, and midline shifts.[10] According to an observational study conducted in a pediatric emergency department in Spain, CT scan is the gold standard that must be performed on symptomatic patients and in children with a high risk of ICH, especially in the case of head trauma.[11]

In hemophilia patients with suspected ICH, CFC should be administered immediately without waiting for laboratory and radiology investigations. Our data has shown that doses and duration of clotting factor replacement therapy in our center were given according to the World Federation of Hemophilia guidelines. Intensive clotting factor exposure with high dosage and long duration is a risk factor of inhibitor development. Inhibitors to FVIII developed in one patient with severe hemophilia A who had a family history of FVIII inhibitor and had previously been diagnosed with a high titer FVIII inhibitor. The presence of FVIII inhibitor significantly raised the burden of treatment in this patient and resulted in prolonged hospitalization (23 days) compared to patients without FVIII inhibitor.

According to Witmer *et al*.,[12] the mortality from ICH in children with hemophilia has significantly improved over the last few decades, from 20% to current estimates of 2.5%. In the United States, factors contributing to this improvement are the wide availability of clotting factor concentrates, the use of prophylaxis in children with severe hemophilia, and improved hemophilia care.[12] We also noted that 2/18 patients in our study died of ICH. These results were similar to the study conducted in our center in 2007-2011, in which 1 out of 11 patients died.[5] The mortality rate in our center was higher compared to that in developed countries where prophylactic therapy is widely implemented as the standard of care.

Central nervous system injury affects neurocognitive

and academic function, impacting children's long-term quality of life.[13] Neurological complications following intracranial hemorrhage in children with hemophilia include motor dysfunction, seizure or epilepsy, hearing and visual impairment, as well as delayed cognitive and neuropsychological development.[2,3] In our study, two patients developed neurological sequelae, including epilepsy and hemiparesis with visual impairment (loss of visual acuity).

Prophylaxis has become the standard of treatment, especially in moderate and severe hemophilia patients. To date, several published trials on prophylaxis for hemophilia have shown that it effectively prevents recurrent joint bleeding, which would lead to arthropathy and disability, compared to on-demand treatment.[14,15] However, on-demand treatment is still applied in Indonesia due to high cost and limited financial support. For patients receiving CFC as on-demand treatment, short-term intermittent prophylaxis is indicated following an ICH episode, with the objective to prevent recurrent life-threatening bleeding.[8,9] In children with severe hemophilia A, low-dose FVIII tertiary prophylaxis (10 IU/kg twice a week) compared to on-demand FVIII treatment has been shown to be effective in reducing the annual joint bleeding rate ($P<0.0001$; 95%CI -14 to -3).[16] The newly released *2021 National Guidelines for the Diagnosis and Management of Hemophilia in Indonesia* recommends low-dose prophylaxis as the therapeutic option of choice, especially in severe hemophilia.[17] Although the effectiveness of low-dose prophylaxis to prevent recurrent ICH needs further investigation, it is considered superior to on-demand treatment in reducing the risk of spontaneous bleeding episodes and recurrent intracranial hemorrhage in patients with severe hemophilia.[3,7]

In our center, short-term intermittent prophylaxis was given at a median dose of FVIII 20 IU/kg twice a week and FIX 30 IU/kg twice a week for a median duration of 8 (5-12) weeks. The World Federation of Hemophilia defined periodic administration of CFC within a certain period (usually three to six months) as short-term intermittent prophylaxis.8 During the study period, one hemophilia B patient had a recurrence of subdural hematoma six months after the first occurrence. This finding supports the postulation that short-term intermittent prophylaxis must be given to prevent recurrent ICH in children with hemophilia. Despite its clear advantages, the implementation of prophylactic treatment as the standard in developing countries still faces several obstacles, including affordability of clotting factor concentrates and compliance of the patient's family or caregivers.[18,19] A comprehensive, multidisciplinary hemophilia care team, including trainers to educate the family or caregivers, is important for improving the quality of life in children with hemophilia.

This study is the first in Indonesia to evaluate short-term intermittent prophylaxis following ICH in children with hemophilia. This study had several limitations, such as the small sample size and single-center focus. Hence, our findings may not represent the incidence and overall outcome of ICH in children with hemophilia in Indonesia.

In conclusion, short-term intermittent prophylaxis is recommended for children with hemophilia following ICH. Surveillance and monitoring are needed to evaluate the long-term outcomes of ICH in children with hemophilia.

Conflict of interest

None declared.

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