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Case Report

INTRACRANIAL HEMORRHAGE IN PATIENTS WITH HEMOPHILIA A

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ABSTRACT

Introduction: Intracranial hemorrhage in inherited bleeding disorders is a medical emergency. The location of bleeding in most children is subdural and the most common cause is hemophilia. Although intracranial bleeding that occurs in people with hemophilia ranges from less than 5% of events, it is a life-threatening medical emergency so appropriate treatment is needed. **Case Report:** A boy patient 11 years old, 20kg weights have a seizure at home and followed by a decrease in consciousness. It was founded abnormalities in the form of anemia, prolonged FH (PPT 4x and APTT 4x), and hypocalcemia. The patient then was given main therapy; FVIII 100 IU/dL according to the FVIII target level calculated. The therapy continued with 500IU/12 hours according to the daily target of FVIII 50IU/dL. **Discussion:** The patient's condition was getting better day by day. The patient's consciousness started to improve after 14 days of postoperative. One month after that, the patient received *koate* treatment as the episodic handler. Diagnosing the exact cause in patients who have intracranial hemorrhage provides appropriate management so that the patients could be helped. **Conclusion:** Good collaboration between anesthesiologists, neurosurgeons, and pediatrics will increase the probability of successful management of critical bleeding without major sequelae.

Keywords: Intracranial Hemorrhage; Hemophilia; FVIII Therapy; Bleeding Therapy

ABSTRAK

Pendahuluan: Perdarahan intracranial akibat kondisi penyakit bawaan (turunan) merupakan sebuah kondisi kegawatdaruratan. Lokasi perdarahan yang paling sering terjadi pada anak – anak adalah perdarahan subdural dan penyebab terseringnya adalah hemophilia. Meski perdarahan intracranial yang terjadi akibat hemofilia kurang dari 5% kejadian, namun hal tersebut merupakan kondisi mengancam nyawa yang membutuhkan penanganan yang tepat. **Laporan Kasus:** Seorang anak laki – laki usia 11 tahun, berat 20kg, mengalami kejang dan penurunan kesadaran secara mendadak di rumahnya. Pasien dibawa ke rumah sakit dan mendapatkan penanganan. Dari pemeriksaan laboratorium, didapatkan anemia, pemanjangan FH (PPT 4x dan APTT 4x), dan hipokalsemia. Pasien diberikan FVIII 100 IU/dL berdasarkan penghitungan target FVIII. Terapi dilanjutkan dengan terapi lanjutan (maintainance) 500IU/12 jam sesuai dengan target harian FVIII 50 IU/dL. **Pembahasan:** Kondisi pasien berangsur – angsur membaik. Kesadaran pasien meningkat sejak 14 hari setelah operasi. Satu bulan kemudian, pasien menerima *koate* sebagai terapi lanjutan untuk pencegahan serangan perdarahan berulang. Diagnosis yang tepat dapat membuat pasien yang mengalami perdarahan intracranial mendapatkan penangnan yang tepat, sehingga pasien dapat tertolong. **Kesimpulan:** Kolaborasi yang baik antara dokter spesialis anestesiologi, dokter spesialis bedah saraf, dan dokter spesialis anak dapat meningkatkan kemungkinan keberhasilan dari suatu manajemen kondisi perdarahan kritis tanpa meninggalkan sekuele.

Kata Kunci : Perdarahan Intrakranial; Hemofilia; Terapi Faktor VIII; Terapi Perdarahan

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INTRODUCTION

Intracranial bleeding in inherited bleeding disorders is a medical emergency. (1) The location of bleeding in most children is subdural and the most common cause is hemophilia. (2) Although Intracranial Bleeding that occurs in people with hemophilia tends to be less than 5% of events, it is a medical emergency that requires the necessary soul needed. (1)(2)

Hemophilia is a disorder of X-linked congenital bleeding caused by a lack of coagulation factor VIII (hemophilia A) or factor IX (hemophilia B). This lack of coagulation factor is due to mutations from the clotting factor gene.(1) the incidence is around

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1 in 10,000 births. Based on the World Federation of Haemophilia's (WFH) annual global survey shows that the hemophilia sufferers around the world were 400,000 in 2012. Hemophilia A dominates hemophilia B, about 80-85% of the total patients were suffered Hemophilia A. Hemophilia commonly happens in boys than girls. However, the F8 and F9 genes are susceptible to mutation which explains why a third of cases have no prior family history. (1)(3)

The right diagnosis provides the right management. Hemophilia presumed in patients who have an easy bruising history in their early childhood, spontaneous hemorrhage, especially internal hemorrhage such as hemorrhage in joints (70-80%), muscle (10-20%) and soft tissue (5-10%) where symptoms of bleeding occur when the child starts learning to walk or run. (1) In patients with mild hemophilia, excessive bleeding usually occurs after trauma or surgery. Family history of hemorrhage in about twothirds of total patients. A definitive diagnosis depends on the factor test to show FVIII or FIX deficiency. (1)(3)

CASE REPORT

A patient of a boy, 11 years old, weighing 20 kg, had a seizure at home and was followed by a decrease in consciousness at home and taken to the nearest hospital and treated. During treatment at the hospital, abnormalities such as anemia, longitudinal FH (4x PPT and 4x APTT) were found, and hypocalcemia was then given a PRC transfusion, vitamin K injection, calcium gluconate injection. The results of other examinations found that SDH appeared without the occurrence of trauma with 1.3 cm thick and MLS 1 cm which had been indicated as being operated (Thickness of cm1 cm and MLS $\geqslant$ 0.5 cm) but not due to blood coagulation abnormalities.

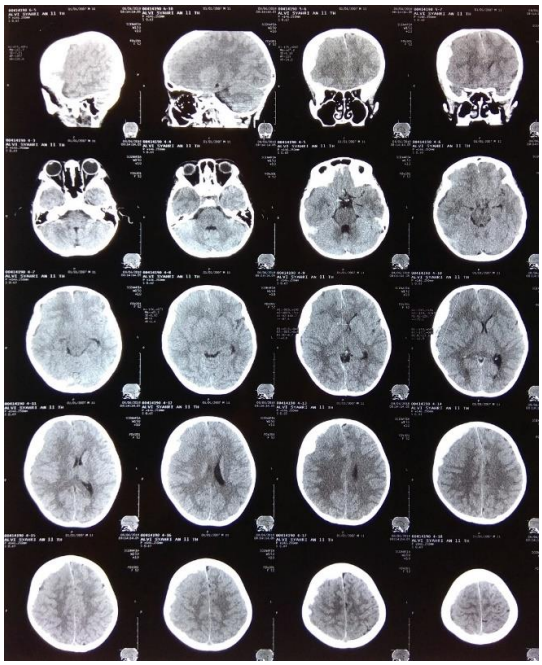

Figure 1. The CT Scan of Patient's Head Transverse View

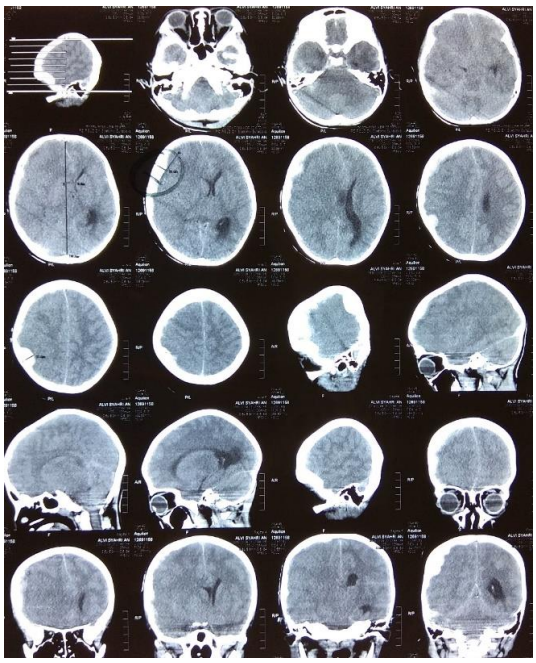

Figure 2. The CT Scan of Patient's Head Sagittal and Coronal View

The patient's condition deteriorated the following day because GCS decreased and FH remained being longer but for PPT it dropped to 2x normal while APTT but 4x normal so

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being referred to Dr. Soetomo General Hospital was further examined found an abnormality in the form of FVIII which was so low that hemophilia A was diagnosed in this patient while waiting for the results of the FVIII examination to be given FFP because there was an extension of the FH both PPT and APTT while preparing for the surgery. In this patient after entering 1 unit of FFP (100 ml) there is an improvement in the physiology of hemostasis namely normal PPT and 2.5x normal APTT and when the results of measurement FVIII come out to indicate a hemophilia A disorder whose main therapy is given FVIII 1000 IU according to the FVIII target level calculation 100 IU / dL should be maintained at 500 IU / 12 hours according to the daily target of FVIII 50 IU / dL.

During surgery, the hemorrhage that occurs in patients can be controlled by the surgeon and after surgery, the patient is maintained FVIII for 14 days as recommended by WFH. And FVIII treatment of patients is given episodically, for example, if the bleeding occurs significantly because the availability of FVIII is difficult to obtain. But the condition of the patient from day to day is getting better and even consciousness begins to improve after 14 days post-surgery and 1 month later the patient gets back coagulation as an episodic handler.

DISCUSSION

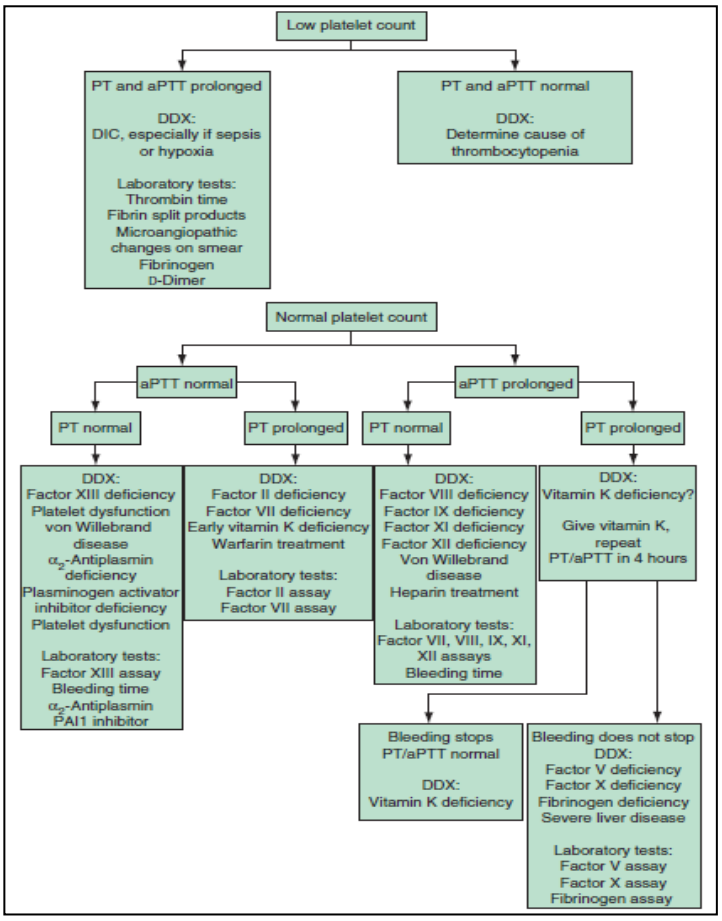

Figure 3. Differential Diagnosis of Bleeding Disorders (4)

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Initially, the patient experienced subdural hemorrhage due to blood clotting disorders in the form of vitamin K deficiency. (3) Because of PPT and aPTT were extended to 4 times normal without thrombocytopenia and after being given vitamin K treatment, PPT was repaired but the aPTT was extended so that deficiency factors were suspected. (3)(5)(6) Indicates the presence of severe factor VIII deficiency (1%) and upright diagnosis of Hemophilia A in this patient.

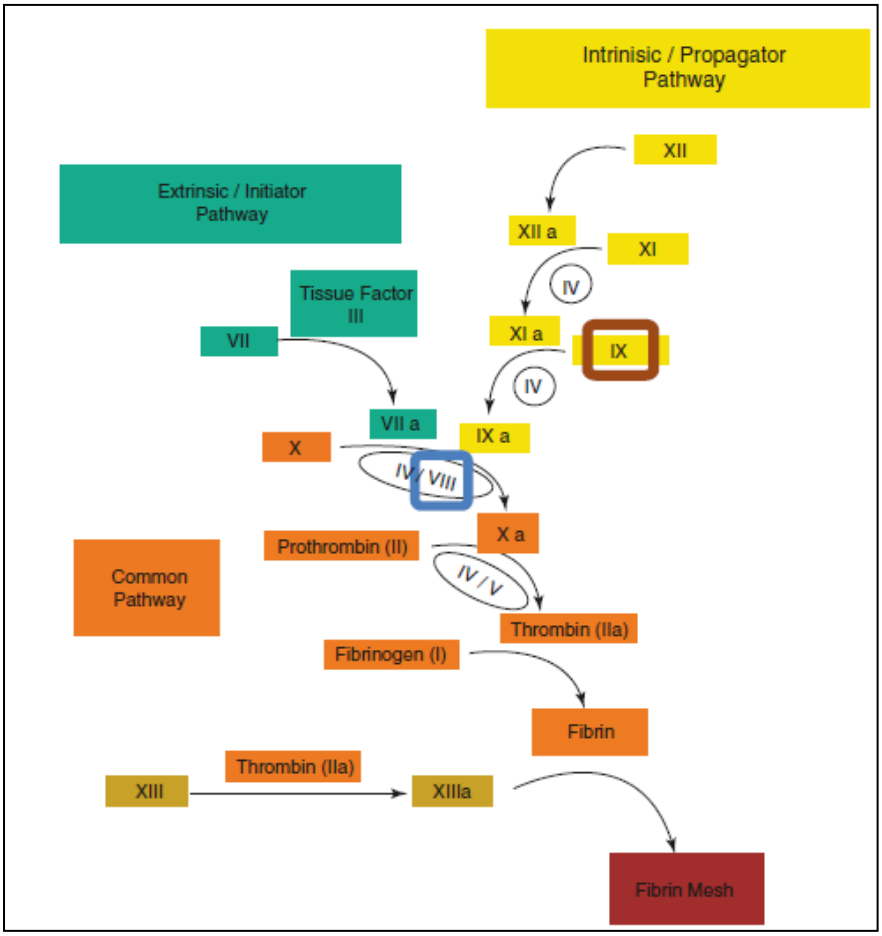

Figure 4. Coagulation Cascade (5)

Finally, the patient can be given FVIII treatment and undergo clot evacuation craniotomy with controlled hemorrhage.

FVIII Concentrate is the first-line treatment for hemophilia A. All plasma derivative products currently on the market are listed in the WFH Registry of Clotting Factor Concentrates. Consult with product inserts for specific details. (1)(2)

One bottle of factor concentrate is available in each dose ranging from 250 to 3000 units. In the absence of an inhibitor, each FVIII unit per kilogram of intravenous weight will increase plasma FVIII levels by about 2 IU / dl. Around 8 until 12 hours is the half-live of FVIII. Fifteen minutes after infusion to verify the dose, the patient factor level must be measured. The desired factor level in plasma (IU/dl) calculated by multiplying the patient's weight in kilograms by 0.5. (1)(2)

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Clotting factor number	Clotting factor name	Function	Plasma half-life (h)	Plasma concentration (mg/L)
I	Fibrinogen	Clot formation	90	3000
II	Prothrombin	Activation of I, V, VII, VIII, XI, XIII, protein C, platelets	65	100
III	TF	Co factor of VIIa	-	-
IV	Calcium	Facilitates coagulation factor binding to phospholipids	-	-
V	Proacclerin, labile factor	Co-factor of X-prothrombinase complex	15	10
VI	Unassigned			
VII	Stable factor, proconvertin	Activates factors IX, X	5	0.5
VIII	Antihaemophilic factor A	Co-factor of IX-tenase complex	10	0.1
IX	Antihaemophilic factor B or Christmas factor	Activates X: Forms tenase complex with factor VIII	25	5
X	Stuart-Prower factor	Prothrombinase complex with factor V: Activates factor II	40	10
XI	Plasma thromboplastin antecedent	Activates factor IX	45	5
XII	Hageman factor	Activates factor XI, VII and prekallikrein		-
XIII	Fibrin-stabilising factor	Crosslinks fibrin	200	30
XIV	Prekallikerin (F Fletcher)	Serine protease zymogen	35	
XV	HMWK- (F Fitzgerald)	Co factor	150	
XVI	vWf	Binds to VIII, mediates platelet adhesion	12	10 µg/mL
XVII	Antithrombin III	Inhibits IIa, Xa, and other proteases	72	0.15-0.2 mg/mL
XVIII	Heparin cofactor II	Inhibits IIa	60	-
XIX	Protein C	Inactivates Va and VIIIa	0.4	-
XX	Protein S	Cofactor for activated protein C		-

HMWK – High molecular weight kininogen; vWf – Von Willebrand factor; TF – Tissue factor

Figure 5. Table of Nomenclature of Coagulation Cascade (5)

Table 1. Expected peak levels of plasma FVIII and duration of administration in hemophilia A patients who have central nervous system bleeding

		Desired Level (IU/DL)	Duration (days)
No Significant Resource Constraint	**Initial**	80–100	1-7
	Maintenance	50	8 – 21
Significant Resource Constraint	**Initial**	50-80	1-3
	Maintenance	30-50	4-7
		20-40	8-14

For example: 20 kg × 100 (IU / dl desired level rises) × 0.5 = 1,000 units of FVIII. See Tables 1 and 2 for the recommended factor level and the duration of replacement needed based on the type of hemorrhage.

FVIII must be infused by slow IV injection with a speed not exceeding 3 ml for adults and 100 units per minute in children. Subsequent doses are ideally based on half of FVIII and recovery in individual patients for certain products. It is best to use all FVIII bottles after they are dissolved, although many products have been shown to have increased stability after being dissolved. (1)(2) Continuous infusion avoids peaks and troughs and is considered by some to be profitable and more comfortable. However, patients must often be monitored for pump device failure.

Table 2. Expected peak levels of plasma FVIII and duration of administration in hemophilia A patients who undergo major surgery

		Desired Level (IU/DL)	Duration (days)
No Significant Resource Constraint	**Initial**	80–100	
	Maintenance	60-80	1 – 3
		40-60	4-6
		30-50	7-14
Significant Resource Constraint	**Initial**	60-80	
	Maintenance	30-40	1-3
		20-30	4-6
		10-20	7-14

Continuous infusion decreases the amount of clotting factor concentrate used and can be more affordable for hemophilia sufferer. However, this affordable comparison hanging on the dosage used for continuous and intermittent bolus infusions. Doses for continuous infusion are adjusted based on

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factor tests and elimination calculations. Because FVIII concentrate with very high purity is stable in IV solution for at least 24-48 hours at room temperature with a potential loss of less than 10%, continuous infusion for the same number of hours is possible. (1)(2)

Other therapies

So far many therapies can be used to treat hemophilia but depend on the severity of the disease. The following are therapies that can be used to treat hemophilia with their respective limitations.

Fresh Frozen Plasma (FFP)

FFP contains all coagulation factors. FFP contains FIX which is used to treat hemophilia B in countries that cannot afford FIX concentrates derived from plasma. (1)(2) The dose is 1 ml FFP = 1 unit factor. But in Hemophilia A it is difficult to reach FVIII levels higher than 30 IU / dl with FFP alone. FIX levels above 25 IU / dl are difficult to achieve. The initial acceptable dose is 15-20 ml/kg.

Cryoprecipitate

Cryoprecipitate is obtained by liquefying FFP slowly at 4 ° C for 10-24 hours and found deposits that are insoluble and separated by centrifugation. Cryoprecipitate contains FVIII (about 3-5 IU / ml), VWF, fibrinogen, and FXIII but not FIX or FXI. The resulting supernatant is called cryo-poor plasma and contains factors VII, IX, X, and XI. The dosage is 1 cryoprecipitate bag made from one FFP unit (200-250ml) which can contain 70–80 FVIII units in volumes of 30–40 ml. (1)(2)

Desmopressin

Desmopressin (1-deamino-8-D-arginine vasopressin) is a vasopressin synthetic analog that increases plasma levels of FVIII and VWF. Desmopressin does not affect FIX. The intranasal desmopressin response is more varied and less predictable. Increase FVIII 3-6 times the baseline level for patients with mild hemophilia, and maybe moderate. (1)(2)

Desmopressin is not for pregnancy but can be used during labor and in the post-partum period in a normal pregnancy. This drug is contained of a high level of VWF, so it has to avoid for pre-eclampsia and eclampsia patients. (1)(2)

The advantage of desmopressin compared to plasma products is the cost and risk of transmission of viral infections. Controlling hemorrhage is associated with hemostasis disorders. The decision to use DDAVP is the initial concentration of FVIII, the improvement achieved, and the duration of treatment needed because it can only be used for patients with mild and possibly moderate hemophilia. (1)(2) Repeated use can cause a decrease in response (tachyphylaxis). The rapid infusion causes tachycardia, redness, tremors, and abdominal discomfort.

Dosage:

1. 4 µg / ml for use i.v.
2. 15 µg / ml for use i.v. and s.c.
3. 150 µg per 1time nasal spray for BW <40 Kg
4. Single-dose 0.3 µ g / kg BW, route i.v. or s.c. can increase FVIII 3-6 times.
5. Desmopressin i.v. diluted 50-100 ml of physiological saline and given by slow intravenous infusion for 20-30 minutes. The peak response is seen about 60 minutes after administration either intravenously or subcutaneously. (1)(2)

Water retention and hyponatremia probably can be caused by antidiuretic activity results. The given of repeated doses must be accompanied by the measurement of plasma osmolality or sodium concentration. Hyponatremia is rare. Contraindications to

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children less than 2 years increase the risk of cerebral edema due to water retention. There are reports of thrombosis (including myocardial infarction) after desmopressin infusion in patients prone to cardiovascular disease. (1)(2)

Tranexamic acid

Tranexamic acid is an anti-fibrinolytic agent which competitively inhibits plasminogen activation into plasmin. Promotes clot stability and can be used as an adjunct therapy to hemophilia and several other hemorrhage disorders. Regular administration of the single-use of tranexamic acid does not prevent the hemarthroses in hemophilia. It is important to control the hemorrhage from the skin and mucous surfaces (for example; oral bleeding, epistaxis, menorrhagia). (1)(2)

Dosage of administration:

1. oral tablets 3-4 times/day.

2. i.v. 2-3 times / day

Gastrointestinal disorders (nausea, vomiting, or diarrhea) infrequently happen as a side effect, but heal if the dose is reduced. The infusion should be slow because the rapid injection can cause dizziness and hypotension. (1)(2)

Tranexamic acid is usually specified for 7 days after tooth extraction to discourage postoperative hemorrhage. The dose of Tranexamic acid must be reduced if there was a kidney disorder. The reduction of the dose will highly avoid the accumulation of toxins. (1)(2)

In the treatment of hematuria, it prevents the dissolution of clots in the ureter which can cause serious obstructive uropathy. And on thoracic surgery causes the development of an insoluble hematoma. (1)(2)

CONCLUSION

Diagnosing the exact cause in patients who have intracranial hemorrhage provides appropriate management so that the patients could be helped. Good collaboration between anesthesiologist, neurosurgeons, and pediatrics will increase the probability of successful management of critical bleeding without major sequelae.

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