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Short insight of pediatric cerebral venous thrombosis and the safety of intra-arterial heparin flushing as a new therapeutic method

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ABSTRACT

Introduction: The incidence rate of Cerebral Venous Thrombosis (CVT) in children has been increased quite significantly due to the availability of advanced imaging technology and the trends of increasing awareness about health-related problem. Systemic anticoagulant was mainstay treatment for CVT. The author proposed a method of heparin deliveries through existing Digital Subtraction Angiography (DSA) procedure called Intra-arterial Heparin Flushing (IAHF). The safety of this procedure in children was still few known and reported. The purpose of this study is to provide insights on CVT and the potential complication of IAHF as the primary therapeutic modality.

Methods: This was a descriptive longitudinal study involving all patients with age 0-18 years diagnosed with Cerebral Venous Thrombosis whom admitted in RSPAD Gatot Soebroto from 2016 to 2018 through MRI examination and will undergo IAHF Procedure as the primary treatment. All subject had signed informed consent regarding the nature of the study. The descriptive data were presented in tables and narratives.

Results: The study found that the highest age group found in this study was between 6-12 years old (46,6%) with male-predominant (70,6%). The origins of the patients were mostly from Indonesia (88%) and several from Vietnam (12%). The most common symptoms of CVT in this study was the speech/communication problem (12%). The most common complication after IAHF procedure was wound swelling at the puncture site (2,6%).

Conclusion: CVT predominantly affect male aged 6-12 years old with speech problem was the most common symptoms. IAHF procedure shown minimal side effects in pediatric with CVT.

Keywords: Cerebral venous thrombosis, Heparin flushing, Intraarterial, IAHF, DSA

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INTRODUCTION

Cerebral Venous Thrombosis (CVT) described as a thrombosis of intracranial venous sinuses and cerebral veins, which can lead to disrupted venous drainage and can induce intracranial hypertension and venous infarcts.[1] The cerebral venous system is a network of cortical, medullary, and deep veins from which the venous blood will drain into the dural venous sinuses. Thrombosis in the cerebral venous system impedes venous outflow, resulting in increased central venous pressure, which in turn causes intracranial hypertension and leads to cerebral ischemia, which may evolve to infarction or hemorrhage.[2,3]

Most of the times, CVT cases can only be found in adult patients. According to a previous study by de Veber et al. in 2001, the incidence rate of CVT is at least 0.67 per 100.000 children per year.[4] This number showed us that CVT is not only a problem present in adult patients but also for pediatric patients. CVT in pediatric patients generally underdiagnosed, but it is an important cause of stroke in childhood which occurs most frequently in the neonatal period.[5] However, when MRI (Magnetic Resonance Imaging) examination was performed on children who suffer from symptoms resembled an ASD (Autism Spectrum Disorder) such as poor concentration, repetitive movement and lack of communication, the results showed that there were signs of CVT. According to deVeber et al., The signs & symptoms of CVT in pediatric patients may vary, but the most common clinical features are seizures, headache, respiratory distress, focal neurological deficits and even lead to comatose state.[6] Patients whose diagnosed with CVT may also present with deficits related to venous infarction which ranging from developmental delays, learning disabilities, hemiparesis and hemisensory loss.[5] A study by Carvalho et al. even shows that pediatric patients who suffer from CVT after a follow up around 22 months showed a developmental delay.[7]

The known mechanism of CVT signs and symptoms can be divided into two, thrombosis of the cerebral veins and thrombosis of the major sinuses which both processes occur simultaneously.[1]

The first mechanism is occlusion of the cerebral veins, which causes localized edema of the brain and venous infarction. MRI has shown that both cytotoxic and vasogenic edema occurs in cerebral vein thrombosis.[8] While in the second mechanism, intracranial hypertension develops as the result of occlusion of the major venous sinuses. Thrombosis of the sinuses leads to increased venous pressure, impaired absorption of cerebrospinal fluid, and consequently increased intracranial pressure. It is assumed that increased intraluminal venous pressure causes a decrease in cerebral blood flow and cerebral perfusion pressure. This might induce an energy failure and a disruption of the blood-brain barrier that results in vasogenic edema and hemorrhagic transformation from increased venous pressure.[9]multicenter (89 centers In most infants, the connection of cavernous sinus with the cerebral veins were no fuly formed, resulting in less reserve and increased vulnerability within the venous drainage system.[10]

The diagnosis of CVT not only based on patients signs and symptoms but also requires a further examination like using an imaging technique such as CT Scan, MRI, or Ultrasonography. According to Sajjad et al., Magnetic Resonance imaging in combination with MRV is the single most sensitive diagnostic technique for CVT.[11] The diagnosis of CVT is established by demonstrating a lack of flow in the cerebral veins with or without typical images of brain infarcts.[6] A study by Teksam et al. shows that the most common locations for CVT in both neonates and older children are the transverse sinuses, the superior sagittal sinus and followed by the straight sinus in the neonates and infants and the sigmoid sinus in older children. The location of brain lesions correlated with the corresponding venous drainage territory.[12]

There are a few treatment strategies for CVT cases in children and neonates. The increased cases of CVT in pediatric patients call for more immediate comprehensive therapy. Most of the time, supportive treatment are the therapy of choice for all pediatric age groups which includes rehydration, antibiotics for suspected sepsis, antiepileptic drugs for seizure control and measures to reduce intracranial hypertension.[8] Therapy using Unfractionated Heparin (UFH) or LMWH were reasonable.[13] Treatment includes standard or low molecular weight heparin for 7–10 days followed by oral anticoagulants for 3–6 months. Thrombolytic therapy and mechanical thrombectomy are sometimes used for extensive thrombosis of superficial and deep venous structures.[14,15]

Regimens vary between centers, but many older infants and children receive anticoagulation in the acute setting with either parenteral unfractionated heparin, subcutaneous low molecular weight heparin (LMWH), or oral warfarin. Some centers prefer to use unfractionated heparin acutely, as the effects of heparin can be reversed if intracranial hemorrhage occurs.[5] The delivery method of anticoagulants therapy may vary between medical centers, in RSPAD Gatot Soebroto Jakarta DSA method was used both as a diagnostic tool and a therapeutic method. DSA has been known to have advantages of looking at all three phases of blood flow (i.e., arterial, capillary and venous).[16] According to Terawan et al, a modified DSA (Digital Subtraction Angiography) procedure was a method of delivering anticoagulation therapy (in this case the author was using UFH) directly to the occluded vessels guided by imaging technique in which this modified method was then called IAHF (Intra Arterial Heparin Flushing), where the only difference between IAHF and the original DSA was the continuous directed local flushing of heparin into the occluded vessels.[17] DSA itself consists of a procedure where the femoral vein was punctured then the catheter will be inserted through the punctured wound using a guidewire. In some angiographic protocols, continuous flushing of the sheath with heparinized saline was maintained throughout the procedure, the dosage of heparin was 30mL/h, 4000 heparin U/L of normal saline solution. Also when the femoral access was gained, a bolus of heparin around 100U/kg with max dose 2000U was delivered for maintenance.[18] While in this study the amount of heparin dosage used was 5000 heparin U/L.

Due to limited literature discussing CVT and IAHF, this study aims to provide insights on CVT and the potential complication of IAHF as the primary therapeutic modality.

METHODS

This was a descriptive longitudinal study conducted in the RSPAD Gatot Soebroto Hospital for three years (2016-2018). Patients of both gender and age from 1 month to 18 years presenting with clinical symptoms of poor concentration, speech & communication problem, headache, dizziness, developmental delay, seizure and syncope which then undergone MRI (Magnetic Resonance Image) & MR Perfusion examination. Complete history taking and neurological examinations were conducted by a group of consultants such as Neuropediatrics, Psychiatrist and Physiatrist. Patients were subjected to MRI, MRV and MR perfusion, Mental status examination, and CARS scoring system to establish a fixed diagnosis. Additional laboratory checkups

are added such as complete blood count, coagulation profile, electrolytes, and chemical profiles to investigate the suspected diagnosis. A case of CVT defined as the presence of CVT clinical symptoms and filling defect in cerebral venous sinuses from MRI/MR Perfusion Imaging. Written informed consents about the nature of the procedure, and the study was given from the patient's parents. The timeline of the follow up after the procedure to see the complications in these patients were one month after the procedure. Data regarding patients profile, presenting symptoms and complications after IAHF procedure were collected and presented as tables and narratives.

RESULTS

A total of 75 cases of CVT were enrolled in this study. Table 1 shows the characteristics of the pediatric patients that underwent IAHF procedure.

Table 1 shows that the child group (6-12 years old) was found more dominant than the rest of the age groups. Male consistently more dominant than female. This study also collects patients data regarding country of origins since RSPAD Gatot Soebroto patients were not only from Indonesia but also from the Global community. In this study, in 2017 there are around 4 Vietnamese patient came to RSPAD to receive specific medical treatment for their condition. Each year the number of Vietnamese patients seek IAHF increased. This data might provide early insight into the potential of Indonesia as a medical tourism destination.

The predominant clinical findings of suspected CVT are difficulty in focusing and speech problem while other symptoms of neurological deficits such as motor deficits, headache, and dizziness were found in a lower frequency.

In table 3 shown that wound swelling at the puncture site, a local post procedural complication, which was found only 2 from 75 patients. No systemic and neurological complication was found.

DISCUSSION

Child age group which ranges from 6 to 12 year was the most age group suffers from CVT 3 years in a row. These findings might give us more insights of which age group population are most suffers from CVT. The findings of CVT in this study might not give us a full picture of CVT case distribution in children population. These limitations might be caused by the initial time the parents start looking for help might differ from the time of the

Table 1 Patients characteristics

Groups	Years			
Age	**2016 (n=10)**	**2017 (n=30)**	**2018 (n=35)**	**Total (n=75)**
Infant (0-2)	0 (0%)	1 (3,3%)	1 (2,8%)	2 (2,6%)
Young child (2-6)	1 (10%)	4 (13.3%)	7 (20%)	12 (16%)
Child (6-12)	6 (60%)	13 (43,43%)	16 (45,7%)	35 (46,6%)
Adolescent (12-18)	3 (30%)	12 (40%)	11 (31,4%)	26 (34,6%)
Sex				
Male	6 (60%)	20 (66,6%)	27 (77,1%)	53 (70,6%)
Female	4 (40%)	10 (33,3%)	8 (22,8%)	22 (29,3%)
Origins				
Local	10 (100%)	26 (86,6%)	30 (85,7%)	66 (88%)
Foreign	0 (0%)	4 (13,3%)	5 (14,2%)	9 (12%)

Table 2 Symptoms characteristics

	Years		
Symptoms	**2016 (n=10)**	**2017 (n=30)**	**2018 (n=35)**
Difficulty focusing	4 (40%)	10 (33,3%)	6 (17,1%)
Speech/Communication	5 (50%)	11 (36,6%)	24 (68,5%)
Motor deficits	1 (10%)	3 (10%)	2 (5,7%)
Headache	0 (0%)	2 (6,6%)	1 (2,8%)
Dizziness	0 (0%)	2 (6.6%)	0 (0%)
Etc. (Developmental delay, seizures, syncope)	0 (0%)	2 (6,6%)	2 (5,7%)

Table 3 Complication of IAHF Procedure

Complications	Subjects (n=75)
Local (Puncture Site)	
Hematoma	0 (0%)
Wound swelling	2 (2,6%)
Hemorrhage	0 (0%)
Systemic	
Anaphylaxis	0 (0%)
Headache	0 (0%)
Nausea / Vomiting	0 (0%)
Neurologic	
Stroke	0 (0%)
Blindness	0 (0%)
Seizure	0 (0%)

symptoms starts to emerge. While in the matter of sex dominance, the patient that admitted in this case predominantly were male children. These results were similar with the study by Johnson et al. where the male patients were more dominant than the female patients.[19] These findings might open new possibilities to further research of what might affect the development of CVT in the male population. In this study, the authors also report the geographic distribution of foreign patient visiting Indonesia for medical second opinion regarding the CVT case. It showed that some patients that visit RSPAD Gatot Soebroto were Vietnamese origins.

In symptoms characteristics, we can see in this study that in the timeline from 2016-2018 the most common symptoms found in these patients were speech/communication problem and difficulty in concentration or paying attention similar with ASD (Autism Spectrum Disorder). While other common symptoms to be found are headache, dizziness and in a very small case of developmental delay, syncope, and seizure. These findings quite differ from the study by deVeber et al. which the most commonly found symptoms were headache, seizures and other neurological disorders.[4] While in another study the developmental delay would be developed in patients with CVT around 22 months after diagnosed.[7]

As the CVT diagnosis was established the suggested therapy was anticoagulation therapy which in this case will be delivered directly to the occluded site with catheter guide help using a digital imaging technique called DSA (Digital Subtraction Angiography) which in this case the technique has been developed and modified by Terawan which now specifically called IAHF.[17] The idea of this therapy was to deliver the anticoagulation therapy to the site of thrombus directly. Anticoagulation therapy was already used in CVT in several studies. One series of the study suggested that cognitive outcome might be better in the anticoagulated group.[6] The choice of using UFH was based on a safety reason where the effects of heparin can be reversed if unwanted adverse events such as intracranial hemorrhage occur.[5]

The unique anatomy and physiology of pediatric cerebral vascular fragility and size make pediatric patients more susceptible to complications secondary to catheter-based angiography.[20] This makes the Interventional Radiologist team in RSPAD Gatot Soebroto takes any necessary measures to make sure the safety of the patient is guaranteed. In this study in the timeline of 2016-2018, there is only 2 reported cases of wound swelling in the femoral puncture site which both managed by applying elastic bandage at the puncture site for 6 hours. After the compression, the swelling started to decrease. Another series of cold compress application for 5 to 10 minutes in the morning and evening for around 3 days was suggested to the patient parents to prevent any further local complication such as hematoma. There is no report of adverse events caused by the anticoagulation drugs or contrast which used in the IAHF procedure. Even after follow up through telephones to the parents for around 28 days after the procedure there was no complication has been reported such as leg pain, limping, and difficulty walking. Therefore, the rate of immediate complications after DSA procedure in children patients is very low because when DSA is performed by experienced angiographers, they can provide better diagnostic even therapeutic results. The experience with thrombolytic therapy and mechanical thrombectomy in pediatric CVT is limited to individual case reports or case series Despite its effectiveness in achieving recanalization or patency of thrombosed intracranial sinuses, safety, and availability was the main limitations of thrombolysis.[21] In this study, the author intended to show the reader that the delivery system of heparin into the vessels through a catheter-mediated method in pediatric patients with Cerebral Venous Thrombosis is safe.

The minimal complication found in this study may have been a result from proper preparation, preventive measures, modern device and good communication to the patients and the family about the do's and don'ts after the procedure. The availability of the device suitable for the procedure in children may also contribute to minimalize the after procedure complications. In term of communication, the doctors will inform the patients to minimize movement such as flexing the right inguinal region and minimize body weight pressure on the right side of the patient body. Before the patients

underwent the procedure, the patients must pass some essential examination from several specialties such as Internist, Pulmonologist, Cardiologist, Neurologist, Psychiatrist, and also Anesthesiologist to make sure that the patient condition is suitable for this procedure and make sure the safety of the patient.

CONCLUSION

CVT awareness in the pediatric population is starting to increase in global communities where it is quite common in the male child population. Until recently, the known CVT clinical manifestation limited to headache, seizure and other similar symptoms, but in this study, it was proven that the CVT manifestation could vary to mental development disorders. The IAHF procedure showed minimal complication. Future study is needed to investigate another potential complication that may occur if the follow up is performed on a longer timeline.

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CONFLICT OF INTEREST

The author reports no conflicts of interest in this work.

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