REVIEW ARTICLE

GMJ.2016;5(Supp.1):48-61
www.gmj.ir

Cerebral Venous Sinus Thrombosis

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Abstract

Cerebral venous thrombosis (CVT) is occlusion of dural sinuses and/or cortical veins due to clot formation. It is a potentially life-threatening condition that requires rapid diagnosis and urgent treatment. Cerebral venous thrombosis is more common in females and young people. Pregnancy, postpartum state, contraceptive pills, infection, malignancy, hyper-coagulable state, rheumatological disorders, trauma are among the major etiologies of cerebral venous thrombosis. Headache, focal neurologic deficits and seizure were the most common clinical presentations. Different techniques of unenhanced and contrast enhanced brain computerized tomography (CT scan) and, magnetic resonance imaging (MRI) are the most helpful ancillary investigations for diagnosis of Cerebral venous thrombosis. Specific treatment of the underlying cause of cerebral venous thrombosis should be considered as the mainstay of the treatment. Anticoagulation with heparin or low molecular weight heparinoids is the most accepted treatment. In acute phase, medical or surgical management to decrease intracranial pressure (ICP) is also recommended. If the patient's clinical condition aggravates despite adequate anticoagulation, thrombolysis or mechanical thrombectomy can be an additive option. **[GMJ.2016;5(Supp.1):48-61]**

Keywords: Cerebral venous thrombosis; Stroke; Hypercoagulable disorders; Virchow's triad

Introduction

Cerebral venous thrombosis (CVT) is a form of cerebrovascular disease primarily affecting cerebral venous sinuses. Although considered to be more common in Asia and central/ south America most of the published data is reported from Europe or North America. It affects about 5 people per million and accounts of 0.5% of all strokes [1]. The largest reported series of CVT patients were published by ISCVT (International study on CVT) investigators; reporting 630 patients predominantly from European countries [2]. A frequency of 7 CVT patients per 100,000 hospitalized patients was reported by Daif in Saudi Arabia [3]. Number of Indian studies have reported a very high frequency of CVT among young stroke patients ranging from 10-20% [4]. Pungayara *et al* [5] reported that CVT accounts for half of all young strokes and 40% of strokes in women.

A study of young women from Asian countries reported a frequency of 20% CVT cases among all stroke [6]. The age of the patients of a cumulative data of published Iranian studies were between 29.5-43.8 [7].

CVT in children and neonates is increasingly recognized. A Canadian study reported annual incidence of 6.7 cases per million popula-

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tion [8]. It is more common in women which is probably related to women specific risk factors for CVT especially pregnancy, puerperium and use of oral contraceptives. In the last three decades advances in neuroimaging and neurointerventions have completely revolutionized the diagnosis and management of CVT. More cases are being diagnosed with up to 85% patients in whom risk factors could be identified. Outcome is favorable with mortality less than 8-10%.

This chapter intends to cover anatomy of cerebral venous system, etiologies, pathophysiology, clinical and radiological manifestations, medical and interventional management and prognosis of CVT.

Anatomy

Venous drainage of skull and brain is done by a network of extracranial veins, diploic veins, dural venous sinuses, and superficial and deep cerebral veins. External jugular vein drains retromandibular venous plexus, posterior auricular, transverse cervical, suprascapular and anterior jugular veins and ends in the subclavian vein. Internal jugular vein originates from jugular bulb and takes branches from common facial, lingual, pharyngeal, superior thyroidal and middle thyroidal veins. Occipital emissary vein, suboccipital venous plexus, and deep cervical veins go to the vertebral vein, which ends in the suclavian vein. Internal jugular vein unites with the subclavian vein to form the brachiocephalic vein. Inferior thyroidal vein directly pours to brachiocephalic vein. Diploic veins are valveless veins course through the calvarium and connect with meningeal veins and dural sinuses to pericranial veins. Diploic veins are not usually seen in conventional angiography.

Cerebral venous sinuses are pockets of blood between two layers of dura. They drain the venous blood from superficial and deep cerebral veins and communicate with extracranial venous system through diploic veins. For better understanding, it is better to divide the cerebral dural sinuses to anterior and posterior systems. The main sinus of the anterior system is cavernous sinus. Posterior system includes superior sagittal, inferior sagittal, straight, occipital, transverse and sigmoid sinuses.

Cavernous sinus drains blood from sphenoparietal sinus, and superior and inferior ophthalmic veins. Two cavernous sinuses connect via a circular (intercavernous) sinus in a butterfly appearance. Cavernous sinus communicates with the transverse sinus and internal jugular vein via superior petrosal sinus and inferior petrosal sinus, respectively. Oculomotor(III), trochlear(IV), abducent(VI) , ophthalmic(V1) and maxillary branches(V2) of trigeminal nerves and the syphon of the internal carotid artery are located within the cavernous sinus.

Superior sagittal sinus travels from anterior to posterior in a groove between falx cerebri and dura of inner table and terminates to torchular herophili (confluence of sinuses).Occipital sinus, located in the margin of falx cerebelli, run into confluence as well. It is absent in about of one third of persons. Inferior sagittal sinus and vein of Galen unite to form the straight sinus, which runs posteriorly to the confluence of sinuses. The venous blood drained from superior sagittal, occipital and straight sinuses goes into internal jugular vein through transverse and sigmoid sinuses. Each Transverse sinus begins from internal occipital protuberance and run to petrous bone. It receives superior petrosal sinus and then forms sigmoid sinus. Transverse sinuses are asymmetric in most of the individuals and one of them can be aplastic or hypolplatic. The right one is the larger in the majority of the individuals. Sigmoid sinus is a S-shaped structure turn into jugular bulb.

Cerebral veins can be categorized to superficial, deep and posterior fossa veins. Superficial cerebral vein courses along sulci and drain cortical gray matter and subcortical white matter. Of the numerous superficial cerebral veins, vein of Labbe and vein of Trolard worth mentioning. Superior anastomotic vein of Trolard travels posterosuperiorly and connects superior middle cerebral vein into the superior sagittal sinus. Inferior anastomotic vein of Labbe courses along the occipitotemporal sulcus and connects superior middle cerebral vein and the transverse sinus.

Deep cerebral veins drain venous blood from deep white matter and basal ganglia through subependymal veins and from superficial

white matter through medullary veins. Anterior caudate vein and terminal vein form the thalamostriate vein. Thalamostriate vein unites to septal vein to form the internal cerebral vein. Internal cerebral vein and basal vein of Rosental form the short U-shaped greater vein of Galen.

Posterior fossa veins include superior (Galenic), anterior (petrosal) and posterior (tentorial) groups of veins with numerous small veins [9-11].

Etiologies

More than one hundred risk factors have been reported in published literature. About 50% patients have multiple risk factors. A rational approach to identify risk factors is warranted after confirmation of diagnosis. A comprehensive list of established risk factors is provided in table 1.

Table 1. Risk Factors for CVT

Pregnancy	**Medications Related**
Puerperium	Oral contraceptive pills
	Androgens
Infection Related	Anti estrogen therapy
Direct septic trauma	Anti-neoplastic agents: Cisplatin, L asparaginase
Cerebral abscesss	Sildenafil
Subdural empyema	Carbamazepine
Meningitis	
Tuberculous meningitis	**Malignancy**
Otitis media	Squamous cell metablastic cervical cancer
Orbital cellulitis	Non hodgkins lymphoma
Tonsillitis	Bilateral glomus tumors
Dental infections	Colorectal cancer
Stomatitis	Epidermoid carcinoma of tongue
Cellulitis	Dysgerminoma
Septicemia	Ewing's sarcoma
TB	Allogenic transplant for acute lymphoblastic leukemia
Endocarditis	
Measles	Paraneoplastic syndrome
Hepatitis	Meningioma
Herpes simplex	
Varicella Zoster	**Rheumatologic Diseases**
Cytomegalovirus	Bachet's disease
HIV	Antiphospholipid antibody syndrome
Malaria	Systemic Lupus erythematosus
Trichinosis	Wegeners granulomatosis
Toxoplasmosis	Churg-strauss syndrome
Aspergillosis	
Cryptococcosis	**Nephrotic Syndrome**
	Paroxysmal nocturnal hemoglobinuria
Hypercoagulable Disorders	Iron deficiency anemia
Protein C deficiency	Sickle cell anemia
Protein S deficiency	Inflammatory bowel diseases
Anti thrombin III deficiency	Trauma
Factor V leiden mutation	Lumbar puncture
Prtothrombin gene mutation	Endocrine disorders: Diabetes, thyroid disease
Homocystinemia/ homocystinuria	Renal allograft
Essential thrombocythemia	Dehydration
Primary polycythemia	Anemia
Plasminogen deficiency	Prolonged flights
TPa deficiency	
Elevated plasminogen activator inhibitor-1	**Idiopathic**
Dysfibrinogenemia	
Evans syndrome	
Heparin induced thrombocytopenia (HIT)	
Increased Factor VIIIc	

Pathophysiology

Cerebral venous thrombosis refers to complete or partial occlusion of either the main sinus/ sinuses or the feeding cortical veins leading to secondary effects of vascular congestion and focal or generalized neurological deficits. Thrombosis in venous channels draining the brain is a consequence of the characteristic risk factors under the heading of Virchow's triad, which includes local trauma to vessel wall, stasis and hypercoagulable state.

Predominant involvement of superior sagittal sinus in large number of cases could be related to the fact that the superficial cortical veins draining against the blood flow in the sinus. Presence of fibrous septa present at inferior angle of the sinus causes turbulence hence making it more susceptible to thrombosis. A thrombosed sagittal sinus leads to compression of the arachnoid villi, which drain CSF from the ventricles, leading to raised intracranial pressure [12]. Hypercoagulable state has been attributed as one of the major risk factors in the development of CVT. Mutations in genes encoding for coagulation factors, increased basal production of these factors in certain physiological and pathological states and certain malignancies and autoimmune disorders lead to an imbalance between prothrombic and antithrombotic factors. Pregnancy and puerperium is a state of compensated, accelerated intravascular coagulation, which is necessary for maintenance of the uterine-placental interface and preparation for the haemostatic challenge of delivery. This is achieved by a physiological increase in production of coagulation factors that induce a prothrombotic state. This is considered to be most likely explanation of its association with CVT.

Mechanism of Neuronal injury

Mechanism of neuronal injury in CVT could be attributed to four pathophysiologic stages of CVT [12].

Increased dural sinus pressure

Venous flow obstruction

Development of cytotoxic and vasogenic edema

Infarction and hemorrhage

Thrombosis of dural sinus especially superior sagittal sinus leads to a rise in dural sinus pressure. This pressure could range from mild to severe and is an important factor underlying initial symptomatology of CVT. Presence of collateral channels and recanalization are important as all venous occlusions do not necessarily end up in the neuronal injury or infarction. Location of occlusion may be important. One study showed that occlusion of posterior SSS leads to significantly reduced cerebral blood flow and hemoglobin oxygen saturation. It may lead to reduced capillary perfusion pressure and increased cerebral blood volume. Reduction of capillary perfusion pressure and increased cerebral blood volume may lead to neuronal injury at this stage.

When the veins get thrombosed, there is increase in backpressure, resulting in reversal of flow direction (predominantly in setting of transverse sinus and straight sinus thrombosis) and increased in flow velocity. In the setting of transverse sinus occlusion, compensatory increase in flow velocity in the contra lateral sinus is also documented. In sigmoid sinus thrombosis, increased flow velocity may lead to enhanced drainage into cavernous sinus.

Venous flow obstruction leads to raised intracranial pressure (ICP) leading to blood brain barrier (BBB) disruption, resulting in decreased cerebral blood flow. Declining consciousness level could be directly related to the extent of venous flow velocity. Venous outflow obstruction leads to moderate enlargement of extracellular spaces. Blood brain barrier is prone to get damaged in the setting of raised retrograde venous pressure. Hence, leakage of fluid (vasogenic edema) ensues with increase post capillary venules pressure and opening of tight junctions. Alternatively, increased venous pressure leads to increased intracranial pressure, decreased capillary perfusion pressure and remarkably decreased cerebral blood flow. This causes translocation of water content from the extracellular to the intracellular space (cytotoxic edema) where water movement is more restricted, a pattern observed in acute arterial infarction.

Development of cytotoxic and vasogenic edema represent an important landmark in CVT cascade. Neuronal injury at this point is still reversible and has been shown by many studies especially Diffusion weighted Imaging (DWI) [13].

Infarctions and hemorrhage are endpoints of CVT cascade. Hemorrhagic tendency in venous thrombosis is more frequent as contrary to arterial thrombosis, occurring approximately in 10-50% of cases. Hemorrhagic infarctions principally affect the cortex and gray-white matter junction. The bleeding in CVT is attributable to increase venous and capillary pressure.

There are anecdotal reports of association of CVT with accelerated myelination. It is proposed that cerebral venous thrombosis with the consequent restriction of venous outflow could be a possible key factor in the induction of accelerated myelination. The exact association of accelerated myelination and neuronal injury in patients with CVT is not well understood.

Clinical Manifestations

Clinical manifestations of CVT are diverse but could be grouped under four patterns; isolated intracranial hypertension, focal cerebral signs (deficit/ seizures), encephalopathy and unusual presentations. Headache is by far the most common presenting symptom. Number of patients has normal neurological examination at presentation. In about 15% cases headache is the only abnormal finding. Headache does not have any localizing value. One study suggested that occipital headache was more common in sigmoid sinus thrombosis [14].

Isolated intracranial hypertension may be present in 10-15% cases with headache, papilledema and otherwise normal neurological examination. Course is sub-acute to chronic. Likely pathology is thrombosis of superior sagittal sinus. It is recommended that CVT must be ruled out in patients diagnosed with isolated intracranial hypertension (pseudotumor cerebri).

Focal cerebral signs are present in 20-50% of CVT cases. Focal neurological deficits are being more common in adults while seizures being more common in children. This pattern of neurological involvement is subacute in presentation as compared to acute presentation of arterial ischemic stroke. Majority of these patients have evidence of focal cerebral involvement on imaging especially MRI including infarct, hemorrhagic infarct, hemorrhage, focal cerebral edema etc.

20-30% of patients with CVT with encephalopathy or coma usually have involvement of deep venous system or large parenchymal lesions due to thrombosis of cortical veins. Mass effect, midline shift and hydrocephalus may be identified on imaging of these patients. Encephalopathy could be related to seizures, post ictal state and status epilepticus in some patients.

Unusual or rare presentation is not uncommon in CVT (10-30%). These include thunderclap headache, tinnitus, transient ischemic attack, cavernous sinus syndrome, isolated headache, and migraine with aura, psychiatric symptoms and cranial nerve palsies. Those patients pose a diagnostic dilemma for number of clinicians and high index of suspicion is needed to make an early diagnosis.

Imaging

Unenhanced brain CT scan is unremarkable in most patients of acute CVST. In other patients, hyperdensity of a cortical vein or dural sinus can be seen in unenhanced brain CT scan [15]. If CVST is in subacute or chronic state, thrombosis may be isodense, hypodense, or have mixed density.

Brain CT scan with contrast may show enhancement of the dural lining of the sinus with a filling defect within the vein or sinus which called empty delta sign [16]. In unenhanced brain MRI, signal intensity of thrombosis can be very different. Early signs of CVST include absence of a fluid void signal in the sinus and/or T2 hypointensity suggestive of a thrombus. In First week of evolution of CVST thrombosis has deoxyhemoglobin and usually presents as isointense to brain tissue on T1-weighted images(T1-WI) and hypointense on T2-weighted images(T2-WI) . In second week thrombus has methemoglobin and presents in hyperintensity on bothT1-WI and T2-

WI.In chronic stages thrombus present iso- to hyperintense both in T1-WI and T2-WI. In MRI with gadolinium central isodense lesion in a venous sinus with surrounding enhancement is counterpart of empty delta sign in CT[17].(Figure-1)

Susceptibility-weighted images can be a help with revealing thrombosis as a low signal lesion in the area of dural sinuses.

The T2*-weighted conventional GRE sequences may be the best method for detecting of cerebral venous thrombosis [18]. (Figure-2)

If CVST cause venous infarction CT or MRI can show infarction with or without hemorrhagic transformations. Diffusion-weighted images (DWI) may show high signal intensities as restricted diffusion and perfusion-weighted MRI may reveal prolonged transit time. Venous infarcts do not respect arterial territories and usually are seen in higher brain cuts [19]. Deep cerebral vein thrombosis may cause bilateral thalamic and/or basal ganglionic infarctions. Isolated cortical vein thrombosis may induce small cortical infarctions [20].

Vascular imaging studies for CVST include computerized tomographic venography (CTV), magnetic resonance venography and digital subtraction angiography (DSA).

CTV can provide a rapid and reliable modality for detecting CVST. Due to dense cortical bone neighboring to venous sinuses, bone artifact may interfere with the visualization of enhanced dural sinus [21].

The most commonly used MRV techniques are time-of-flight (TOF) MRV and contrast-enhanced magnetic resonance. The 2-dimensional TOF technique is the most commonly used method currently for the diagnosis of CVT, because 2-dimensional TOF has excellent sensitivity to slow flow compared with 3-dimensional TOF (Figure-3). Contrast-enhanced MRV improved visualization of cerebral venous structures. Some authorities believe drawbacks to CTV include concerns about radiation exposure, potential for iodine contrast material allergy, and issues related to use of contrast in the setting of poor renal function [17, 21].

As noninvasive vascular imaging methods MRV and CTV have their own advantages and drawbacks. CTV is a rapid and available method with less motion artifacts, which can be done in patients with metal pieces or devices in their body or brain. MRI plus MRV. Issues related to CTV include radiation exposure, contrast allergy, and contrast induced nephropathy [17].

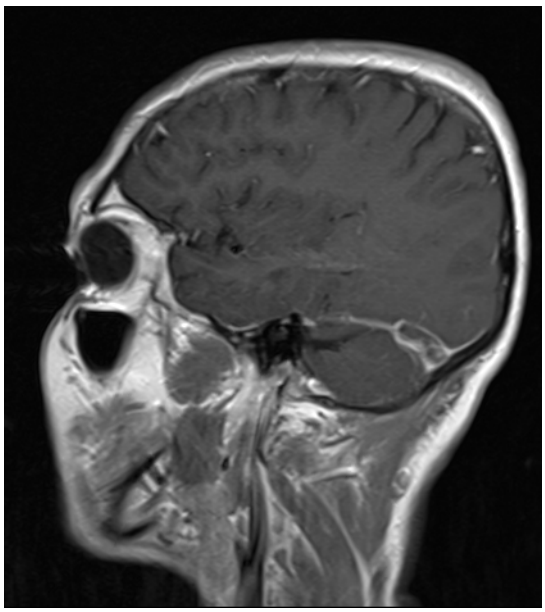

Figure 1. Contrast enhanced T1- images showing filling defect in torcular herophili

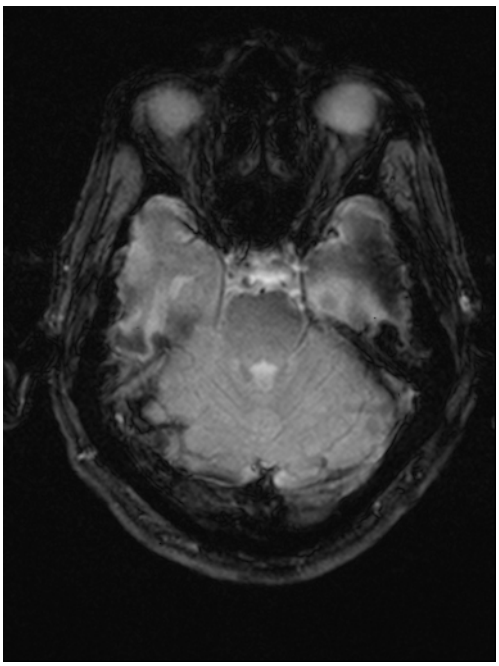

Figure 2. T2*-weighted image showing clot in right transverse sinus

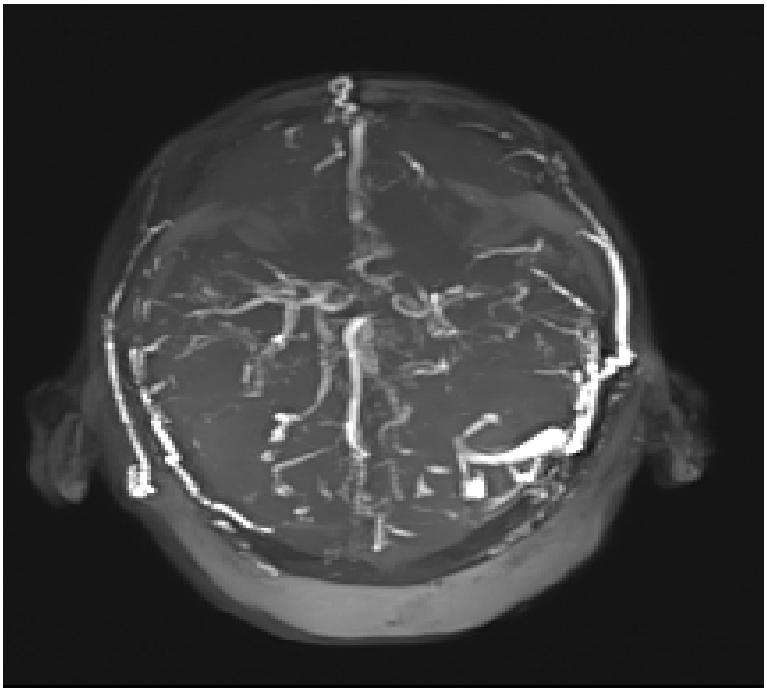

Figure 3. Time of flight (TOF) magnetic resonance venography (MRV) showing clot in transverse and straight sinuses

Laboratory Tests

In a prospective, multicenter study of 343 patients, D-dimer for CVST had sensitivity of 97.1%, specificity of 91.2%, negative predictive value of 99.6%, and positive predictive value of 55.7%. Consequently, a normal D-dimer level can't rule out the diagnosis of CVST [22].

Prognosis

The overall prognosis of CVST is better than outcome of the arterial stroke [22].
Multivariate logistic regression showed older age [1-4,23-26], stupor or coma[3-5,25,26], intracerebral hemorrhage at time of presentation [1,4,6,23,26,27], and underlying hematological disorders [1,23] ، malignancy [1-3,5,7,23,24,28] or infection [1,6,7,23,27,28] as independent predictors of mortality in studies.
Venous infarcts and hyperintensity on DWI were associated with clinical deterioration in patients with CVT [8, 29]. In addition, prognosis of CVST is overall good in women with hormonal-dysregulation [9, 22].

Medical Treatment

Extent of neurological damage in CVT depends on the rate at which occlusion occurs and collaterals are formed. Occlusion of cerebral venous sinuses leads to acute raise in intracranial pressure. In this acute phase, medical management to decrease intracranial pressure (ICP) is recommended. This includes head elevation, hyperventilation to a target PaCO2 of 30-35 mmHg and use of mannitol. Carbonic anhydrase inhibitors such as acetazolmide or topiramate is recommended for acute to subacute phases. Steroids have no proven benefit in this condition.
Specific treatment must address underlying cause of cerebral venous thrombosis. For drug induced CVT, the drug has to be discontinued while malignancy requires its own specific therapy besides treatment for CVT. For infections related CVT especially mastoiditis or middle ear infections high dose antibiotics are the mainstay of treatment. Additionally local collections of pus at these sites may have to be drained. Patients with nephrotic syndrome related CVT should be treated with steroids. Those patients who achieve remission of ne-

phrotic syndrome may discontinue anticoagulation after six months following remission if there is no other indication for anticoagulation.

Role of anticoagulation in management of CVT has long been debated [30]. Lyons and colleagues reported two cases of infective cavernous sinus thrombosis that greatly benefited from a combination of antibiotics and heparin [31]. In 1991, the first randomized controlled trial on anticoagulation in CVT was published [32]. Twenty patients with CVT were randomized into a placebo arm (n=10 patients) and heparin arm (n=10 patients). Patients in the heparin arm showed a clear improvement at day 3 ($p<0.05$) and the difference remained significant after 8 days of treatment ($p<0.01$). After 3 months, 8 of the heparin-treated patients had a complete clinical recovery and 2 had slight residual neurological deficits. In the placebo group, only 1 patient had a complete recovery, 6 patients had neurological deficits, and 3 patients died ($P < 0.01$).

The authors concluded that anticoagulation with dose-adjusted intravenous heparin is an effective treatment in patients with CVT and that ICH is not a contraindication to heparin treatment in these patients. The study was criticized for its small sample size, use of an outcome measure that was not previously validated and a significant delay from symptom onset to the initiation of therapy. This was followed by another double blind, placebo-controlled multicenter trial. Patients (n=59) were randomized to subcutaneous nadroparin (n=30) and matching placebo (n=29) for 3 weeks (double-blind part of trial), followed by 3 months of oral anticoagulants for patients allocated nadroparin (open part). After 3 weeks, 6 of 30 patients (20%) in the nadroparin group and 7 of 29 patients (24%) in the placebo group had a poor outcome, defined as death or Barthel Index score of <15. After 12 weeks, 4 of 30 patients (13%) in the nadroparin group and 6 of 29 (21%) in the placebo group had a poor outcome [33]. Authors concluded that patients with cerebral sinus thrombosis treated with anticoagulants (low-molecular-weight heparin followed by oral anticoagulation) had a favorable outcome more often than controls, but the difference was not statistically significant. Anticoagulation proved to be safe, even in patients with cerebral hemorrhage. A recently published Cochrane review used these two trials for meta-analysis and concluded that based upon the limited evidence available, anticoagulant treatment for cerebral sinus thrombosis appeared to be safe and was associated with a potentially important reduction in the risk of death or dependency which did not reach statistical significance [34].

Endovascular treatment

Indications for Endovascular Treatment

Intrasinus thrombolysis and/or mechanical thrombectomy should be only considered for a limited number of the patients with defined critheria:

Refractory to medical regimen

Refractoriness to non-invasive treatments is the most agreed indication of thrombolysis. (Class IIb, level of evidence C). Refractoriness could be defined in clinical and radiological aspects. Clinical failure can be defined as progression of focal or generalized neurologic deficits, and/or unresponsive high intracranial pressure (ICP). Persistent headache, deepening coma, progressive weakness or uncontrolled seizures can be examples. Radiological refractoriness can be defined as expansion of infarcts in CTs or MRIs, and/or absence of signs of recanalization in CTA, MRA or DSA. Obviously, this indication should be considered at least afew days after initiation of anti-coagulations [21, 35].

Early Poor Prognostic Factors

Although pharmacological or mechanical thrombolysis were advocated mostly in patients with progressive course despite adequate anti-coagulation, there have been some arguments that adopting this policy may deprive some patient s from potentially life-saving therapeutic modalities. Some researchers proposed some early poor prognostic factors such as coma at the time of admission or predominant involvement of deep cerebral veins can be used for indications of the early endovascular interventions [21, 35].

Contraindication for Endovascular Intervention

Most authorities are against administration of pharmacological and mechanical intervention in the patients with impending cerebral herniation. For the patients with very high ICP presented with unequal pupils, abnormal postures or breathing rhythms, bilateral Babinski's sign and other signs of herniation, urgent action to decrease ICP rather than thrombolytic measures should be carried out [21,35]. Hyperventilation, Intravenous mannitol or 3% saline and Hemicraniectomy could be used sequentially [36].

Technique

Both common femoral vein and internal jugular vein can be used as access site, but common femoral vein seems to be more convenient for both patient and neuro-interventionist. Introducer sheath (6 or 7 F) is inserted to common femoral vein and then guide catheter (5 or 6F) advanced into inferior vena cava. Catheter can be navigated from inferior vena cava to superior vena cava by a rotation maneuver in right atrium. Guide catheter then advance to internal jugular vein and parked in jugular bulb. A retrograde venogram is obtained. A microcatheter is loaded with micro-guide wire (0.014 inch) and advanced to thrombus site. Thrombus is gently tried to be mechanically disrupted and then micro-guidewire is withdrawn and thrombolytic administration is started [37].
Both Urokinase and recombinant tissue plasminogen activator (rTPA) have been used. In most reports a bolus dose of thrombolytic agent was injected and then thrombolytic agents was infused through the catheter for hours or even days.

rTPA Dose
Frey *et al*.[37] advocated a loading dose of rtPA into the clot at 1 mg/cm, followed by continuous intrathrombus infusion at 1 to 2 mg/h, simultaneous with intravenous heparin infusion.
In Kim and Suh series, thrombolysis was started with injection of 10 mg of rTPA over 10 minutes, then by a continuous infusion of 50 mg in 3 hours, and finally a continuous infusion at 5 mg per hour until complete thrombolysis or a total dose of 100 mg per day had been reached. Repeat thrombolysis was tried the following day if complete recanalization did not occur at 100 mg per day [38]. Mohammadian *et al*. advocated rTPA injection with 30 mg/3o minutes single infusion schedule [39].In Sood *et al*. case successful thrombolysis with a bolus of 10 mg rt-PA injection followed by 1 mg/hr infusion was performed [40].

Urokinase dose
Li G *et al*, 2013 underwent urokinase 100 to 1500 × 10 IU intravenous sinus injection via a jugular catheter [41]. In Kothur K, case thrombolysis was performed by bolus 100,000 units urokinase injection followed by continuous 70,000 units/hour urokinase infusion [42] .In Guo XB *et al*.[43] 2012, series A microcatheter was put in the superior sagittal sinus or straight sinus and thrombolysis was performed with continuous urokinase (42,000 U/h, total 1,000,000 U/day) infusion.
In Xia ZK, series the initial dose of urokinase was 2000 - 4000 U/kg/24 hour: the bolus dose was 20 000 - 40 000 U (given in 15 - 30 minutes), and the remainder was infused through the first day. Thereafter, urokinase 2000 U/kg/24 hour was infused for 3 to 7 days [44].
To sum up, it has been accepted that if the patient's clinical condition aggravates despite adequate anticoagulation, thrombolysis can be a good therapeutic option. But the optimal administration route (local or intravenous), thrombolytic agent (urokinase or alteplase) and their dose are remained to be elucidated [48].
Administered bolus doses were 80000-250000 IU Urokinase or 10-25 mg rTPA and infusion rates were 20000-150000 IU/hour for urokinase and 1-5 mg/hour for rTPA [37, 45]

Complication
The risk of significant bleeding is increased by thrombolysis in comparison to heparin. Mortality for cerebral bleeding is about 0.5% [46]. Evolution or aggravation of intracerebral hemorrhage after thrombolysis was re-

ported in 2 out of 12 in Frey *et al* series [37] but none of patients in Mohammadian *et al*. series [39].

Mechanical thrombectomy

Mechanical thrombectomy for CVST has been conducted by different types of catheters, balloons, stents or snares [1-18, 47-63].

Rheolytic thrombectomy

Rheolytic thrombectomy is based upon Bernoulli's principle stating an increase the velocity of fluid in a vessel cause a decrease in pressure. This principle was applied in Angiojet Rheolytic catheter by induction of vacuum with infusion of very high-speed saline. The AngioJet catheter is an over-the-wire catheter with multiple outflow pores for about 2500-9000 psi saline jet and one-inflow lumina for aspiration of the thrombus [47, 48]. Clot disruption can be performed by micro-guidewire movements and suction caused by rheolytic catheter. Several case reports [1-3, 47-49] and case series [51, 52] have be [4, 5] en attest to efficacy of rheolytic thrombectomy.

Balloon Angioplasty and/or Stenting

Balloon catheter can be dexpanded to macerate the clot [6, 53] or be inflated distal to the clot and pulled back to aspirate it [7, 54]. Angioplasty can also dilate the stenotic lesions which predispose venous thrombosis [1]. Using compliant microballoon catheters, undersizing of the balloon and low-pressure inflation is recommended for decreasing the risk of vascular injury [8, 9, 55, 56]. Stenting of the site of clot formation can be performed after angioplasty [10, 57].

Manual Aspiration

Instead of using mechanical devices, there is a report of manual aspiration of thrombus with relatively large catheters in addition to intrasinus infusion of tPA. Manual aspiration was safe and efficacious in a small group of patients with CVST who had progressive deterioration despite early anticoagulation [18, 64].

Craniotomy

Decompressive surgery may be life saving also in patients with lesions producing mass-effect and clinical deterioration.
Until recently, the information on decompressive surgery in CVT was limited to case reports and results from small series from referral centres, which are difficult to generalise [36, 65-69].

Conclusion

The variable natural history of the CVT is a great obstacle to consider straightforward directions for initiating of intrasinus thrombolysis or mechanical clot disruption. The diameter of the cerebral dural sinuses are larger and consequently venous thrombi are bigger [1].Accordingly intrasinus thrombolysis needs a considerable amount of time in comparison to intraarterial thrombolysis. In contrast, mechanical thrombectomy has an immediate effect and can decrease the intracranial pressure much more promptly [9].The rate of hemorrhagic transformation is higher in cerebral venous thrombosis in comparison to arterial stroke. Meanwhile, the thicker dural wall of the sinuses decreases the risk of vessel dissection. All of the above-mentioned rationalization favors the mechanical thrombetomy in comparison to intrasinus thrombolysis alone. In combined pharmacological and mechanical thrombectomy the dose of thrombolytic drug and the duration of infusion can be decreased due to increased surface area of thrombus exposed to the drug [8, 11]. Higher cost of devices is against the mechanical thrombectomy.
To sum up, it has been accepted that if the patient's clinical condition aggravates despite adequate anticoagulation, thrombolysis can be a good therapeutic option. But the optimal administration route (local or intravenous), thrombolytic agent (urokinase or alteplase) and their dose are remained to be elucidated. To best of our knowledge, there has been no clinical randomized trial comparing the effect of intrasinus thrombolysis and/or mechanical thromectomy to standard-of-care anticoagulation.

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