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Good Outcome Following Catastrophic Cerebral Sinus Thrombosis due to Heparin-Induced Thrombocytopenia: Case Report and Review of Literature

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Abstract

Introduction: Systemic anticoagulation with heparin is the primary treatment of acute cerebral venous sinus thrombosis (CVT). Treatment of CVT due to heparin-induced thrombocytopenic thrombosis (HITT) is a management conundrum. In the acute phase when continuous parenteral anticoagulant is necessary, argatroban, a direct thrombin inhibitor, has been used for HIT-associated thrombosis. In cases of catastrophic CVT with severe neurologic compromise or when anticoagulation does not result in clinical improvement, the safety and efficacy of combination therapy with systemic anticoagulation, directed thrombolysis and thrombectomy is unknown.

Case Report: We report a patient with catastrophic CVT due to HIT presenting with unresponsiveness. CT brain showed intracranial hemorrhage, cerebral edema, cerebral herniation and extensive cerebral sinus thrombosis. She was treated initially with argatroban and subsequently had decompressive craniectomy for intracranial hypertension. Cerebral angiography showed persistent sinus thrombosis despite systemic anticoagulation, endovascular thrombolysis and mechanical thrombectomy. Continuous intra-sinus alteplase infusion was started concurrently with systemic argatroban infusion x 24 hours. The patient made a remarkable recovery and achieved a mRS=1 in 6 months.

Conclusion: Aggressive multimodal therapy with systemic anticoagulation, continuous intra-sinus thrombolytic infusion, mechanical thrombectomy and neurointensive treatment is a reasonable management option for patients with catastrophic CVT who failed initial anticoagulation therapy. Argatroban is an effective alternative when heparin is contraindicated.

Keywords: Cerebral venous thrombosis; Heparin induced thrombocytopenia; Argatroban, Intrasinus thrombolysis; Mechanical thrombectomy

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Introduction

Cerebral venous thrombosis (CVT) affects approximately 5 people per million annually, representing about 0.5% of all strokes It most commonly affects reproductive aged women [1-4]. The major risk factors include any conditions that promote pro-thrombotic state including genetic pro-thrombotic diseases, pregnancy, oral contraceptives, malignancy, infection and trauma [1-5]. Pathogenesis of CVT is due to venous congestion that can cause impaired cerebrospinal fluid absorption, venous infarction, cerebral edema, and hemorrhage [3].

Headache is the most common symptom of CVT, present in more than 90% of the cases. It is usually a diffuse progressive headache, however other types of headaches including migrainous or thunderclap headaches have been reported [1,3-5]. Isolated headache without symptoms of increased intracranial pressure represent a significant number of the patients [6,7]. Other common signs and symptoms include papilledema, focal neurological deficit, seizure, altered mental status, and coma [1,3-5]. Cavernous sinus thrombosis can present with ocular symptoms from cranial nerve involvement. The superior sagittal and left transverse sinuses are the most frequent site of

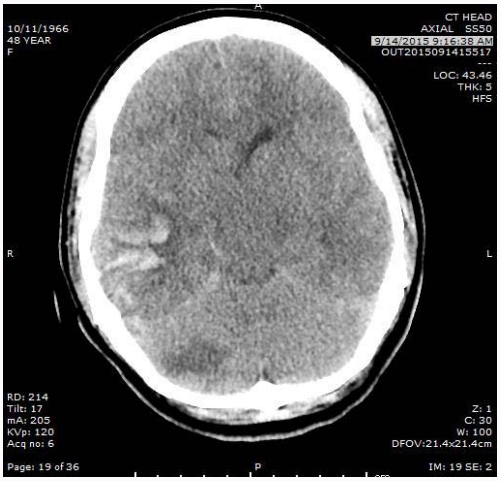

Figure 1: CT brain showing R temporal lobar hemorrhage and R cerebellar infarction.

involvement [1,5].

Neuroimaging is the main mode of diagnosis in CVT. Although Computed Tomography (CT) is the first line imaging modality in patients with clinical findings consistent with neurovascular diseases, it has limited use in diagnosis of CVT. A filling defect known as the "empty delta sign" was observed with contrast enhanced CT in 28.6% of the cases in one study where it was associated with poor prognosis [8]. The average delay in diagnosis is 7 days from the onset of the symptoms, and early diagnosis and treatment is essential in improving prognosis [4]. The gold standard is a combination of Magnetic Resonance Imaging (MRI) and Magnetic Resonance Venography (MRV). Findings equivalent to the "delta sign" can be observed on MRI, and age of thrombus can be estimated based on signal characteristics on different sequences. Due to thrombus age dependent signal intensity, MRI alone may miss the diagnosis and should be supplemented with MRV when suspicious of sinus thrombosis [1,3-5,9-11]. Some authors report that MRV is more sensitive than CTV, while others report that they are equivalent in detection of the disease. While CTV can be limited by bony artifact and requires IV contrast and added radiation exposure, MRV is more sensitive to motion artifact, requires more time to perform, and is more costly, and less available [9-13]. Although digital subtraction angiography can aid in the diagnosis and demonstrate additional flow characteristics of the cerebral circulation, it is neither necessary nor first line imaging study for the diagnosis, and MRI has the advantage of differentiating an occluded sinus from congenital hypoplasia [14-17].

Treatment of CVT usually involves anticoagulation and management of neurologic sequelae, such as seizure, coma, and intracranial hypertension, when present. Given the need for anticoagulation, control of intracranial pressure is primarily non-surgical. Anticoagulation is necessary to manage the overall prothrombotic state and to prevent further progression of thrombosis while physiologic recanalization of the occludedcerebral venous outflow occurs. Benefits of anticoagulation are weighed against the risk of expanding intracranial hemorrhage, especially in those patients with intracranial hemorrhage on presentation. Existing studies on effectiveness of anticoagulation in the setting of CVT are limited by their power and study design due to the severity and rarity of the disease [1,3-5]. Meaningful randomized control trials would require at least 300 patients, which has not yet been performed [3]. Although not statistically significant, two existing randomized controlled trials and various observational trials suggest overall safety and potential benefits of anticoagulation regardless of presence or absence of ICH [4,18-26]. Based on this evidence, American Heart Association/American Stroke Association and The European Federation of Neurological Societies recommend anticoagulation with heparin during the acute phase of CVT followed by an oral Vitamin K antagonist (VKA) for three to six months [5,6]. Although, intravenousheparin has historically been the primary anticoagulant, some recent data suggest that low molecular weight heparin (LMWH) offers equivalent or better treatment, with decreased hemorrhagic complications, simplified dosing, and less occurrence of thrombocytopenia [27,28]. A randomized controlled trial of 52 patients revealed no difference in outcome between heparin and LMWH [29].

Recent concerns over possible publication bias resulting in underestimation of adverse effect of anticoagulation in treatment of CVT have surfaced. A comprehensive literature review of studies published between 1999 and 2013 suggests that anticoagulation with heparin or LMWH offers statistically significant decrease in mortality at the cost of increased major bleeding, intracranial hemorrhage and thrombocytopenia, though authors were not convinced by the statistical significance due to publication bias of only positive outcomes [30].

Non-vitamin K antagonist oral anticoagulants (NOAC) (dabigatran, rivaroxaban, apixaban, edoxaban) and argatroban (an IV direct thrombin inhibitor) have demonstrated safety and efficacy in treatment of peripheral Deep Venous Thrombosis (DVT) and Pulmonary Embolism (PE) with reduced major bleeding risks compared to VKA. In a small retrospective series, Rivaroxaban was shown to be effective after initial heparin treatment in the acute phase of CVT [38]. Other case reports support similar use of rivaroxaban in patients with antiphospholipid syndrome and Crohn's diseases [34,35]. Dabigatran has been shown to be effective and safe in place of VKA after initial heparin or LWMH treatment in 15 patient case series [36]. Argatroban was successfully used in a patient with CVT who was resistant to heparin [39]. Lepirudin was also reported to be used in a patient with heparin induced thrombocytopenia (HIT) and CVT [40]. Despite these small series to suggest these drugs are safe and effective in treatment of CVT [31-40], VKA remains standard of care for eligible patients. Given the success of these drugs in parallel, non-cranial disease, and the ongoing development of adequate reversal agents, further study is warranted to address their in CVT.

Cerebral venous thrombosis remains a dangerous disease, even with standard therapies. Between 9% to 13% of CVT patients deteriorate despite anticoagulation treatment. Treatment failure may result from sub therapeutic anticoagulation, or failure of anticoagulation despite adequate dosing, where serum assay data is available [5]. Although no randomized controlled trials have been performed to demonstrate safety and efficacy of thrombolysis in CVT, thrombolysis can be considered for patients who are clinically deteriorating despite adequate anticoagulation treatment [1,3-5,42,43]. Available thrombolytics include urokinase, streptokinase and recombinant tissue plasminogen activator (rtPA). A systematic review of thrombolytics in CVT published between 1966 and 2001 suggested that thrombolytics are reasonably safe. They included 72

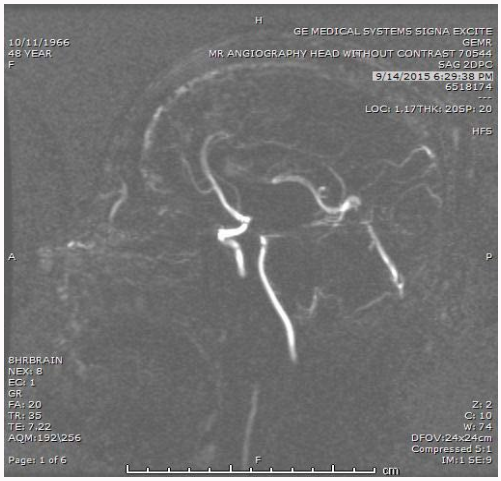

Figure 2: MR angiogram showing absent signal along superior sagittal , transverse and sigmoid sinus on the right.

studies with a total of 169 patients who were most commonly treated with locally infused urokinase [44]. Another systematic review of 15 studies with a total of 156 patients published before 2010 showed that thrombolytics are associated with non-negligible incidence of major bleeding [45]. A multicenter, prospective, randomized, open-label, blinded endpoint trial of 164 patients who have poor prognosis defined by presence of mental status disorder, coma, intracranial hemorrhagic lesion or thrombosis of the deep cerebral venous system is currently ongoing [46]. Most studies have used either anticoagulation or thrombolytics, though there has been a surge of reported cases where combination of thrombolysis and anticoagulation were utilized with positive outcomes.

Combination of rtPA with heparin has been used in the past due to its possible benefit of short half-life of 7-8 minutes, selective clot lysis compared to other thrombolytics and reduced hemorrhagic risk [47]. Two studies involving combination therapy showed faster and more frequent complete recanalization with the combination therapy compared to that of heparin alone, but it had higher incidence of bleeding, especially with existing hemorrhage. The study was also inconsistent in showing a correlation between recanalization and clinical improvement [48,49]. Similarly, transvenouscatheter directed thrombolysis with urokinase has been successfully used with concurrent anticoagulation with heparin [50-53]. Overall, the combination of thrombolysis with concurrent systemic anticoagulation is a possible treatment option in patients who are worsening despite anticoagulation. Clinical judgement must be made case by case due to lack of quality literature on efficacy and safety of the treatment.

Mechanical thrombectomy is a final treatment option when patients are not responsive to anticoagulation and thrombolysis. A systematic review of literature published between January 1995 and February 2014 where all cases of CVT were treated with thrombectomy with or without thrombolysis reported an 84% positive outcome, suggesting that mechanical thrombectomy is a relatively safe treatment option for patients who failed anticoagulation and thrombolysis treatment. Although rheolytic catheter thrombectomy device AngioJet was most commonly used (40%), it was associated with lower rate of complete recanalization and good outcome [54]. The Merci retrieval device and Penumbra systems are other options, but evidence of their efficacy and safety are only anecdotal [5]. Balloon assisted thrombectomy is another option. It is thought to reduce washout of fibrinolytic agents and occurrence of hemorrhage [5]. Regardless, 10% of the patients had new or worsening intracerebral hemorrhage, which is a major risk of the treatment.

The largest cohort to date, including 624 CVT patients, demonstrated an 8% mortality, either from CVT or other causes. Risk factors associated with poor prognosis were male gender, age over 37 years, coma, mental status change, intracranial hemorrhage on admission, thrombosis of the deep cerebral venous system, central nervous system infection and cancer [4]. We report a patient with hemorrhagic presentation of cerebral venous sinus thrombosis secondary to heparin-induced thrombocytopenic thrombosis (HITT) after craniotomy, with rapid clinical deterioration to deep coma despite systemic anticoagulation, who made a remarkable recovery after combination mechanical thrombectomy, continuous intra-sinus tPA infusion, and concurrent systemic argatroban infusion.

Case

A 48 year old previously healthy female presented to a separate institution with nausea and headaches one year status post status post cyber knife surgery of a 4.2 cm parafalcine meningioma. MR imaging evaluation showed increased cerebral edema around the treated meningioma, and she was admitted for steroid treatment and observation. Five days after admission, she became acutely unresponsive and underwent emergent CT imaging demonstrating an acute right cerebellar ischemic infarct and a right temporal intraparenchymal hemorrhage (Figure 1), for which she underwent emergent right temporal craniotomy for hematoma evacuation. Postoperatively, she remained intubated, opening her eyes to noxious stimulation, localizing with her right upper extremity, withdrawing her lower extremity, and hemiplegic on the left.

A post-operative head CT without contrast revealed only expected post-surgical changes, and MRI/MR Angiography (Figure 2) revealed superior sagittal sinus thrombosis extending into the right transverse, sigmoid and internal jugular vein, with evidence of early restricted diffusion without FLAIR changes in the bilateral parietal and temporal cerebral cortex concerning for developing venous infarction. She was started on heparin drip and transferred to our institution for higher level of care. Given the acuity of onsent, MRI findings, and her poor neurological exam despite anticoagulation, she was taken for emergent transfemoral cerebral angiogram and transvenous mechanical thrombectomy and thrombolysis of the superior sagittal sinus, right transverse sinus, sigmoid sinus, and right jugular vein with aspiration thrombectomy followed by infusion of 6 mg of tPA into the superior sagittal sinus. Continuous tPA infusion into the cerebral venous sinus system was not performed at that time because of concern for hemorrhagic complications related to craniotomy performed earlier the same day. Flow was successfully reestablished at the time of thrombectomy and she was transported back to the neurosurgical ICU where an intraparenchymal monitor (Licox) was placed without complication. Serum laboratory evaluation revealed thrombocytopenia, and all heparin products were discontinued and anticoagulation was transitioned to argatroban.

Unfortunately, 3 days after endovascular treatment, she developed elevated intracranial pressure and deterioration of neurological examination to include loss of all motor function and brainstem reflexes, despite therapeutic anticoagulation. Emergent

non contrast repeat head CT demonstrated new hyperdensity consistent with recurrent cerebral venous sinus occlusion, without radiographic evidence of new or worsening hemorrhagic or ischemic infarction. She was taken for emergent repeat endovascular treatment, repeat transfemoral diagnostic cerebral angiography and transvenous thrombectomy, followed by placement of a micro catheter in the posterior superior sagittal sinus for continuous tPA infusion. She received10 mg intra-sinus bolus of tPA followed by 50 mg infusion over 3 hours followed by 2.5mg/hr continuous infusion of intravenous sinus tPA. The tPA infusion was continued for 24 hours and maintained concurrently with argatroban infusion for therapeutic anticoagulation. A CT scan of the brain post sinus catheter placement during infusion did not demonstrate hemorrhagic or ischemic complications.

Her cerebral edema, intracranial hypertension, and venous infarction were managed with hypertonic saline, mannitol, and dexamethasone, and she underwent continuous EEG monitoring in the ICU for concern of subclinical status epilepticus. Her mean arterial pressure was supported with vasopressors to maintain cerebral perfusion. Her clinical course was further complicated by sepsis and electrographic evidence of seizure managed with antibiotic therapy and antiepileptic mediations. The argatroban was ultimately transitioned to coumadin with INR goal between 2-3. She eventually underwent tracheostomy and PEG tube placement. After inpatient rehabilitation, she was eventually discharged back to home. On her most recent follow up at 1 year post-discharge, she has a near normal neurological exam, living independently, with a persistent lefthomonymous hemianopsia, and mRS of 1.

Discussion

Systemic anticoagulation is the primary treatment of CVT; however, thrombolysis and thrombectomy are indicated in cases of severe neurologic compromise and / or where anticoagulation does not result in clinical improvement. The main risk of treatment in CVT is major intracerebral hemorrhage, and benefits of any of the treatments are yet to be supported by randomized controlled trials [1-4]. Thus, more data on treatments of CVT is necessary to develop a treatment algorithm for CVT.

We present a case of CVT that was managed with concurrent systemic anticoagulation with argatroban and continuous catheter directed infusion of tPA, in addition to thrombectomy. Two unique aspects of our case are use of argatroban as an anticoagulant during an acute phase of CVT, and the concurrent use of systemic anticoagulation and intracerebral sinus tPA infusion.

NOACs have been used in treatment of CVT in place of VKA after initial heparin therapy based on case reports [31-38], but reports of their use as the primary anticoagulant during the acute phase of CVT are limited. There is only single reported use of NOACs in place of heparin and LMWH in acute phase of CVT in a patient who was resistant to heparin [39]. Our case is the second reported case with use of argatroban as an anticoagulant during an acute phase of CVT. These two cases show some evidence that argatroban is an alternate agent for systemic anticoagulation in the setting of heparin resistance or HIT.

There are two studies involving combination therapy of systemic anticoagulation and thrombolysis. The first study included 9 patients who received transfemoral direct thrombolysis treatment with a rapid injection of 10 mg alteplase followed by continuous infusion until complete recanalization or a total dose of 100 mg per reached. The procedure was repeated if complete recanalization did not occur. The range of a total alteplase dosage was between 50 mg to 300 mg with average of 135 mg. Four patients received initial heparin treatment, while all 9 patients received post-procedure warfarin treatment, which 7 of them continued for 3 months. During the treatment, two patients had oozing at a puncture site and intraperitoneal hematoma. All patients have shown some level of clinical improvement post-treatment [48].

The second study included 12 patients, 7 of whom had some type of hemorrhage somewhere in their the body, who received transfemoral direct thrombolysis with rtPA with a loading dose of 1mg/cm followed by continuous direct infusion at 1 mg/h to 2 mg/h until flow was restored with concurrent IV heparin dosed to reach PTT twice the control value. A total rtPA dose ranged between 23 mg to 128 mg with average of 46 mg. Symptoms improved in all patients except three, with one not improving and two patients having worsening hemorrhage. Although most patients improved clinically, already existing hemorrhage worsened with treatment, limiting its safety in this population [49].

Similarly, transfemoral direct thrombolysis with urokinase has been successfully used with concurrent anticoagulation with heparin with PTT twice the control value [50-53]. The first study included five patients who were treated with continuous urokinase infusion of 3,500 units/kg/hr for six to nine hours following 7,500 units of IV heparin, and then the combination therapy (30,000 units/day to 40,000 units/day by continuous IV heparin; urokinase, 3,000 units/kg every six to eight hours) was continued for 2-6 days [50]. The second study included seven patients who were treated with constant urokinase infusion through peripheral IV with total infusion times ranging from 88 to 244 hours (average 163 hours) while being anticoagulated with IV heparin with PTT 1.5 to 2 times the control. The loading dose ranged between 80,000 and 250,000 [51].

Another case reported administration of 1,50,000 unit bolus of urokinase into the straight sinus followed by 1,00,000 unit/hr infusion twice 9 hrs apart while systemically anticoagulated with heparin. Infusion was stopped due to spontaneous retroperitoneal and psoas muscle hematoma after 20 hrs of treatment [52]. The last case reported an initial bolus of 250,000 U of urokinase into superior sagittal sinus in a pulse-spray manner over 2 hours followed by a constant infusion at a rate of 80,000 U/h for total of 165 hours, with a total urokinase dose of 13.79 million units [53]. The patient was concurrently systemically anticoagulated with IV heparin with a loading dose of 5000 U and a maintenance dose of 1000 U/h [53].

Our case along with other reported studies show that the combination of thrombolysis with concurrent systemic anticoagulation is a reasonable treatment option for patients who worsening despite anticoagulation. Our experience also shows that argatroban is a reasonable alternative to heparin for anticoagulation when heparin is contraindicated.

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