A review of therapeutic strategies for the management of cerebral venous sinus thrombosis

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Object. Although initially described in the 19th century, cerebral venous sinus thrombosis (CVST) remains a diagnostic and therapeutic dilemma. It has an unpredictable course, and the propensity for hemorrhagic infarction produces significant consternation among clinicians when considering anticoagulation. It is the purpose of this review to analyze the evidence available on the management of CVST and to provide appropriate recommendations.

Methods. A thorough literature search was conducted through MEDLINE and PubMed, with additional sources identified through cross-referencing. A classification and level of evidence assignment is provided for recommendations based on the American Heart Association methodologies for guideline composition.

Results. Of the publications identified, the majority were isolated case reports or small case series. Few prospective trials have been conducted. Existing data support the use of systemic anticoagulation as an initial therapy in all patients even in the presence of intracranial hemorrhage. Chemical and/or mechanical thrombectomy, in conjunction with systemic anticoagulation, is an alternative strategy in patients with progressive deterioration on heparin therapy or in those who are moribund on presentation. Mechanical thrombectomy is probably preferred in patients with pre-existing intracranial hemorrhage.

Conclusions. Effective treatments exist for the management of CVST, and overall outcomes are more favorable than those for arterial stroke. Further research is necessary to determine the role of individual therapies; however, the rarity of the condition poses a significant limitation. (DOI: 10.3171/2009.8.FOCUS09154)

KEY WORDS • sinus thrombosis • thrombectomy • thrombolysis • tissue plasminogen activator • angioplasty

Cerebral venous sinus thrombosis has remained a diagnostic and therapeutic dilemma since its initial description by Ribes in 1825.6 He described a 45-year-old man who had suffered a 6-month course of headache, seizures, and delirium before succumbing to his disease. An autopsy revealed thrombosis of the SSS, straight sinus, and cortical veins. Since then, numerous publications, largely in the form of case reports and small clinical series, have been added to the literature; however, a consensus regarding the appropriate treatment remains elusive.

As a rare cause of stroke, CVST is estimated to occur with an incidence of 2–4 per million per year.57,66 In contrast to arterial infarction, CVST most commonly affects those of middle age with a female predominance.50,61 The lack of pathognomonic features obscures its presentation so that the correct diagnosis is initially reached in < 60% of cases.61 Headache represents the most common symptom (80–90%), with a usual pattern similar to that of benign intracranial hypertension. Other features include seizures, focal neurological deficits, and decreased mental status.7,21,50,57,63 Identification is further complicated by the subtle nature of its signs on noncontrast CT, and definitive diagnosis requires MR imaging, MR angiography and venography, or digital subtraction angiography.

Although described as carrying an extremely grave prognosis,35 the disease’s clinical course varies considerably, with reported rates of dependency and death ranging from 8 to 40%,28,30,44,45,63,72 Factors commonly found to predict a poor outcome include male sex, older age, coma, hemorrhage, infection of the CNS, and cancer.23,30,36 While the presence of such factors can provide some indication of the possible outcome, reliable prediction is impossible—which in turn complicates therapeutic strategies. When infection and trauma represented the most common causes, therapy involved watchful waiting and antibiotics. And while trauma remains a frequent

Abbreviations used in this paper: CVST = cerebral venous sinus thrombosis; ICH = intracranial hemorrhage; ICP = intracranial pressure; ISCVT = International Study of Cerebral Vein and Dural Sinus Thrombosis; LMWH = low-molecular-weight heparin; NS = not significant; PTT = partial thromboplastin time; SSS = superior sagittal sinus.
cause, aseptic thrombosis occurring as a result of a multitude of factors (puerperium, malignancy, dehydration, oral contraceptives, and thrombophilia) is now more common than infection. This change in etiology has shifted treatment to systemic anticoagulation, endovascular thrombectomy (either chemical or mechanical), and occasionally surgical decompression or open thrombectomy. Despite evidence supporting the efficacy of anticoagulation, clinicians remain apprehensive about its use given the concomitant propensity for ICH, which occurs in ~40% of affected patients. It is our purpose in this paper to analyze existing evidence and provide recommendations for the most appropriate course of management, with a focus on the role of endovascular modalities. Classification of the recommendations and levels of evidence are assigned based on the American College of Cardiology (ACC) and the American Heart Association (AHA) Methodology Manual for ACC/AHA Guideline Writing Committees.

Systemic Anticoagulation

Lyons described the first successful use of systemic heparin in 1941, when it along with antibiotics was used to treat 2 cases of infectious cavernous sinus thrombosis. Subsequently, numerous reports were published, including one by Bousser et al. who retrospectively reviewed 38 cases of CVST. Twenty-three patients had been treated with heparin, all of whom experienced improvement, with 19 making a complete recovery. The correlation of treatment with outcome was not attempted given the retrospective nature of the study. However, not a single death occurred in those receiving anticoagulants, and the majority of these patients experienced a dramatic clinical improvement the day after treatment was initiated. Given these findings, the authors concluded that heparin was the treatment of choice in any patient experiencing clinical deterioration, including those with hemorrhagic infarcts. To better elucidate the effect of treatment on outcome, Einhaupl and colleagues conducted a randomized, prospective placebo-controlled trial of heparin therapy. Although enrollment was intended to include 60 patients, the trial was stopped prematurely after a planned interim analysis of the first 20 patients (10 in each arm) revealed a significant difference in outcomes. Outcome was assessed using a newly designed, unvalidated sinus thrombosis severity scale (0 = asymptomatic, 9 = dead). Heparin was administered as a bolus followed by continuous infusion with a target PTT of 80–100 seconds. After 21 days of treatment, the treatment group had an average score of 0.6 versus 3.9 for the control group (p < 0.005) on the above described scale. At the 3-month follow-up 8 patients in the treatment group had completely recovered and 2 had minor neurological deficits. Conversely, in the control group only 1 patient made a complete recovery, 6 had neurological deficits, and 3 died (p < 0.01). One of these deaths was believed to be due to a pulmonary embolism, a not infrequent complication of sinus thrombosis, occurring in up to 11% of patients; note that systemic heparinization provides the additional benefit of reducing this risk.

With regard to ICH, 3 patients in the treatment group and 2 in the control group had a hemorrhage on the institution of therapy; however, no new cases of hemorrhage occurred in the heparin group. Three patients in the control group experienced a new (2 patients) or worsened (1 patient) hemorrhage. Included in Einhaupl and colleagues’ report was a retrospective review of patients treated at the same institution but outside of the clinical trial. Among patients with an ICH at the start of therapy, there was a 15% mortality rate (4 of 27 patients) in those receiving heparin versus 69% (9 of 13 patients) in the group treated without anticoagulation. While these data provided considerable support regarding the safety and efficacy of heparinization, the study was criticized for several reasons: In addition to its small sample size, there was a significant delay from symptom onset to the initiation of therapy (~30 days in each group). The authors also used an outcome measure that had not been previously validated.

In an attempt to alleviate these deficiencies, de Bruijn and Stam conducted the second randomized, placebo-controlled trial of anticoagulation for CVST. Instead of unfractionated heparin, these authors chose to use LMWH in the form of nadroparin. This usage was justified based on trials demonstrating equitable results for LMWH and intravenous unfractionated heparin in the treatment of extracranial deep venous thrombosis and pulmonary embolism. Based on the treatment effect observed in the earlier study, a sample size of 60 patients was determined to be appropriate. Patients received 180 antifactor Xa U/kg/24 hrs (the treatment dose of deep venous thrombosis) or placebo for 3 weeks following diagnosis, after which the nadroparin group received oral anticoagulants for an additional 10 weeks. Following 3 weeks of therapy, 20% (6 patients) of the LMWH group, as compared with 23% (7 patients) in the control group, had a poor outcome (Barthel Index score < 15). At 12 weeks after the start of therapy, 13% (4 patients) of the treatment group versus 20% (6 patients) of the control group had a poor outcome—that is, death or an Oxford Handicap Scale score ≥ 3 (NS). Seven percent (2 patients) of the nadroparin group died versus 13% (4 patients) of the control group (NS); 1 patient in the former group died of a pulmonary embolism. No new episodes of ICH occurred; however, 1 patient in the treatment arm did suffer from a significant gastrointestinal hemorrhage. Although not significant, there was a trend toward improved outcomes in the treatment group, and this trend further reaffirmed the safety of anticoagulation in the setting of ICH. Subsequently, a meta-analysis of these 2 studies was performed by the Cochrane Collaboration, with those in the initial trial being reclassified according to standard outcome measures. Under these conditions there was a 0.33 relative risk of death (95% CI 0.08–1.21) and a 0.46 risk of death or dependency (95% CI 0.16–1.31) for those treated with anticoagulation. The patients also maintained the additional benefit of deep venous thrombosis and pulmonary embolism prevention. Overall, the authors concluded that anticoagulation was safe and associated with a nonsignificant, yet potentially important, improvement in outcome.

More recently, investigators in the International Study of Cerebral Vein and Dural Sinus Thrombosis (ISCVT), an observational study, found that 83% of patients under-
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went anticoagulation with either unfractionated or intravenous heparin at therapeutic dosages. Although a trend toward improved outcomes in the anticoagulation group was found (12.7% dead or dependent in the anticoagulation group vs 18.3% in the control group), the difference was not significant. Despite the lack of definitive evidence, multiple reviews and the recently published European Federation of Neurological Societies (EFNS) guidelines continue to support anticoagulation's safety and probable efficacy in CVST (Class IIa, Level B). Given the rarity of this condition, it is estimated that a trial enrolling 300 patients would be necessary to statistically confirm the treatment effect as determined by the Cochrane review.

Interventional Therapies

Although systemic anticoagulation appears to provide considerable improvement over the more conservative method of watchful waiting, there are some patients in whom it is insufficient. Consequently, several additional modalities have been used to facilitate recanalization and symptomatic improvement in this patient population. Bolstered by the initial successes of these treatments, clinicians have, in some instances, used them as primary modalities in patients not presenting in extremis; however, this approach is not widely supported, especially when considering thrombolysis.

Fibrinolytic Agents

In 1971 Vines and Davis described 10 patients with sinus thrombosis, 5 of whom received systemic urokinase. All 5 of these patients went on to demonstrate some improvement, with dramatic improvement occurring in 1 patient. Several other studies followed, but the results were inconsistent. Therefore, Scott et al. sought to improve the safety profile through local infusion. A 33-year-old man presented with progressive headache, but his condition quickly deteriorated to a comatose state. Computed tomography scanning and subsequent digital subtraction angiography revealed thrombosis of the superior, straight, and both transverse sinuses. The insertion of an ICP monitor revealed pressures ranging from 60 to 90 mm Hg. Given these findings, a frontal cranietomy was performed, and an infusion catheter was guided into the SSS through a small incision. After obtaining a sinogram, the local infusion of urokinase was instituted and continued for 8 hours, at which time a temporal hemorrhage was discovered on CT. Nonetheless, the patient experienced clinical improvement from decerebrate posturing to only mild dysphasia and short-term memory impairment. Despite persistent skepticism regarding the risk of hemorrhagic transformation, this early report provided the foundation for a novel avenue in the management of CVST.

Multiple case reports and small case series have subsequently appeared as therapy has moved from direct puncture to a transfemoral approach. Horowitz et al. treated a series of 13 patients via this method, 5 of whom had a pretreatment ICH. Clinical improvement occurred in all but 1 patient, and 8 had an excellent outcome. The patient without improvement had protein C deficiency with a more than 2-month history of sinus thrombosis, and it was believed that the clot was sufficiently organized, thereby decreasing the efficacy of fibrinolytics. Importantly, in no instance was there worsening of a preexisting ICH or any new cases of hemorrhage. Data in this study, while not conclusive, provided considerable support for the safety of local fibrinolytic infusions in sinus thrombosis. To better elucidate the role of this methodology, several trials and case studies have been conducted (Table 1), of which are particularly notable. Frey et al. treated 12 consecutive patients with combined tissue plasminogen activator and heparin. All 12 patients had significant symptoms without evidence of convalescence, and there was MR imaging evidence of hemorrhage in 7.

Therapy consisted of systemic heparin to achieve a PTT twice that of controls and local injection of tissue plasminogen activator throughout the clot (1-mg boluses at 1- to 2-cm intervals via transfemoral catheterization) followed by local infusion (1–2 mg/hour). Complete flow restoration occurred in 6 patients, partial recanalization in 3, and no improvement in 3. Clinically, 5 patients experienced a complete recovery and 6 had a symptomatic benefit. Two patients had worsening of a preexisting ICH, requiring surgical evacuation in 1. This latter patient made a full recovery; however, the patient who did not undergo surgical evacuation experienced a worsening language deficit requiring rehabilitation. Later, Wasay and colleagues performed a multianstitutional retrospective analysis comparing the local infusion of urokinase with systemic heparinization. Twenty patients were included in each treatment group, and segregation by centers was present because of policies regarding management. Seven hemorrhagic infarctions were present before treatment (4 heparin and 3 urokinase). The heparin group received a systemic dose titrated to a PTT between 50 and 60 seconds, while the urokinase group received an intranidal bolus of 250,000 U followed by a continuous infusion of 80,000 U/hour. Pretreatment characteristics were similar for the 2 groups. Neurological status at discharge was better in the urokinase group, with 16 versus 9 patients in the heparin group making a complete recovery (p = 0.019). Remarkably, no patient in the urokinase group experienced a worsening or new ICH, although 1 instance of subdural hematoma and 1 of retroperitoneal hemorrhage did occur.

While these studies were encouraging, a subsequent prospective trial by Stam et al. demonstrated less positive results. These authors chose 20 patients whose disease was presumed to have a poor prognosis; 14 had hemorrhagic infarcts at the time of enrollment, and the average initial Glasgow Coma Scale score for the entire group was 7.6. All patients except 1 were treated with heparin at the time of diagnosis, with thrombolysis administered as a bolus of urokinase (120,000–600,000 U) followed by a continuous infusion (100,000 U/hour). Fifteen of these patients also underwent mechanical thrombectomy with either a rheolytic or Fogarty catheter, and 1 patient did not receive treatment because of the treating physician’s inability to enter the sinuses. Nine patients had a complete recovery, 3 had a minor deficit, 2 had a severe...
<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>No. of Patients</th>
<th>Treatment Modality†</th>
<th>Complications</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scott et al., 1988</td>
<td>1</td>
<td>direct urokinase infusion</td>
<td>temporal hemorrhage</td>
<td>mild dysphasia, short-term memory impairment</td>
</tr>
<tr>
<td>Higashida et al., 1989</td>
<td>1</td>
<td>direct urokinase infusion</td>
<td>none</td>
<td>neurologically intact</td>
</tr>
<tr>
<td>Persson &amp; Lilja, 1990</td>
<td>1</td>
<td>direct streptokinase infusion, open thrombectomy</td>
<td>small cerebellar hemorrhage</td>
<td>quadripareisis w/ speech difficulties but independent</td>
</tr>
<tr>
<td>Barnwell et al., 1991</td>
<td>3</td>
<td>urokinase infusion</td>
<td>sepsis, bleeding from jugular puncture site</td>
<td>all clinically improved</td>
</tr>
<tr>
<td>Smith et al., 1994</td>
<td>7</td>
<td>urokinase infusion &amp; angioplasty (1)</td>
<td>infected femoral site, hematuria</td>
<td>all clinically improved, 1 required angioplasty, 1 required surgical repair of DAVF</td>
</tr>
<tr>
<td>Horowitz et al., 1995</td>
<td>13</td>
<td>urokinase infusion</td>
<td>PE, hematuria, groin hematoma, retroperitoneal hematoma, bacteremia</td>
<td>11 of 12 patients experienced good clinical outcome, 1 died of PE</td>
</tr>
<tr>
<td>Kim &amp; Suh, 1997</td>
<td>9</td>
<td>alteplase infusion</td>
<td>small intrapelvic hemorrhage, bleeding at femoral site</td>
<td>all clinically improved</td>
</tr>
<tr>
<td>Renowden et al., 1997</td>
<td>1</td>
<td>tPA infusion</td>
<td>none</td>
<td>recovery w/ minimal neurological deficit</td>
</tr>
<tr>
<td>D'Alise et al., 1998</td>
<td>1</td>
<td>urokinase infusion</td>
<td>none</td>
<td>symptomatic resolution</td>
</tr>
<tr>
<td>Frey et al., 1999</td>
<td>12</td>
<td>tPA infusion</td>
<td>worsening ICH (2);‡ groin hematoma</td>
<td>complete recovery (5), symptomatic improvement (6), treatment-associated worsened language deficit w/ functional recovery (1)</td>
</tr>
<tr>
<td>Kuether et al., 1998</td>
<td>1</td>
<td>urokinase infusion</td>
<td>none</td>
<td>intact except for a CN VI palsy</td>
</tr>
<tr>
<td>Philips et al., 1999</td>
<td>6</td>
<td>urokinase infusion &amp; mechanical thrombectomy (2)</td>
<td>hematuria, UTI, pneumonia</td>
<td>good to excellent outcome in all patients</td>
</tr>
<tr>
<td>Malek et al., 1999</td>
<td>1</td>
<td>mechanical thrombectomy, balloon angioplasty, stenting</td>
<td>none</td>
<td>neurologically intact</td>
</tr>
<tr>
<td>Opatowsky et al., 1999</td>
<td>1</td>
<td>urokinase infusion, rheolytic thrombectomy</td>
<td>femoral pseudoaneurysm</td>
<td>slight Lt upper extremity weakness, otherwise intact</td>
</tr>
<tr>
<td>Dowd et al., 1999</td>
<td>1</td>
<td>urokinase infusion, rheolytic thrombectomy</td>
<td>none</td>
<td>minimal cognitive deficit</td>
</tr>
<tr>
<td>Chaloupka et al., 1999</td>
<td>1</td>
<td>urokinase infusion, balloon angioplasty</td>
<td>none</td>
<td>near-complete resolution of deficits</td>
</tr>
<tr>
<td>Scarrow et al., 1999</td>
<td>1</td>
<td>rheolytic thrombectomy</td>
<td>none</td>
<td>complete symptomatic resolution</td>
</tr>
<tr>
<td>Gomez et al., 2000</td>
<td>1</td>
<td>rheolytic thrombectomy, urokinase infusion</td>
<td>none</td>
<td>near-complete resolution of deficits</td>
</tr>
<tr>
<td>Chow et al., 2000</td>
<td>2</td>
<td>urokinase infusion, rheolytic thrombectomy</td>
<td>increased parenchymal hemorrhage &amp; IVH</td>
<td>near-complete resolution of deficits</td>
</tr>
<tr>
<td>Wasay et al., 2001</td>
<td>20§</td>
<td>urokinase infusion</td>
<td>subdural hematoma, retroperitoneal hemorrhage</td>
<td>complete resolution (16), mild deficit (3), moderate deficit (1)</td>
</tr>
<tr>
<td>Baker et al., 2001</td>
<td>5</td>
<td>rheolytic thrombectomy, urokinase infusion</td>
<td>femoral pseudoaneurysm (2), posterior fossa hematoma requiring evacuation¶</td>
<td>4 of 5 recovered w/o significant disability, 1 had persistent disability</td>
</tr>
<tr>
<td>Curtin et al., 2004</td>
<td>1</td>
<td>rheolytic thrombectomy, balloon angioplasty, tPA infusion</td>
<td>pneumonia, anemia</td>
<td>neurologically intact</td>
</tr>
<tr>
<td>Chahlavi et al., 2004</td>
<td>2</td>
<td>direct mechanical thrombectomy</td>
<td>none</td>
<td>recovered to baseline w/ mild residual deficits</td>
</tr>
<tr>
<td>Yamashita et al., 2005</td>
<td>1</td>
<td>balloon angioplasty, urokinase infusion</td>
<td>none</td>
<td>neurologically intact</td>
</tr>
<tr>
<td>Agner et al., 2005</td>
<td>1</td>
<td>rheolytic thrombectomy, tPA infusion</td>
<td>none</td>
<td>neurologically intact</td>
</tr>
</tbody>
</table>

(continued)
Sinus thrombosis

TABLE 1: Literature summary of studies on the interventional management of CVST* (continued)

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>No. of Patients</th>
<th>Treatment Modality†</th>
<th>Complications</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prasad et al., 2006</td>
<td>1</td>
<td>tPA infusion, balloon angioplasty</td>
<td>none</td>
<td>near-complete resolution</td>
</tr>
<tr>
<td>Kirsch et al., 2007</td>
<td>4</td>
<td>rheolytic thrombectomy</td>
<td>none</td>
<td>4 of 5 w/o deficit, 1 died</td>
</tr>
<tr>
<td>Tsai et al., 2007</td>
<td>15*</td>
<td>tPA or urokinase infusion, mechanical thrombectomy</td>
<td>none reported</td>
<td>complete recovery (8), mild residual deficit (6), DAVF (1)</td>
</tr>
<tr>
<td>Stam et al., 2008</td>
<td>20</td>
<td>mechanical thrombectomy, urokinase infusion</td>
<td>increased ICH (5)</td>
<td>to minimal symptoms (9), minor handicap (3), moderate to severe handicap (2), deceased (6)</td>
</tr>
<tr>
<td>Sidani et al., 2008</td>
<td>1</td>
<td>tPA infusion</td>
<td>none</td>
<td>improved aphasia</td>
</tr>
<tr>
<td>Zhang et al., 2008</td>
<td>6</td>
<td>tPA infusion, rheolytic thrombectomy</td>
<td>none</td>
<td>excellent (2), good (2), deceased (2)</td>
</tr>
<tr>
<td>Sujith et al., 2008</td>
<td>3</td>
<td>urokinase infusion</td>
<td>none</td>
<td>complete recovery (2), persistent visual deficit (1)</td>
</tr>
<tr>
<td>Hocker et al., 2008</td>
<td>1</td>
<td>tPA infusion</td>
<td>none</td>
<td>neurologically intact</td>
</tr>
<tr>
<td>Bishop et al., 2009</td>
<td>1</td>
<td>balloon angioplasty‡††</td>
<td>none</td>
<td>ambulatory, verbal, following commands</td>
</tr>
</tbody>
</table>

* Numbers in parentheses refer to the number of patients. Abbreviations: CN = cranial nerve; DAVF = dural arteriovenous fistula; IVH = intraventricular hemorrhage; PE = pulmonary embolism; tPA = tissue plasminogen activator; UTI = urinary tract infection.
† Describes the modality used to achieve acute recanalization. In almost all cases, this was combined with systemic heparin and subsequent oral anticoagulation.
‡ One of the 2 patients with worsening ICH required surgical evacuation.
§ The study was conducted as a nonrandomized comparison of local thrombolysis versus heparinization with 20 patients in each group.
¶ One patient had subarachnoid hemorrhage at baseline and therefore a rheolytic thrombectomy catheter was used in isolation. This patient suffered from reoclusion requiring multiple procedures as well as posterior fossa hemorrhage requiring evacuation.
** The study was conducted as a retrospective analysis of patients treated for CVST. Ten patients received heparin therapy only, whereas 15 underwent thrombolysis or thrombectomy with or without systemic anticoagulation.
††† The patient had previously undergone hemicraniectomy and suboccipital decompression.

Mechanical Thrombectomy

Mechanical thrombectomy has been advocated as both a solution to the limitations imposed by chemical thrombolysis and a means of augmentation as described above. First performed for the treatment of CVST in the 1990s,62 this method provides a means of clot removal while affording a decreased risk of hemorrhagic complications when used independently of fibrinolytics. There are several methods by which to perform mechanical thrombectomy: balloon angioplasty, stenting, clot maceration, and rheolytic thrombectomy (Table 1). Several small case series have been published; however, few have been focused on the evaluation of the mechanical methods in isolation.62,64 Soleau and colleagues65 documented a retrospective series of 31 patients who had been treated using a variety of methods between 1992 and 2001. Eight patients underwent thrombectomy using an endovascular Fogarty balloon catheter in conjunction with systemic anticoagulation. Seven patients (88%) demonstrated clinical improvement, and 1 patient died as a result of excessive anticoagulation. Two hemorrhagic complications were
encountered, 1 occurring in the patient who died and the other in a patient in whom therapy was unsuccessful. In comparison, 10 patients were treated with chemical thrombolysis, with 6 (60%) having improvement and 4 (40%) experiencing significant deterioration or dying. In 3 of these 4 patients hemorrhagic complications were believed to be responsible for the deterioration. Subsequently, Kirch et al. described a series of 4 patients who had been treated with a rheolytic thrombectomy catheter as well as systemic heparin. Three of these 4 patients experienced a complete clinical recovery, and there were no periprocedural complications. In the fourth patient, there was extensive thrombosis of all the dural venous sinuses and involvement of the deep cerebral venous system. It was not technically feasible to evacuate this clot, and the patient subsequently died. These reports as well as numerous others in which mechanical and chemical thrombolysis were combined demonstrate a reasonable safety profile for this treatment modality and support it as an alternative to chemical thrombolysis in the setting of hemorrhagic infarction (Class IIb, Level B).

Surgical Thrombectomy and Decompression

Surgical therapies have a limited role in the management of CVST. Although occasionally used to provide access to the cerebral sinuses or performed for open thrombectomy or hematoma evacuation, their role is largely limited to decompression for elevated ICP (Fig. 1). Coutinho and colleagues, driven by the limited success of other modalities in the setting of impending herniation, adopted a strategy of hemicraniectomy in this population. They describe 3 cases in which hemicraniectomy was implemented, 2 of which had excellent clinical outcomes. In the third case there was a period of prolonged coma prior to surgery, and the patient died despite decompression. Again, this procedure represents a therapeutic option in an isolated patient population with refractory elevations in ICP (Class IIb, Level C).

Symptomatic Therapies

Multiple other therapeutic measures, including steroids, antiepileptics, acetazolamide, diuretics, hyperventilation, and shunting procedures, have been used in the management of CVST. These therapies are directed at managing the symptoms of increased ICP and seizures consequent to the underlying disease, without an effect on the thrombosis itself. The use of steroids was evaluated in a case-control study utilizing the ISCVT data. There was no benefit in their use, and in patients without parenchymal lesions they were in fact detrimental (Class III, Level B). Concerning the other modalities for reducing ICP, no controlled data exist. One must remember that diuresis has the potential to increase blood viscosity and potentiate thrombosis. The use of osmotic therapy can also be injurious, as elimination can be compromised in the setting of venous obstruction.

Although the use of prophylactic antiepileptic therapy is also controversial, it is probably indicated in a certain subset of patients. Masuhr et al. prospectively evaluated the risk and influence of early seizures on 194 patients with sinus thrombosis. Forty-four percent had early symptomatic seizures, and the mortality rate was 3 times higher in this group. Significant independent predictors of seizure included motor deficit, ICH, and cortical vein thrombosis. Ferro and colleagues also conducted a prospective observational study to further characterize the risks and benefits of antiepileptics in the acute setting.
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They reviewed 624 patients, 39.3% who presented with seizures. In their analysis, the presence of a parenchymal lesion in the supratentorial compartment on CT or MR imaging (OR 3.09, 95% CI 1.56–9.62), seizure on presentation (OR 1.74, 95% CI 0.90–3.37), and motor deficits (OR 3.63, 95% CI 1.63–5.88) were associated with additional seizures. Furthermore, the use of prophylactic therapy significantly lowered the risk of early seizures (OR 0.006, 95% CI 0.001–0.05). Given these findings, it is reasonable to place patients presenting with a supratentorial ICH, motor deficit, evidence of cortical venous thrombosis, or seizure on prophylactic anticonvulsant therapy (Class IIb, Level B).

Oral Anticoagulation

The use of long-term oral anticoagulation following acute therapy is yet another area lacking evidentiary support. Many clinicians follow treatment paradigms established for extracranial thrombosis; however, significant pathophysiological differences make this practice questionable. The cerebral venous circulation, as opposed to the extremities, is not dependent on valves and muscle contraction; therefore, flow is continuous in nature. Furthermore, studies focused on the long-term outcome of patients with CVST have not consistently demonstrated a significant increase in the risk of recurrence. Strupp et al. evaluated the outcomes of 40 patients with sinus thrombosis over a mean follow-up period of 12.1 years (range 4–23.4 years). Acutely, all patients received systemic heparinization for at least 10 days, with 35 subsequently receiving oral anticoagulation for at least 2 months (median 6.1 months). Sinus patency was analyzed using MR venography. No patient experienced a recurrence during the follow-up period, even those without complete recanalization. Baumgartner and colleagues prospectively enrolled 33 consecutive patients in an observation study. All patients were treated with unfractionated heparin followed by oral anticoagulation for at least 4 months (median duration 12 months, range 4–12 months). There was no evidence of recurrent sinus thrombosis on MR venography, and no other systemic thromboembolic complications occurred. Later, in the Cerebral Venous Thrombosis Portuguese Collaborative Study Group (VENOPORT) trial, Ferro et al. reviewed the outcomes in 142 patients—51 retrospectively and 91 prospectively, with a mean follow-up period of 3.5 and 1 year, respectively. During this time, only 2 patients in the retrospective group and none in the prospective group had a recurrent episode of CVST. However, 6 patients in the former and 4 in the latter group suffered from systemic thromboembolic events. Combined, 83% of the study population received some form of anticoagulation, but the details of treatment were not provided. Finally, in the ISCVT, over a median follow-up of 16 months, 2.2% of patients (16 patients) experienced recurrent sinus thrombosis, with 4.3% (27 patients) having other thromboembolic events. The median time for such therapy was 7.7 months in the ISCVT. Given the paucity of data there is considerable difficulty in composing recommendations. The European Federation of Neurological Societies guidelines mirror those established for extracranial thromboses, suggesting a 3-month period of anticoagulation for a first-time event in the setting of a temporary risk factor, 6 months in patients with “mild” thrombophilia (heterozygous factor V Leiden mutations, protein C and S deficiency, or prothrombin G20210A mutations), and indefinitely in those with recurrent events of “severe” thrombophilia (homozygous factor V Leiden mutations or antithrombin deficiency; Class IIb, Level C).

Conclusions

Cerebral venous thrombosis remains a therapeutic challenge despite its initial description more than 150 years ago. Based on available evidence, systemic anticoagulation is reasonable as an initial step in the treatment of most patients even in the setting of preexisting ICH (Class IIa, Level B). For those who are moribund on presentation or who experience clinical deterioration, both mechanical and chemical thrombolysis in addition to systemic anticoagulation are viable options (Fig. 2). In patients with ICH the safety of fibrinolysis is uncertain, and mechanical thrombectomy in conjunction with systemic anticoagulation is probably preferred (Class IIb, Level B). Surgical decompression is an option in patients with refractory elevations in ICP as a temporizing measure until sinus patency can be restored (Class IIb, Level C). Although quality prospective trials are needed to accurately evaluate the efficacy of the described interventions, the rarity of CVST is relatively prohibitive.

Disclaimer

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