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Endovascular Treatment of Thrombosis and Embolism

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Abstract

Deep venous thrombosis (DVT) is a common disorder with a significant mortality rate. Successful endovascular treatment of acute DVT is most likely to be achieved in patients with recently formed thrombus, (<10–14 days) with acute iliofemoral DVT. Endovascular treatment options include: Catheter-directed thrombolysis (CDT), pharmacomechanical catheter-directed thrombolysis (PCDT), percutaneous aspiration thrombectomy (PAT), vena cava filter protection, venous balloon dilatation and venous stent implantation. Current practice shows strong clinical tendency for the use of PCDT with or without other endovascular methods and an individualized approach for each DVT patient. PMT has not received general acceptance because of the associated risk of PE and damage to venous valves caused by thrombectomy devices. PAT is most commonly used as an adjunctive endovascular technique like balloon maceration to fragment thrombus, balloon angioplasty, stent implantation and vena cava filter placement. Interventional endovascular therapies for DVT have the potential to provide PE protection and prevention of PTS. Patient centered individualized approach for endovascular DVT treatment is recommended to optimize the ideal clinical result.

Acute stroke is the leading cause of death for people above the age of 60 and the fifth leading cause in people aged 15–59. Mortality during the first 30 days of ischemic stroke is 20 % and 30 % of survivors will remain permanently disabled. Acute stroke patients within the therapeutic window must receive IVrtPA unless there is a contraindication. In case of contraindication to IVrtPA or for patients out of the therapeutic window

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for thrombolytics, standart of care is the intraarterial treatment. Patients have to be transferred to a comprehensive stroke center with capacity of dedicated neurovascular imaging and interventional neuroradiology. Noncontrast head CT that is used to rule out hemorrhage is followed by imaging studies dedicated to show if there is reasonable penumbra to save. Intraarterial thrombolysis has the main advantage of extended therapy window, earlier and more efficient recanalization and less risk of hemorrhage due to lower doses of thrombolytics. Mechanical thrombectomy has several advantages over IV/IA fibrinolysis including faster recanalization and less risk of hemorrhage especially in large artery occlusions. ASA guidelines recommend choosing stent retrievers over other devices for mechanical thrombectomy. Better recanalization rates and less infarct volume after mechanical thrombectomy result in higher numbers of functionally independent patients compared with other treatments. Two landmark studies that were published recently, SWIFT PRIME and MR CLEAN, showed that IA treatment especially with the new stent retrievers lead to a significant increase in functional recovery and independence in daily life after an acute stroke.

Cerebral venous and sinus thrombosis (CVST) comprises nearly 0.5–1 % of all stroke cases. CVST causes different neurological deficits depending on the sinus/cortical vein involved. CVST may cause death and dependency in 13.4 % of patients. CT/CT venography and MR/MR venography can be effectively used to diagnose and to follow up CVT cases. Anticoagulation with heparin is the most widely accepted therapy to prevent the expansion of the thrombus. Patients deteriorating despite heparinization and patients presenting with very severe neurological deficits must receive endovascular treatment. Endovascular methods include intrasinus infusion of thrombolytics or heparin, balloon angioplasty, mechanical thrombectomy or a combination of different techniques. There is a higher rate or recanalization with endovascular methods compared to other medical therapies.

Keywords

Endovascular • Deep venous thrombosis • Catheter • Thrombolysis • Thrombectomy • Stroke • Stent retrievers • Cerebral venous thrombosis

1 Endovascular Treatment of Deep Venous Thrombosis

Deep venous thrombosis (DVT) is a common life-threatening disorder with a significant mortality rate. Even after appropriate medical therapy, DVT recurs frequently and may cause serious complications such as *pulmonary embolism* (PE) and postthrombotic syndrome [1–3]. Despite these risks of major complications and potentially permanent sequelae, no single effective treatment modality for DVT yet exists. There has been growing experience in the treatment of deep vein thrombosis, but major clinical challenges and a wide variation in practice still remain [4, 5].

The main purpose of any DVT treatment is to improve symptoms and to prevent the development of PE and *postthrombotic syndrome* (PTS)

by eliminating the thrombus material. Conventionally, there have been three acceptable basic treatment options for DVT and the rationale, risks, benefits, and uncertainties associated with these methods are summarized below.

1. **Anticoagulant Therapy:** The main objectives of anticoagulant therapy are to prevent progression of existing thrombi and to lower the incidence of PE by preventing development of recurrent thrombosis. Anticoagulants do not exert a recanalization activity. Recanalization occurs by natural thrombus resorption over time. Many studies have reported that anticoagulation therapy prevented progression of popliteal and tibial vein thrombosis and allowed development of near-complete recanalization in 95 % of patients in the long term. However, recanalization rates are poor (20 %) in patients with iliofemoral vein thrombosis [6].
2. **Systemic Thrombolytic Therapy:** Systemic thrombolytic therapy is markedly superior to anticoagulation therapy (heparin) in terms of reestablishment of venous blood flow [7]. Thrombolytic agents only resolve thrombi with which they come into contact. Thus, if venous occlusion is complete, such agents sometimes do not penetrate blood clots, and treatment failure may result. The most significant concern of thrombolytic therapy is the increased risk of bleeding. Although the efficacy of systemic thrombolytic therapy used to treat DVT is widely acknowledged, the risk of bleeding, the potential development of serious related complications, uncertainties in terms of dosage and route of administration, the requirement for admission to the intensive care unit, a prolonged hospitalization period, and the need to conduct numerous laboratory tests to monitor health status, all indicate that this therapeutic modality is associated with limited indications [6, 7].
3. **Surgical Thrombectomy:** As another therapeutic alternative, surgical thrombectomy, can be used to treat a limited number of patients and is especially preferred in patients with phlegmasia caerulea dolens [8]. However, even in patients with this rare pathological abnormality, it is not possible to achieve adequate venous patency with preservation of venous valvular function using surgical techniques [9].
4. **Endovascular treatment:** Endovascular interventional treatments have been used in the management of DVT for many years, and recently endovascular options increased in number with many different technical advances and new devices. The limitations of conventional treatment options encouraged the progress in endovascular treatment of DVT, and advances in endovascular therapies have delivered a wide range of new treatment options. Acceptable recanalization rates have been reported using endovascular therapeutic methods such as: *catheter-directed thrombolysis (CDT), pharmacomechanical catheter-directed thrombolysis (PCDT), percutaneous aspiration thrombectomy (PAT), vena cava filter protection, venous balloon dilatation and venous stent implantation* [4, 5, 10]. In recent years, endovascular techniques are also undergoing evaluation in many multicenter randomized controlled trials to determine their clinical benefit [4, 5].

Patient Selection for Endovascular Acute DVT Therapy All patients, in whom endovascular DVT therapy is planned, should undergo a detailed evaluation with clinical assessment that covers information from past medical history, physical examination and imaging findings. Patients should be evaluated for the thromboembolic risk factors and previous treatments, and preexisting comorbidities. Successful endovascular treatment of acute DVT is most likely to be achieved in patients with recently formed thrombus, (<10–14 days) with acute iliofemoral DVT [10–12]. Patients with a left-sided iliofemoral DVT are likely to have *May-Thurner Syndrome* with left common iliac vein stenosis that can be eliminated with venous stent placement [4, 13].

According to the *Society of Interventional Radiology (SIR) and Cardiovascular and Interventional Radiological Society of Europe (CIRSE) guidelines,* imaging proven symptomatic DVT in inferior vena cava or iliac, common femoral, and/or femoral veins in a recently ambulatory patient with DVT symptoms for less than 28 days and in whom there is strong clinical suspicion for recently formed DVT are the primary indications for endovascular interventions for lower-extremity DVT thrombus removal [10]. Contraindications for endovascular pharmacologic catheter-directed DVT thrombolysis are summarized in Table 1.

Table 1 Contraindications to catheter-directed thrombolysis and pharmacomechanical thrombolysis for lower extremity DVT

Absolute contraindications:
*Active internal bleeding or DIC
*Recent cerebrovascular event (including TIA)
*Recent neurosurgery or intracranial trauma (<3 months)
*Absolute contraindication to anticoagulation
Relative contraindications:
*Recent CPR, major surgery, obstetrical delivery (< 7–10 days)
*Recent organ biopsy, major trauma, or cataract surgery (<7–10 days)
*Intracranial tumor, other intracranial lesion, or seizure disorder
*Recent major GIS bleeding or internal eye surgery (<3 months)
*Serious allergic reaction to thrombolytic agent, anticoagulant or contrast media
*Known right-to-left cardiac or pulmonary shunt, left heart thrombus
*Severe dyspnea or severe acute medical illness precluding safe procedure
*Suspicion for infected venous thrombus
*Renal failure (GFR < 60 mL/min)
*Short life expectancy
*Severe thrombocytopenia
*Uncontrolled hypertension
*Bacterial endocarditis
*Pregnancy or lactation
*Severe hepatic dysfunction
*Diabetic hemorrhagic retinopathy

DIC disseminated intravascular coagulation, *CPR* cardiopulmonary resuscitation, *BP* blood pressure, *GIS* gastrointestinal system, *DVT* deep vein thrombosis, *GFR* glomerular filtration rate, *TIA* transient ischemic attack

1.1 Endovascular Interventional Options for Deep Vein Thrombosis

1.1.1 Catheter-Directed Thrombolysis (CDT) for DVT

Image-guided, catheter-directed, intra-thrombus drug delivery has been developed for improving the safety and efficacy of thrombolytic therapy for thromboembolic disease. CDT has several advantages for DVT patients and can be used:

1. To achieve high intra-thrombus thrombolytic agent concentrations.
2. To avoid bypass of the drug via collaterals around the thrombosed vein.
3. To reduce thrombolytic agent dose, treatment time, intensive care utilization and hospitalization time.
4. To decrease bleeding complications.
5. To treat underlying venous abnormalities by other endovascular techniques.

Catheter-directed thrombolysis (CDT) means delivery of a thrombolytic drug (rtPa, Urokinase) directly into the thrombus using a catheter or catheter-like device that is embedded within the thrombus by using Doppler ultrasound and fluoroscopy guidance. Usually a standard multisidehole catheter might be used but recently a multisidehole catheter that simultaneously applies ultrasound energy (EkoSoniccatheter; EKOS) to improve drug delivery into the thrombus has also been developed and this device is expected to increase safety and efficacy [4, 5, 10] (Fig. 1).

Currently, the most commonly used fibrinolytic drug for DVT is the *recombinant tissue plasminogen activator (rtPA).* The drug is infused continuously and directly into the thrombus at a low dose (0.5–1.0 mg/h) with systemic intravenous infusion of unfractionated heparin at subtherapeutic levels. Mostly the patient is closely monitored in an intensive care unit.

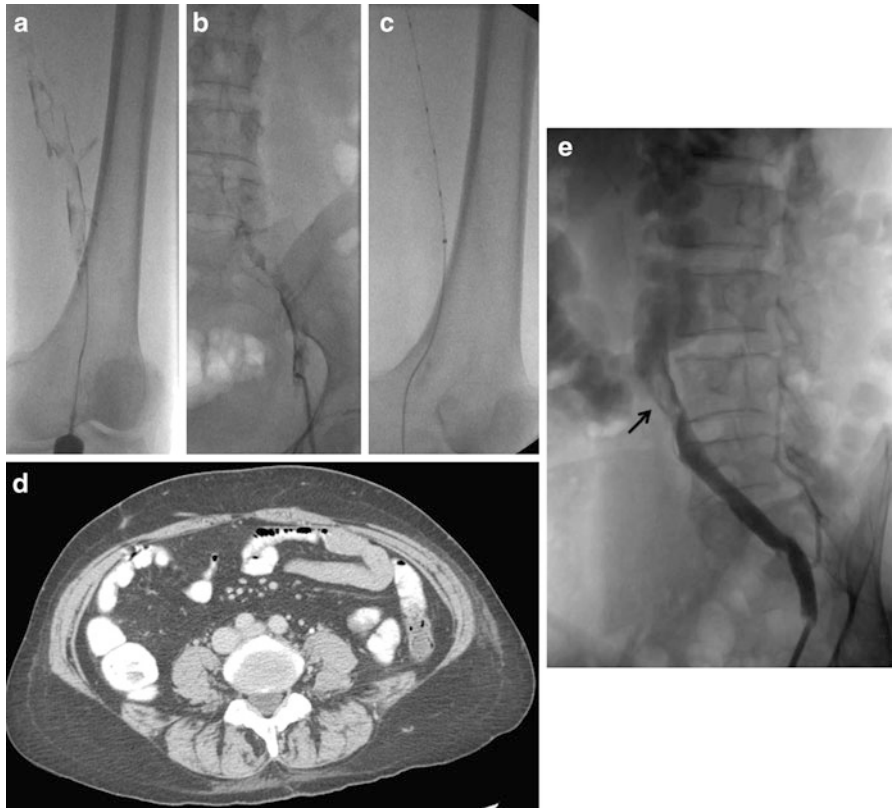


Fig. 1 Left iliofemoral DVT (**a**, **b**), placement of ultrasonic EKOS catheter with improved drug delivery into the thrombus (**c**), CT examination was obtained because of the suspicion of May-Thurner syndrome but the compression on left common iliac vein was moderate (**d**), only a small partial thrombus (*arrow*) was visible after the treatment (**e**)

Infusion might be stopped in case of active bleeding or severely abnormal coagulation parameters. Patients are evaluated by venography 1–2 times a day until the patency is achieved. Venous balloon angioplasty with thrombolytic infusion may also be used after partial thrombolysis [4, 5]. Left iliac anatomical venous stenosis (May-Thurner Syndrome) is usually treated by venous stent implantation and other venous stenoses might also be treated by balloon angioplasty and/or stent placement [4, 13]. Venography is performed to confirm the patency of the venous system. Before the patient is discharged anticoagulant therapy is arranged and compression stockings are prescribed. CDT has been evaluated in many case series and prospective multicenter trials. Major bleeding was observed in 5–12 % of patients in some older studies. However, more recent series with RCT reported much lower major bleeding rates [4, 5, 11, 12]. Fatal PE after CDT has also been reported very rarely [4, 14]. Although CDT is effective, currently the technique is not used widely because of long infusion times with intensive monitoring that are associated with longer hospital stays, and the risk of systemic bleeding still exists.

1.1.2 Pharmacomechanical Catheter-Directed Thrombolysis

Pharmacomechanical catheter-directed thrombolysis (PCDT) includes intrathrombus thrombolytic agent infusion with mechanical thrombectomy devices to improve drug penetration into thrombus and macerate thrombus for aspiration or

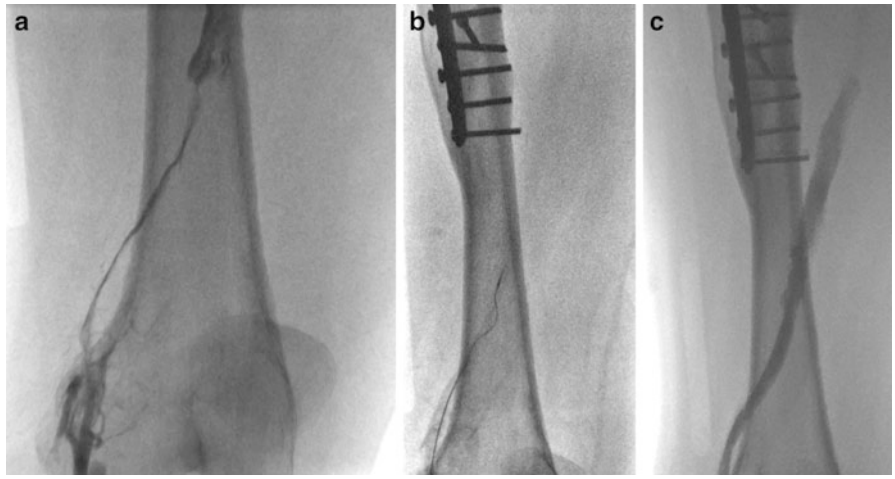


Fig. 2 Right iliofemoral DVT, thrombus is occlusive at the popliteal segment (**a**), oscillating wire activation of the pharmacomechanical thrombectomy device (**b**), recanalization of the thrombosed segment within minutes (**c**)

percutaneous thrombectomy [5, 11]. These devices enable faster penetration of thrombolytic agent within the thrombus, accelerating successful thrombolysis and improving safety by reducing drug dose and exposure time. Successful use of PCDT has been described in a number of published DVT studies [15–17]. Recently, new PCDT devices have been introduced that can enable endovascular DVT therapy to be completed in a single procedure session without the need for further drug infusions or intensive care monitoring. AngioJet Thrombectomy System (Boston Scientific) gives forceful pulse-spray bolus dose of the thrombolytic drug directly into the thrombus [18]. The drug is allowed to interact within the thrombus for a while and the device is used to aspirate the residual thrombus at the end. Isolated thrombolysis is another method performed by Trellis Peripheral Infusion System (Covidien) [5, 19]. With this device two catheter-mounted balloons are inflated to isolate a segment of vein and a bolus dose of a thrombolytic drug is injected directly into the thrombus. Activation of an oscillating wire for 10 min is then used to mechanically disperse the drug within the thrombus, and then the drug and liquefied debris are aspirated through a port on the device. Another similar device is Reya Thrombectomy catheter (Biolas Health) that is designed to use with the implantation of a temporary retrievable vena cava filter for protection before activation of an oscillating wire (Fig. 2). There are also many different endovascular venous thrombus aspiration systems such as Aspirex S Catheter (Straub Medical) and Angiovac Cannula and Circuit (AngioDynamics).

Although definitive multicenter RCTs comparing the most recent PCDT, CDT and combined methods have not been published yet, current practice shows strong clinical tendency for the use of PCDT with or without other endovascular methods and an individualized approach for each DVT patient [4, 5, 20].

1.1.3 Percutaneous Mechanical Thrombectomy

Stand-alone *percutaneous mechanical thrombectomy* (PMT) refers to the percutaneous use of catheter-based mechanical devices that contribute to thrombus removal via fragmentation, maceration, and/or aspiration, without administration of a thrombolytic drug. These methods are not always suitable for every patient and in most of the cases they are reserved for the patients with serious risk of bleeding and/or other contraindications for the thrombolytic therapy. *PMT has not received general acceptance*

because of the associated risk of PE and damage to venous valves caused by thrombectomy devices [10, 13].

1.1.4 Percutaneous Aspiration Thrombectomy

Percutaneous aspiration thrombectomy (PAT) technique can be defined as using a syringe to aspirate thrombus from the vein via a catheter, device, or sheath. PAT has been routinely used to effectively eliminate thrombi located in hemodialysis fistulae with a patency rate of 86 % at 6 months after PAT [21]. PAT also has been accepted as a rapid, safe, and effective method of management of iliofemoral vein thrombosis and provides higher recanalization rates than alternative treatments [13]. However, few clinical studies have been performed. Previous studies reported a recanalization rate of 88.9 % with PAT for the lower extremity DVT. Mechanical thrombectomy devices are not required during PAT and, therefore, the risk of trauma to the vascular wall and valves is thought to be low. Thrombolytic agents are not given to PAT patients, and the bleeding complications associated with systemic therapy are therefore absent [13, 22]. However there is no standardized PAT aspiration method and the technique is not widely accepted. PAT is most commonly used as an adjunctive endovascular technique like balloon maceration to fragment thrombus, balloon angioplasty, stent implantation and vena cava filter placement (Fig. 3).

Interventional endovascular therapies for DVT have the potential to provide PE protection and prevention of PTS. There is increasing number of scientific evidence in support of endovascular treatments. However, patient centered individualized approach for endovascular DVT treatment is recommended to optimize the ideal clinical result.

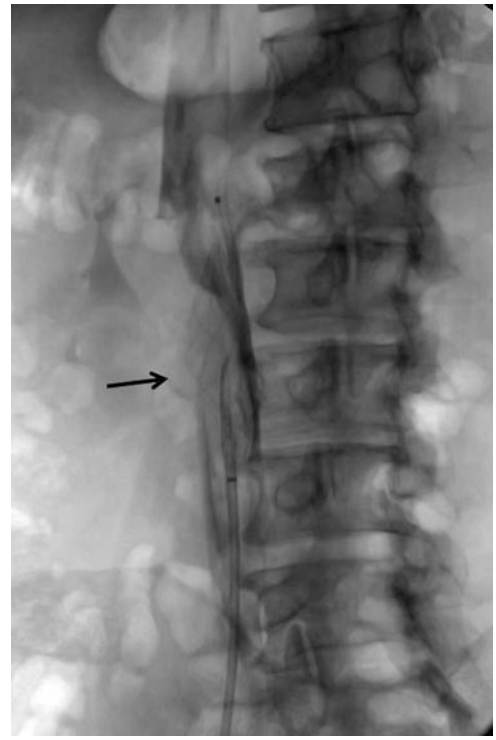


Fig. 3 Retrievable IVC filter was placed for periprocedural PE prophylaxis during pharmacomechanical thrombolytic treatment. Significant thrombus material (*arrow*) was captured by the filter just after the treatment

2 Endovascular Treatment of Acute Stroke

According to the World Health Organization (WHO), *stroke* is the leading cause of death for people above the age of 60 and the fifth leading cause in people aged 15–59 [23]. Stroke is the most common cause of disability worldwide [23, 24]. Every 6 s someone in the world will either be permanently disabled or will die due to stroke. More than 80 % of stroke cases are acute ischemic stroke cases due to cessation or diminution of blood supply to a certain part of the brain after arterial occlusion or hypoperfusion. Acute ischemia occurs mostly due to thromboembolism or local occlusion. Less frequently global hypoperfusion may cause acute cerebral ischemia. Immediate and prompt treatment of acute stroke is very important because of the heavy burden of this disease on a person and the society. Mortality during the first 30 days of ischemic stroke is 20 % and 30 % of survivors will remain permanently disabled [25].

2.1 Primary Management of Acute Stroke Patients

An acute stroke patient first seen in a hospital with the capability of intravenous (IV) fibrinolysis must have a *nonenhanced computerized tomography (NECT)* of the head to rule out cerebral hemorrhage. Patients without significant improvement after IV fibrinolysis can be immediately transferred to higher-level stroke centers. Patients that are seen by the emergency medical services in the field will benefit more if they can be sent to the nearest stroke center with the capability of both intravenous and intraarterial therapy and dedicated neurovascular imaging capabilities. *IV recombinant tissue plasminogen activator (alteplase, rtPA)* was the first approved treatment for acute ischemic stroke within 3 h of stroke onset after the *NINDS* (National Institute of Neurological Disorder and Stroke) trial. There are several exclusion criteria for the IV fibrinolytic therapy (Table 2).

The American Stroke Association (ASA, 2013) published guidelines for the early management of patients with acute ischemic stroke [26] (Tables 3, 4 and 5).

Recommendations with the highest level of evidence and that are directly related with the endovascular management of acute stroke are included. Recommendations regarding the intensive care management of acute stroke patients are not within the scope of this article. According to these guidelines an algorithm for management of acute stroke patients can be formed (Table 6).

2.2 Endovascular Therapy

Recanalization rates after *IV rtPA* in internal carotid artery terminus and MCA M1 segment occlusions range between 10 and 50 % and less than 40 % of patients regain functional independence [27]. Endovascular therapy has the main advantage of extended therapy window, earlier and more efficient recanalization and less risk of hemorrhage due to lower doses of thrombolytics. Endovascular therapies include

Table 2 Inclusion and exclusion characteristics for patients with ischemic stroke who could be treated with IV rtPA within 3 h from symptom onset

Inclusion criteria
Diagnosis of ischemic stroke causing measurable neurological deficit
Onset of symptoms <3 h before beginning treatment
Aged ≥18 years
Exclusion criteria
Significant head trauma or prior stroke in previous 3 months
Symptoms suggest subarachnoid hemorrhage
Arterial puncture at noncompressible site in previous 7 days
History of previous intracranial hemorrhage
Intracranial neoplasm, arteriovenous malformation, or aneurysm
Recent intracranial or intraspinal surgery
Elevated blood pressure (systolic >185 mm Hg or diastolic >110 mm Hg)
Active internal bleeding
Acute bleeding diathesis, including but not limited to
Platelet count <100,000/mm
Heparin received within 48 h, resulting in abnormally elevated aPTT (activated partial thromboplastin time) greater than the upper limit of normal
Current use of anticoagulant with international normalized ratio (INR) >1.7 or partial thromboplastin time (PT) >15 s
Current use of direct thrombin inhibitors or direct factor Xa inhibitors with
elevated sensitive laboratory tests (such as aPTT, INR, platelet count), and
ECT (ecarin clotting time); TT (thrombin time); or appropriate factor Xa activity assays
Blood glucose concentration <50 mg/dL (2.7 mmol/L)
CT demonstrates multilobar infarction (hypodensity >1/3 cerebral hemisphere)
Relative exclusion criteria Recent experience suggests that under some circumstances—with careful consideration and weighting of risk to benefit—patients may receive fibrinolytic therapy despite 1 or more relative contraindications. Consider risk to benefit of IV rtPA administration carefully if any of these relative contraindications are present:
Only minor or rapidly improving stroke symptoms (clearing spontaneously)
Pregnancy
Seizure at onset with postictal residual neurological impairments
Major surgery or serious trauma within previous 14 days
Recent gastrointestinal or urinary tract hemorrhage (within previous 21 days)
Recent acute myocardial infarction (within previous 3 months)

Table 3 ASA recommendations for the evaluation of the stroke patient in the emergency service

1. An organized protocol for the emergency evaluation of patients with suspected stroke (Class 1; Level of evidence B). The goal is to complete and begin fibrinolytic treatment within 60 min of the patient's arrival in an ED (Emergency department). Designation of an acute stroke team. Patients with stroke should have a careful clinical assessment, including neurological examination
2. The use of stroke rating scale preferably the NIHSS (National Institute of Health Stroke Scale) (Class 1; Level of evidence B)
3. A limited number of hematologic, coagulation and biochemistry tests are recommended during the initial emergency evaluation, and only the assessment of blood glucose must precede the initiation of intravenous rtPA (Class 1; Level of evidence B). Because hypoglycemia may mimic stroke signs and hyperglycemia is a risk factor for unfavorable outcomes

Table 4 ASA recommendations for the radiologic evaluation of the stroke patient

1. Either head NECT (Nonenhanced computerized tomography) or MRI (Magnetic resonance imaging) is recommended before intravenous rtPA administration to exclude intracerebral hematoma which is an absolute contraindication (Class 1; Level of evidence A)
2. Intravenous fibrinolytic therapy is recommended in the setting of early ischemic changes (other than frank hypodenisty) on CT, regardless of their extent (Class I; Level of evidence A)
3. A noninvasive intracranial vascular study is strongly recommended during the initial imaging evaluation of the acute stroke patient if either intraarterial fibrinolysis or mechanical thrombectomy is contemplated for management but should not delay intravenous rtPA if indicated (Class I; Level of evidence A)
4. CT perfusion and MRI perfusion and diffusion imaging, including measures of infarct core and penumbra, may be considered for the selection of patients for acute reperfusion therapy beyond the time windows for intravenous fibrinolysis. These techniques provide additional information that may improve diagnosis, mechanism, and severity of ischemic stroke and allow more informed clinical decision making (Class IIb; Level of Evidence B)
5. Frank hypodensity on NECT may increase the risk of hemorrhage with fibrinolysis and should be considered in treatment decisions. If frank hypodensity involves more than one third of the middle cerebral artery (MCA) territory, intravenous rtPA treatment should be withheld (Class III; Level of Evidence A)

Table 5 ASA recommendations for intravenous fibrinolysis

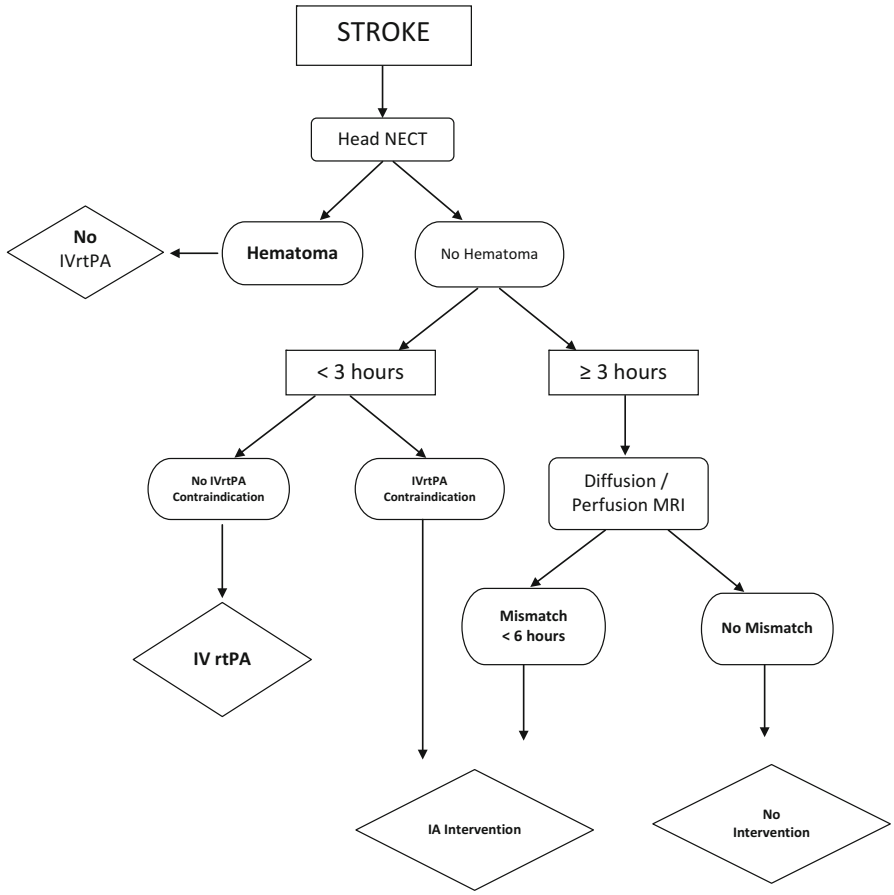
1. Intravenous rtPA (0.9 mg/kg, maximum dose 90 mg) is recommended for selected patients who may be treated within 3 h of onset of ischemic stroke (Class I; Level of Evidence A). Physicians should review the criteria outlined in Table 2 (which are modeled on those used in the NINDS Trial) to determine the eligibility of the patient
2. Intravenous rtPA (0.9 mg/kg, maximum dose 90 mg) is recommended for administration to eligible patients who can be treated in the time period of 3–4.5 h after stroke onset (Class I; Level of Evidence B). The eligibility criteria for treatment in this time period are similar to those for people treated at earlier time periods within 3 h, with the following additional exclusion criteria: patients >80 years old, those taking oral anticoagulants regardless of INR, those with a baseline NIHSS score >25, those with imaging evidence of ischemic injury involving more than one third of the MCA territory, or those with a history of both stroke and diabetes mellitus

either application of local intraarterial thrombolytics in the occluded intracranial segment or mechanical removal of the clot with a thrombectomy device or another endovascular device like a balloon or stent. *According to most recent guidelines safe therapy window for endovascular treatment is the first 6 hours after the stroke onset* [26]. After the development of dedicated mechanical thrombectomy devices, including stent retrievers, the balloon angioplasty has been put aside. Major disadvantages of endovascular therapies include low availability due to requirement of high level of expertise of specialists and complex neurointerventional infrastructure, delay in therapy initiation and invasive nature of the endovascular methods. Potential complications of endovascular stroke treatment are reperfusion hemorrhage, distal emboli, intracranial dissections, hematomas and subarachnoid hemorrhage [28, 29].

2.2.1 Intraarterial Fibrinolysis

The first positive randomized trial [28] to evaluate the efficiency of intraarterial fibrinolysis was PROACT 2 (Prolyse in Acute Cerebral Thromboembolism). In this study IA fibrinolysis with recombinant prourokinase (r-pro-UK) yielded

Table 6 Algorithm for management of acute stroke patients



higher middle cerebral artery recanalization rates than the control group (66 % vs % 18, $p < 0.001$). Fibrinolytics used in acute stroke treatment work as plasminogen activators. Prourokinase did not achieve FDA approval and it is not available any more and today the most frequently used IA fibrinolytic is *Alteplase (rtPA)*. Alteplase is applied directly within the thrombus through a microcatheter. Most neurointerventional specialists would use a maximum dose of 22 mg of IA rtPA [30, 31]. Adjunct mechanical disruption of the clot can be used with microwire maneuvers to increase the interaction surface area of the clot and the medicine. Recanalization rates in large artery occlusion including internal carotid artery, basilar artery or MCA M1 segment is not as high as distal and smaller arteries [32, 33]. Due to this reason in most centers first line treatment for large artery occlusions causing stroke is the mechanical thrombectomy. However, IA fibrinolysis is still used very efficiently in distal small artery occlusions like MCA M2-M3 segments, ACA paricallosal/callosomarginal branches and posterior cerebral artery occlusions. Bridging therapies as combination of IV rtPA and IA rtPA can further increase recanalization rates. Three consecutive trials, interventional management of stroke (IMS) 1, 2 and 3, showed better outcomes with comparable rates of symptomatic intracranial hematoma and mortality compared with NINDS rtPA trial [30, 34, 35].

2.2.2 Mechanical Thrombectomy

Mechanical thrombectomy has several advantages over IV/IA fibrinolysis. First of all, recanalization with mechanical techniques is faster. There is less risk of hemorrhage due to lower dose of fibrinolytics. Atherosclerotic emboli rich of calcium or cholesterol causing stroke are more resistant to pharmacological lysis and this brings the potential benefit of better recanalization by mechanical thrombectomy in these cases. Patients with contraindication to IV/IA fibrinolysis due to recent surgery and abnormal coagulation parameters can be treated only by means of mechanical thrombectomy [36]. Although there are several commercially available mechanical thrombectomy devices, only devices that are most frequently used, and that have been thoroughly studied in the literature, will be mentioned in this chapter. All mechanical thrombectomy devices are deployed in the intracranial arteries through microcatheters. Depending on the device they are either deployed within or distal to the clot and engage with the thrombus when deployed. Then the whole system, device, microcatheter and proposedly engaged clot are retrieved (Fig. 4). For documenting the recanalization/reperfusion rates after IA intervention a scale was proposed by Higashida et al. [37]. TICI (Thrombolysis in Cerebral Infraction) scale is

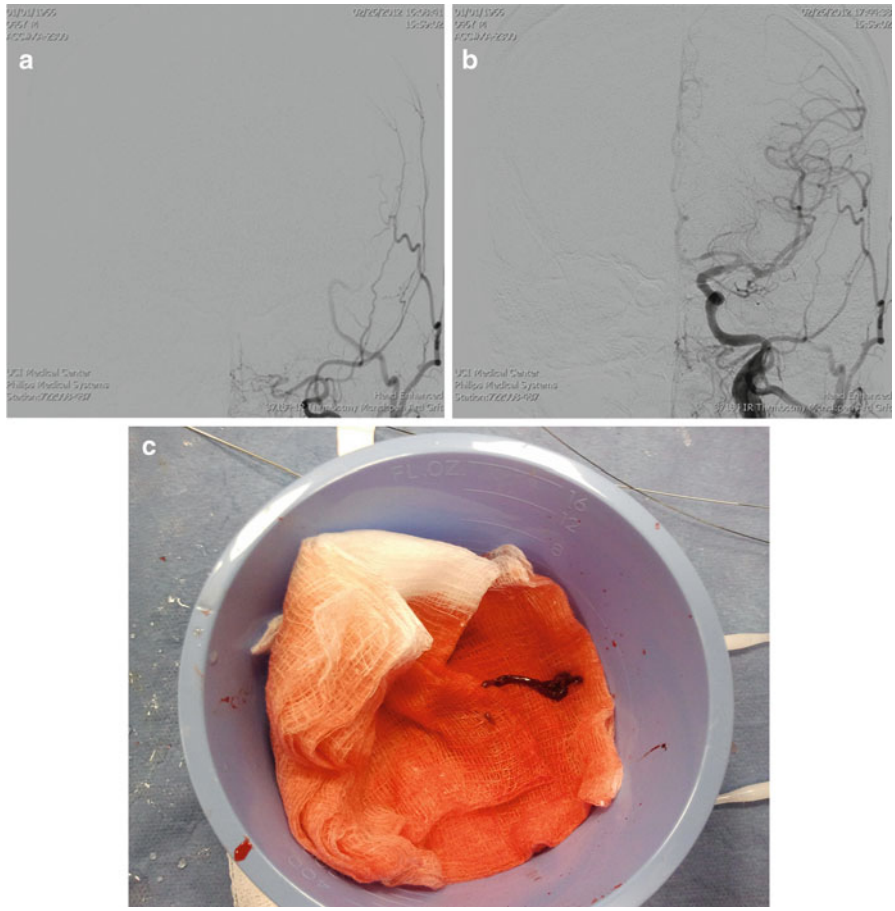


Fig. 4 (**a**) Left common carotid angiogram in an acute stroke patient shows complete occlusion of the internal carotid artery. There is no cerebral blood flow but only external carotid artery branches can be seen. (**b**) Complete recanalization of the left ICA and MCA after aspiration and mechanical thrombectomy. (**c**) Clot that occluded ICA was taken out by the thrombectomy device

commonly used in stroke centers to document the results of their therapies [38]. First FDA approved (2004) device *MERCI* (Concentric Medical, Mountain View, California) is a flexible nitinol wire with coil loops [39, 40]. *Penumbra* (Penumbra, Alameda, California) is another device that works by thromboaspiration by a microcatheter connected to an aspiration pump after mechanical disruption of the clot with a separator [41]. After the Penumbra Pivotal Stroke Trial [42], the Penumbra device was approved by FDA (2008). Newest and most frequently used devices are *stent retrievers including Solitaire* (Covidien, Irvine, CA), *Trevo* (Stryker Neurovascular, Fremont, California), *Catch* (Balt Extrusion, Montmerency, France) and *Preset* (Phenox, Bochum, Germany). ASA guidelines recommend choosing stent retrievers over other devices for mechanical thrombectomy in addition to other recommendations (Table 7).

Table 7 Recommendations for endovascular therapy

1. Patients eligible for intravenous rtPA should receive intravenous rtPA even if intra-arterial treatments are being considered (Class I; Level of Evidence A)
2. Intra-arterial fibrinolysis is beneficial for treatment of carefully selected patients with major ischemic strokes of <6 h duration caused by occlusions of the MCA who are not otherwise candidates for intravenous rtPA (Class I; Level of Evidence B)
3. As with intravenous fibrinolytic therapy, reduced time from symptom onset to reperfusion with intraarterial therapies is highly correlated with better clinical outcomes, and all efforts must be undertaken to minimize delays to definitive therapy (Class I; Level of Evidence B)
4. Intra-arterial treatment requires the patient to be at an experienced stroke center with rapid access to cerebral angiography and qualified interventionalists. An emphasis on expeditious assessment and treatment should be made. Facilities are encouraged to define criteria that can be used to credential individuals who can perform intra-arterial revascularization procedures. Outcomes on all patients should be tracked (Class I; Level of Evidence C)
5. When mechanical thrombectomy is pursued, stent retrievers such as Solitaire FR and Trevo are generally preferred to coil retrievers such as Merci (Class I; Level of Evidence A)
6. Intra-arterial fibrinolysis or mechanical thrombectomy is reasonable in patients who have contraindications to the use of intravenous fibrinolysis (Class IIa; Level of Evidence C)

These devices are self-expandable and retrievable stents that are deployed within the thrombus, jail the thrombus in between the stent struts and the artery wall and remove the thrombus by retrieving (Fig. 5). Both pivotal studies for Solitaire and Trevo showed superiority in recanalization rates compared with Merci [43, 44]. FDA approved both devices in 2012. The main advantage of stent retrievers is that once they are deployed temporary restoration of the blood flow to the deprived brain parenchyma occurs. By technological improvements, smaller microcatheter systems are used to navigate these stent retrievers in distal cerebral vasculature. Two landmark studies that were published recently, *SWIFT PRIME* and *MR CLEAN,* will potentially revolutionize the management of acute stroke [44–47]. *MR CLEAN* (Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands) [47] assessed whether intraarterial treatment plus usual care would be more effective than usual care alone in patients with a proximal arterial occlusion in the anterior cerebral circulation that could be treated intraarterially within 6 h after symptom onset. 195 patients (81.5 %) out of 233 patients treated with IA treatment had mechanical thrombectomy with stent retrievers. Only one patient (0.4 %) had IA thrombolytic agents as monotherapy. This represents the paradigm shift toward a more frequent use of mechanical thrombectomy devices as the first line therapy for IA treatment of acute stroke [48]. There were better recanalization (75.4 % vs 32.9 %), less infarct volume and more functionally independent patients (32.6 % vs 19.1 %) in the IA treatment group than the IV fibrinolysis group. *SWIFT PRIME* (Solitaire with the Intention for Thrombectomy as Primary Endovascular Treatment) trial evaluated the efficacy and safety of mechanical thrombectomy with the stent retriever in conjunction with intravenous t-PA versus intravenous t-PA alone in patients with acute ischemic stroke. Successful reperfusion rates were significantly higher (83 % vs 40 %) in the stent retriever group. Both studies showed that IA treatment especially with the new stent retrievers lead to a

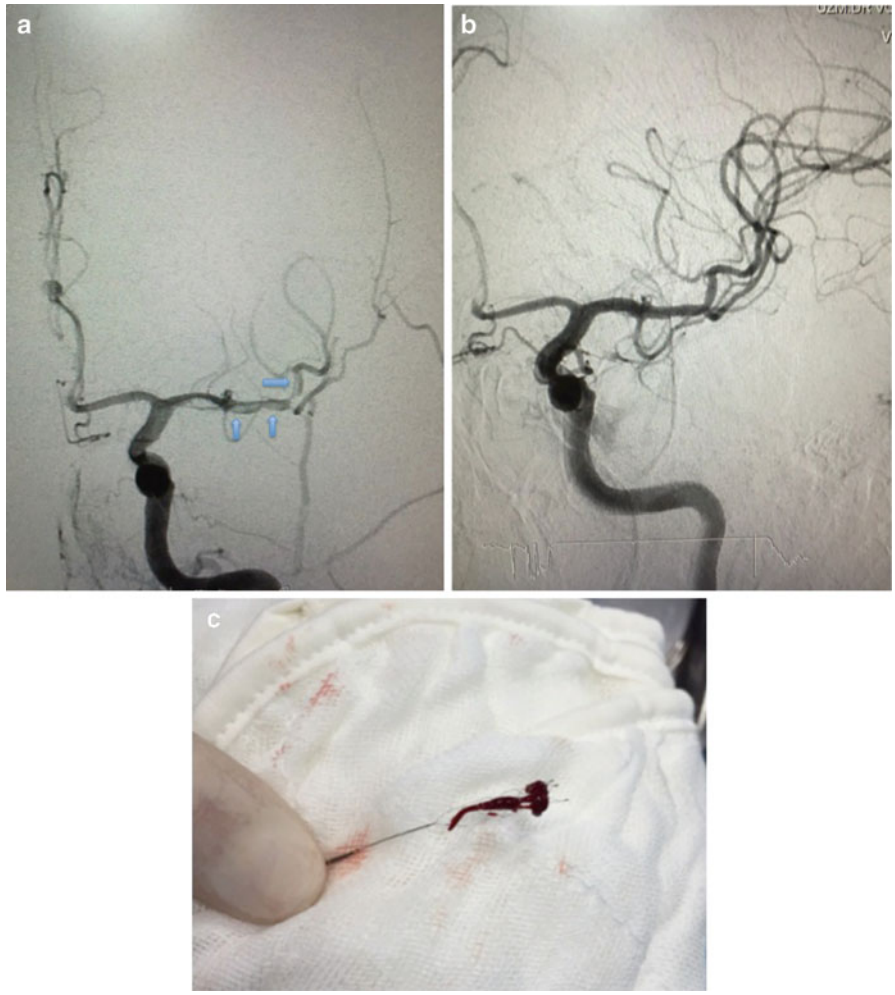


Fig. 5 (**a**) Acute stroke caused by a clot in left MCA M1 and M2 segment that is causing a linear filling defect within the artery. (**b**) Complete recanalization by a stent retriever and normal filling of the left MCA branches. (**c**) Clot engaged to the stent retriever device is seen. Shape and size of the clot correspond well with the angiographic image of the thrombosis in MCA (Fig. 5a)

significant increase in functional recovery and independence in daily life after an acute stroke.

3 Endovascular Treatment Cerebral Venous and Sinus Thrombosis

Cerebral venous and sinus thrombosis (CVST) comprises nearly 0.5–1 % of all stroke cases. Incidence of CVST is 3–4 cases per million in adults and incidence in pediatric population is 0.67 per 100.000 children [49]. In adult population it is more common in women and female predominance is most likely related with oral contraceptive use and hormonal disturbances during pregnancy. Other causes of CVST are infection, dehydration, hypercoagulable states, cardiac disease, surgery and trauma [50–53]. Most commonly affected intracranial venous structure is the *superior sagittal sinus* (SSS) followed by the transverse sinus. Other dural sinuses and cortical veins may also be involved. Clinical presentation is highly variable from completely asymptomatic cases to severe

intracranial hypertension, cerebral hematoma and herniation. Most common symptoms are headache, nausea, seizures, visual disturbances, decreased consciousness level and focal neurological deficits like hemiparesis, aphasia. Different neurological deficits are seen depending on the location of the thrombosis in the cerebral venous system and the affected cerebral lobe drained by that specific vein. For example, whereas thrombosis of the middle 1/3 of the SSS may cause hemiparesis, occlusion of the posterior 1/3 of the SSS may lead to cortical blindness due to occipital lobe involvement. Occlusion of the anterior 1/3 of the SSS may be asymptomatic. Occlusion of the dural sinus accompanied by the thrombosis of a cortical vein may potentially cause a higher risk of hemorrhagic infarct. Ferro et al. in the largest prospective multicenter international study found out 13.4 % death and dependency in 624 CVST patients [54]. Risk factors for an unfavorable outcome were male sex, age >37 years, coma, mental status disorder, intracranial hemorrhage on admission, thrombosis of the deep cerebral venous system, central nervous system (CNS) infection, and cancer [54, 55].

3.1 Radiological Work-up

Computerized tomography of the head is the most frequently used noninvasive radiological exam in patients presenting with headache or focal neurologic deficits. Cerebral infarct with or without hemorrhage can be seen in head CT of severe cases (Fig. 6). Cerebral infarct in venous thrombosis will not follow the arterial territories and will have a more atypical appearance and location than the arterial thromboembolism. The "*empty delta sign*" can be seen in enhanced head CT as enhancement of dura around the nonenhanced thrombosed sinus segment (Fig. 7). The "*cord sign*" defined as a homogeneous, hyperattenuated appearance of thrombosed venous sinuses on nonenhanced CT scans is highly specific and sensitive for deep venous system thrombosis [56].

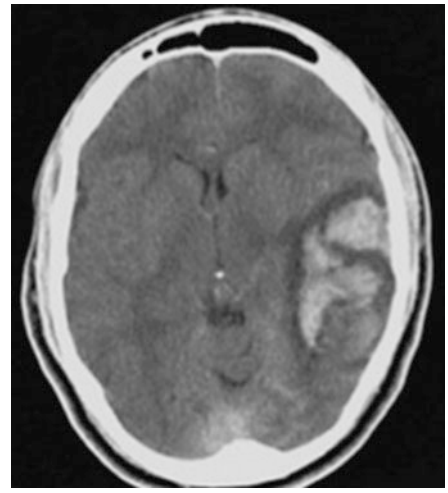


Fig. 6 NECT shows hemorrhagic infarct of the left frontoparietal lobes and mass effect due to cerebral vein thrombosis

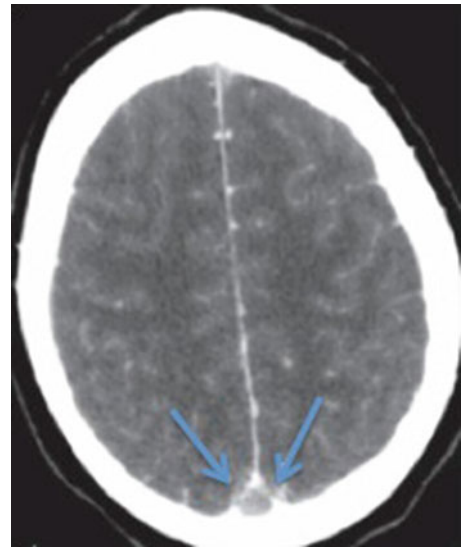


Fig. 7 "Empty delta sign" due to thrombosis of the superior sagittal sinus in contrast enhanced head CT

CT or Magnetic resonance (MR) angiography of the cerebral veins will depict the thrombus and its expansion within the venous system (Fig. 8). *"Cord sign"*, cerebral edema, infarct, subdural hematoma and subarachnoid hemorrhage due to cerebral venous thrombosis can be seen in CT or MR imaging. Both modalities *CT/CT venography* and *MR/MR venography* can be

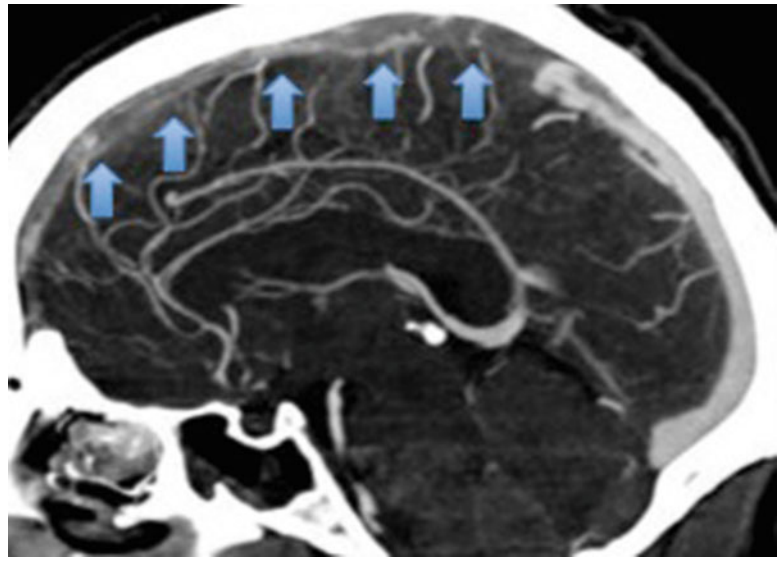


Fig. 8 Occlusion of the anterior 2/3 of the superior sagittal sinus in head CT venography (*Arrows*)

effectively used to diagnose and to follow up CVT cases [57–59].

3.2 Medical Management

Stabilization of the general status of the patient with hydration, treatment for intracranial hypertension and management of symptoms like seizures and headaches are first line measures. *Anticoagulation with heparin* is the most widely accepted therapy to prevent the expansion of the thrombus. Several studies showed better outcomes in CVST patients treated with heparin [60, 61].

Effective systemic anticoagulation targets activated partial thromboplastin times (aPTT) between 60 and 80 s. Cerebral hemorrhage is not a contraindication for heparin use in CVST and a substudy from *ISCVT (International Study on Cerebral Vein and Dural Sinus Thrombosis)* study group suggested a better efficacy and safety of low–molecular weight heparin over unfractionated heparin [62].

3.3 Endovascular Treatment

Despite heparinization, some CSVT patients with negative prognostic factors will fail to recover and mortality rate can be as high as 10 % in these patients [63]. Patients with rapid decompensation despite medical therapies will need more aggressive treatments. Rahman et al. [64], based on their literature review for endovascular treatment of CSVT, proposed a treatment algorithm for CSVT patients. Patients who present with severe neurological deficits (Glasgow coma scale score ≤ 8) are strongly considered for direct thrombolysis/thrombectomy immediately. Patients with Glasgow coma scale score (GCS) scores between 9 and 12 may be considered for immediate endovascular treatment. For other patients (GCS score > 12), direct thrombolysis/thrombectomy would be considered only after a trial of systemic anticoagulation. Endovascular methods include intrasinus infusion of thrombolytics or heparin, balloon angioplasty, mechanical thrombectomy or a combination of different techniques [65–70]. For pharmacological lysis of the clot, intrasinus heparin or thrombolytic infusion can be performed. Either urokinase or tissue plasminogen activators can be used as thrombolytics [71–75]. Infusion of local thrombolytics may increase the size of the hemorrhagic infarct in addition to complications including pulmonary embolism and hemorrhage. Mechanical thrombectomy can be achieved with rheolytic

catheters, balloon angioplasty, Fogarty catheter or dedicated mechanic thrombectomy devices including stent retrievers. There is a higher rate of recanalization with endovascular methods compared to other medical therapies. Even with partial recanalization of the sinus significant clinical recovery may happen. Until today there is no controlled randomized trial to compare the efficacy of intrasinus infusion of thrombolytics/heparin with mechanical thrombectomy for the treatment of CSVT.

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